Original article

Clinicopathological features and oncological outcomes of patients with young-onset rectal cancer

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Background: The incidence of rectal cancer among adults aged less than 50 years is rising. Survival data are limited and conflicting, and the oncological benefit of standard neoadjuvant and adjuvant therapies is unclear.

Methods: Disease-specific outcomes of patients diagnosed with rectal cancer undergoing surgical resection with curative intent between 2006 and 2016 were analysed.

Results: A total of 797 patients with rectal cancer were identified, of whom 685 had surgery with curative intent. Seventy patients were younger than 50 years and 615 were aged 50 years or more. Clinical stage did not differ between the two age groups. Patients aged less than 50 years were more likely to have microsatellite instability (9 *versus* 1·6 per cent; $P = 0·003$) and Lynch syndrome (7 *versus* 0 per cent; $P < 0·001$). Younger patients were also more likely to receive neoadjuvant chemoradiotherapy (67 *versus* 53·3 per cent; $P = 0·003$) and adjuvant chemotherapy (41 *versus* 24·2 per cent; $P = 0·006$). Five-year overall survival was better in those under 50 years old (80 *versus* 72 per cent; $P = 0·013$). The 5-year disease-free survival rate was 81 per cent in both age groups ($P = 0·711$). There were no significant differences in the development of locoregional recurrence or distant metastases.

Conclusion: Despite accessing more treatment, young patients have disease-specific outcomes comparable to those of their older counterparts.

Paper accepted 12 January 2020
Published online in Wiley Online Library (www.bjs.co.uk). **DOI:** 10.1002/bjs.11526

Introduction

Colorectal cancer represents the third most common cancer and third leading cause of cancer-related death worldwide[1]. Although the overall incidence of colorectal cancer has decreased owing to the implementation of population-based screening, there has been an alarming increase in incidence of rectal cancer among young adults under the age of 50 years[2]. It is estimated that by 2030 nearly one in four rectal cancers will be diagnosed in individuals aged less than 50 years[3]. The reasons for this disproportionate increase are unknown. Although young-onset disease may arise in the context of a hereditary cancer syndrome, the majority of cases are sporadic, with considerable genotypic and phenotypic heterogeneity. Environmental risk factors, such as obesity, physical inactivity and a Western diet do not explain the observed trends as they are not age-related.

It is possible that young-onset rectal cancer represents a unique disease process, with an incompletely understood, distinct biomolecular profile characterized by alternative mutations and/or signalling aberrations. In a curious paradox, younger patients typically present with more advanced disease and worse histopathological features than older people, yet have comparable (or better) short- and long-term survival[4–9]. The oncotherapeutic sensitivity of young-onset colorectal cancer to standard neoadjuvant and adjuvant therapies is not known in isolation owing to the (historically) small proportion of patients aged less than 50 years. The paucity of data, lack of standardization and use of varying cut-off ages has hampered the broader applicability of reports on the subject. The aim of this study was to analyse the clinical and pathological features, long-term survival and disease recurrence patterns among patients aged less than 50 years diagnosed with rectal

cancer, and to compare cancer-specific outcomes with those of patients aged 50 years or more.

Methods

A prospectively registered consecutive series of patients with histologically confirmed rectal cancer, undergoing surgery with curative intent at St Vincent's University Hospital, Dublin, between 2006 and 2016, was studied retrospectively. The study protocol was reviewed and approved by the institutional research and ethics board. Rectal cancer was defined as adenocarcinoma within 15 cm from the anal verge on colonoscopy. Clinical staging was done according to the eighth edition of the AJCC TNM system[10], and was based on a combination of pelvic MRI and CT. Baseline demographic, clinical, staging, treatment, histopathological and survival data were retrieved from a prospectively maintained database.

Treatment protocol

After histological diagnosis and radiological staging, all patients were discussed at an institutional multidisciplinary team meeting. Patients with clinical stage III disease or aggressive stage II disease (extramural venous invasion, T4 tumour, threatened mesorectal margin) received long-course neoadjuvant chemoradiotherapy, comprising 45–50·4 Gy delivered in daily fractions over 5–6 weeks and concurrent 5-fluorouracil (5-FU)-based chemotherapy. Following completion of neoadjuvant therapy, patients were restaged by CT of the thorax, abdomen and pelvis, MRI of the pelvis and clinical/endoscopic evaluation. If there was no evidence of local or systemic disease progression and performance status had not deteriorated significantly, total mesorectal excision was performed after an interval of 10–12 weeks. Adjuvant chemotherapy was given routinely to patients with predicted stage III disease and those with histologically node-positive disease who were otherwise fit. For patients with stage II disease, adjuvant chemotherapy was considered on an individual basis after multidisciplinary discussion.

All patients were followed up with annual CT and endoscopy at 1, 3 and 5 years, or when indicated clinically. Locoregional recurrence was defined as that occurring at the site of the anastomosis or within the pelvis. Distant recurrence was defined as that occurring within a solid organ. Cytological, histological or radiological proof was required to confirm a diagnosis of recurrent disease.

Pathology

Tumour stage was classified according to the TNM staging system and AJCC classification[10]. Haematoxylin and eosin sections of the resected specimen were analysed using a minimum data set and a standardized reporting system. Microscopically clear resection (R0) was defined by a tumour-free resection margin of at least 1 mm. The absence of residual tumour cells in the resected specimen was defined as a complete pathological response (pCR). The extent of residual carcinoma was assigned to one of three categories: tumour regression grade (TRG) 1 represents no identifiable residual cancer cells (pCR); TRG 2 indicates residual cancer outgrown by fibrosis; and TRG 3 represents significant fibrosis outgrown by cancer or no fibrosis with extensive residual cancer[11]. Microsatellite instability was assessed in all patients using immunohistochemistry for the mismatch repair (MMR) proteins MLH1, PMS2, MSH2 and MSH6. Germline testing was undertaken as needed following patient counselling and consent.

Statistical analysis

Continuous variables are described as mean(s.d.) or median (range), and were compared using the Student's t test or Mann–Whitney U test, depending on their distribution. Categorical variables are reported numbers with percentages, and were assessed using χ^2 test or Fisher's exact test where appropriate. For follow-up data, date of death or last follow-up was entered. Disease-free and overall survival rates were calculated according to the Kaplan–Meier method, and group comparisons done by means of the log rank test. Independent variables were entered into a

Fig. 1 Study flow chart

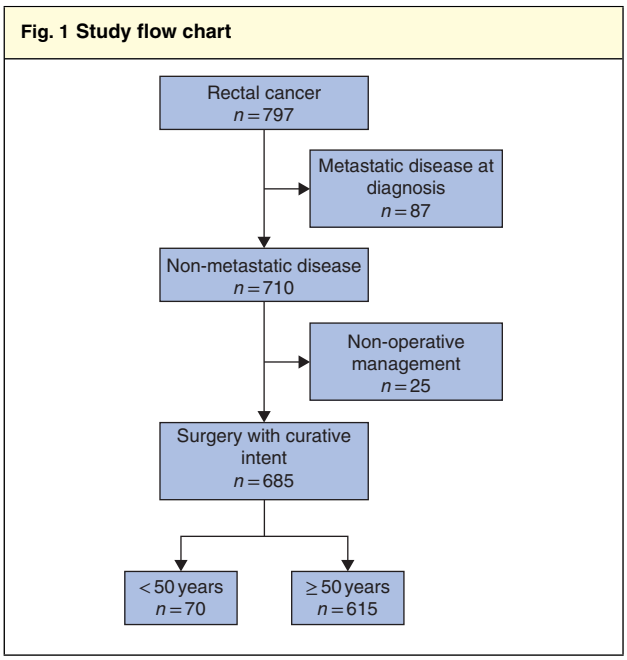


Table 1 Comparison of demographics and clinicopathological data according to age group

	Age < 50 years (*n* = 70)	Age ≥ 50 years (*n* = 615)	*P**
Sex ratio (M : F)	40 : 30	393 : 222	0·295
cTNM stage			
I–II	23 (33)	218 (35·4)	0·298
III	47 (67)	324 (52·7)	0·302
Unknown	0 (0)	73 (11·9)	
Neoadjuvant CRT	47 (67)	328 (53·3)	0·031
Type of operation			
Anterior resection	54 (77)	425 (69·1)	0·101
Abdominoperineal resection	9 (13)	99 (16·1)	0·604
Transanal excision	2 (3)	59 (9·6)	0·074
Pelvic exenteration	4 (6)	8 (1·3)	0·026
Other (e.g. Hartmann's)	1 (1)	24 (3·9)	0·501
(y)pTNM stage			
ypT0N0	7 (10)	62 (10·1)	0·687
I	14 (20)	172 (28·0)	0·201
II	18 (26)	157 (25·5)	1·000
III	31 (44)	221 (35·9)	0·239
Pathology			
Pathological complete resection	7 (10)	62 (10·1)	0·687
R0 resection	67 (96)	585 (95·1)	1·000
MMR status			
Microsatellite instability	6 (9)	10 (1·6)	0·003
Lynch syndrome	5 (7)	0 (0)	< 0·001
Adjuvant chemotherapy	29 (41)	149 (24·2)	0·006

Values in parentheses are percentages. CRT, chemoradiotherapy; MMR, mismatch repair. *χ^2 or Fisher's exact test.

multivariable Cox proportional hazards regression model. Only variables found to be significant on univariable analysis were entered into the multivariable model. A significance level of 0·050 was used for all analyses; reported *P* values are two-tailed. Data were analysed using SPSS® version 24·0 (IBM, Armonk, New York, USA).

Results

Between 2006 and 2016, a total of 797 consecutive patients were diagnosed with rectal cancer. Eighty-seven had metastatic disease at presentation, ten of 83 (12 per cent) aged less than 50 years and 77 of 714 (10·8 per cent) aged 50 years or more. Of those with non-metastatic disease, 685 patients underwent surgery with curative intent and comprise the study group. Among these, 70 were aged under 50 years and 615 were at least 50 years old (*Fig. 1*). Clinicopathological characteristics of the study population are summarized in *Table 1*. Age less than 50 years was associated with microsatellite instability and diagnosis of Lynch syndrome, but not clinical stage, pCR, R0 resection

Fig. 2 Kaplan–Meier overall survival curves for patients aged less than 50 years *versus* those aged 50 years and above

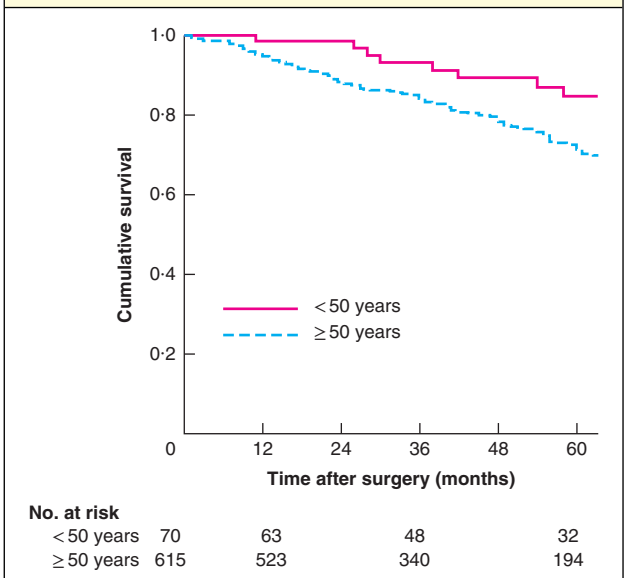
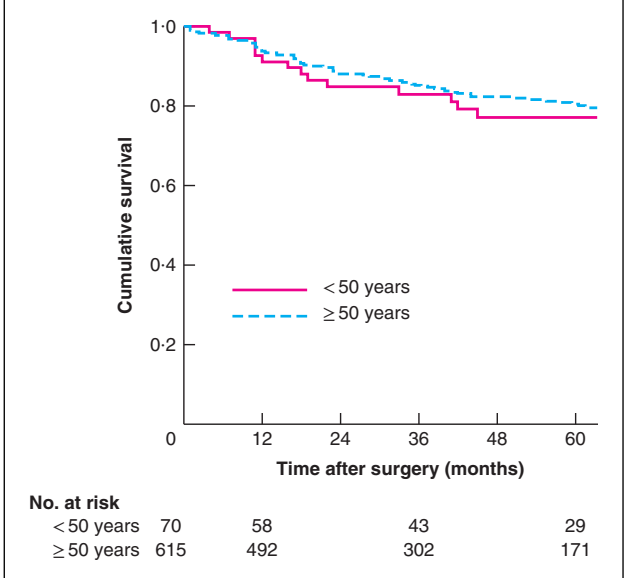


Fig. 3 Kaplan–Meier disease-free survival curves for patients aged less than 50 years *versus* those aged 50 years and above



rate or pathological stage. Young patients were more likely to undergo pelvic exenteration, and to receive neoadjuvant and adjuvant therapy.

Survival

Overall median follow-up was 48 (range 1–169) months. Among patients aged less than 50 years, median overall

Table 2 Age-based univariable logistic regression of factors predicting disease-specific survival

	Age < 50 years		Age ≥ 50 years	
	Hazard ratio	*P*	Hazard ratio	*P*
Age (years)	1·01 (0·92, 1·12)	0·782	1·01 (0·99, 1·03)	0·251
Male sex	0·64 (0·22, 1·87)	0·413	1·25 (0·84, 1·86)	0·270
cTNM stage I–II	0·66 (0·21, 2·09)	0·482	0·88 (0·57, 1·33)	0·535
cTNM stage III	1·51 (0·48, 4·76)	0·482	1·21 (0·79, 1·84)	0·376
Neoadjuvant chemotherapy	1·96 (0·55, 6·93)	0·299	1·90 (1·24, 2·90)	0·003
TRG 2–3	0·56 (0·07, 4·36)	0·581	0·34 (0·15, 0·78)	0·011
R0 resection	4·92 (1·11, 21·93)	0·036	5·32 (3·18, 8·90)	< 0·001
Pathologically node-negative	2·89 (0·99, 8·48)	0·053	2·09 (1·42, 3·10)	< 0·001
Microsatellite instability	1·72 (0·39, 7·62)	0·477	0·97 (0·24, 3·94)	0·966
Adjuvant chemotherapy	2·28 (0·81, 6·41)	0·119	1·47 (0·95, 2·27)	0·087

Values in parentheses are 95 per cent confidence intervals. TRG, tumour regression grade.

survival was 60 (10–166) months, with 1-, 3- and 5-year overall survival rates of 96, 88 and 80 per cent respectively. Equivalent values in the older group were 44 (3–169) months, and 95, 85 and 72 per cent ($P = 0·013$) (*Fig. 2*). Median disease-free survival was 54 (7–166) months among younger patients and 38 (7–169) months for the older group. In patients aged under 50 years, the disease-free survival rate at 1, 3 and 5 years was 96, 87 and 81 per cent, compared with 95, 85 and 81 per cent respectively among those aged 50 years or more ($P = 0·711$) (*Fig. 3*).

Disease recurrence

Fifteen patients (21 per cent) younger than 50 years developed disease recurrence compared with 102 (16·6 per cent) aged 50 years or more ($P = 0·313$). Locoregional recurrence occurred in five patients in the younger group (7 per cent) and 30 (4·9 per cent) in the older group ($P = 0·573$), and distant disease in ten (14 per cent) and 74 (12·0 per cent) respectively ($P = 0·567$). The median time to recurrence was 21 (range 7–157) months after surgery among patients younger than 50 years and 19 (7–103) months in those aged 50 years and over.

Prognostic factors

In univariable analysis, in the group younger than 50 years, the only variable associated with better disease-specific survival (DSS) was R0 resection (*Table 2*). In the group aged years 50 and over, neoadjuvant chemoradiotherapy, pCR, R0 resection and node negativity were associated with better DSS. On multivariable analysis, R0 resection (hazard ratio (HR) 3·44, 95 per cent c.i. 1·93 to 6·11; $P < 0·001$) and (y)pN0 status (HR 1·74, 1·07 to 2·84; $P = 0·025$) were significantly associated with DSS in the older group.

Discussion

Recent data from a large registry-based study in Europe have indicated that rectal cancer rates have increased by 1·8 per cent per year from 1990 to 2016 in adults aged less than 50 years[12]. Similar trends have been observed in the USA, with the greatest annual percentage change among adults aged between 20 and 34 years[3,13]. This highlights the need to understand the underlying aetiology, and biological and pathological mechanisms of young-onset disease. In the present study, younger patients typically presented with advanced disease stage. Several studies[14–17] have reported that patients with sporadic young-onset colorectal cancer typically have microsatellite-stable tumours, demonstrate a higher frequency of LINE-1 hypomethylation, are less likely to harbour *BRAF* and *KRAS* mutations, and have a lower frequency of the CpG island methylator phenotype. The incidence of unfavourable histopathological features is also higher in young individuals. Poor differentiation, mucin and signet ring morphology, all indicative of aggressive tumour biology and associated with worse oncological outcomes, are more frequently encountered among patients with young-onset disease[18,19].

Survival data for young-onset colorectal cancer are conflicting. Several studies have indicated a worse prognosis, whereas others have demonstrated equivalent or better oncological outcomes among younger patients[8,9,20,21]. In the present series, young patients had short- and long-term DSS comparable to that of their older counterparts. The incidence of locoregional recurrence and distant disease failure was also similar between groups. Interestingly,

oncological outcomes were equivalent despite increased neoadjuvant and adjuvant therapy among those aged less than 50 years.

The oncological benefit of standard neoadjuvant and adjuvant therapies in young-onset rectal cancer is unclear. Unsurprisingly, young patients were more likely to receive neoadjuvant chemoradiotherapy than older patients, presumably related to advanced disease stage at presentation and better performance status. It may therefore be anticipated that they would derive a meaningful benefit from such a treatment approach. Pathological response and tumour downstaging, however, are influenced by the specific molecular characteristics of the tumour. Although several large series[22–24] have demonstrated superior oncological outcomes with neoadjuvant chemoradiotherapy compared with surgery alone in locally advanced disease, patients younger than 50 years accounted for only a small percentage of the overall study population in these series. Recent data acquired from a national registry in the USA suggest that multimodal therapy for stage II and III disease may not be associated with an overall survival benefit in patients younger than 50 years[8], despite greater adherence to National Comprehensive Cancer Network treatment guidelines.

Age less than 50 years was also associated with higher rates of adjuvant chemotherapy. Historically, adjuvant chemotherapy has been administered to patients with locally advanced disease to improve oncological outcomes[25–27]; however, its role in the modern era of neoadjuvant therapy is less clear. Four European RCTs[28–31] have failed to demonstrate a significant survival advantage, and the potential for significant treatment-related toxicity and overtreatment of patients with low-risk disease must be considered in the absence of a definitive oncological benefit. Given that alternative signalling aberrations and mutations may be the driving pathogenesis, conventional chemotherapy may differ in efficacy in young-onset rectal cancer. Similar to MMR status predicting response to 5-FU-based adjuvant chemotherapy and immunotherapy, the identification of specific oncogenic mutations in young-onset disease would facilitate targeted treatment tailored to the molecular signature of the tumour[32–34].

Young age at disease onset is a hallmark of inherited cancer predisposition. The prevalence estimates of young-onset colorectal cancer due to pathogenic germline mutations ranges between 5 and 35 per cent[15,35–37]. This proportion is significantly higher than the 2–5 per cent of colorectal cancers overall[15,36]. In the present series, age less than 50 years was significantly associated with microsatellite instability and diagnosis of a hereditary cancer syndrome. The most commonly diagnosed hereditary cancer syndrome implicated in the pathogenesis of young-onset colorectal cancer is hereditary non-polyposis colorectal cancer, also known as Lynch syndrome, which occurs as a result of germline mutations in *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM* genes[36,38,39]. More recently, several additional genes, such as *SMAD4*, *CHEK2* and *POLE*, have also been implicated in cancer predisposition, and gene alterations of uncertain clinical relevance (variations of unknown significance) have been increasingly identified since the introduction of multigene panel testing. The development of next-generation sequencing has enabled genetic testing for hereditary colorectal cancer to transition from phenotype-specific single-gene assessment to broad multigene panels providing evaluation of multiple genes implicated in various hereditary cancer syndromes[37]. This is of particular importance as a significant proportion of patients with germline mutations do not report a colorectal cancer diagnosis in a first-degree relative[38].

This study has limitations, including the single-institution, retrospective nature, and dichotomization by age using an arbitrary integer cut-off (50 years). Considerable variation in survival outcomes has been observed among patients younger than 50 years independent of disease stage, supporting further age-based subgrouping[40]. Owing to the relatively small number of patients aged less than 50 years, further subgrouping was not possible in this analysis. Nonetheless, survival data specific to patients with young-onset disease are lacking, and the roles of environmental risk factors and the microbiome remain to be clarified. The changing epidemiology of colorectal cancer may necessitate the refining of current population-based screening strategies. On the basis of a microsimulation screening analysis model, the American Cancer Society[41,42] has recommended lowering the age of initial screening from 50 to 45 years. However, given that the greatest change in incidence is among those aged 20–39 years, optimal population education is a healthcare priority.

Acknowledgements

The authors thank following colleagues: A. White, M. Loughrey, J. Armstrong, G. McVey, D. Fennelly, R. McDermott, R. Geraghty, H. Mulcahy, G. Doherty, G. Cullen, G. Horgan, J. Sheridan and M. Buckley.
Disclosure: The authors declare no conflict of interest.

References

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018; **68**: 7–30.

2 Malvezzi M, Carioli G, Bertuccio P, Boffetta P, Levi F, La Vecchia C *et al.* European cancer mortality predictions for the year 2018 with focus on colorectal cancer. *Ann Oncol* 2018; **29**: 1016–1022.

3 Bailey CE, Hu CY, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM *et al.* Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975–2010. *JAMA Surg* 2015; **150**: 17–22.

4 McKay A, Donaleshen J, Helewa RM, Park J, Wirtzfeld D, Hochman D *et al.* Does young age influence the prognosis of colorectal cancer: a population-based analysis. *World J Surg Oncol* 2014; **12**: 370.

5 You YN, Dozois EJ, Boardman LA, Aakre J, Huebner M, Larson DW. Young-onset rectal cancer: presentation, pattern of care and long-term oncologic outcomes compared to a matched older-onset cohort. *Ann Surg Oncol* 2011; **18**: 2469–2476.

6 Orsini RG, Verhoeven RH, Lemmens VE, van Steenbergen LN, de Hingh IH, Nieuwenhuijzen GA *et al.* Comparable survival for young rectal cancer patients, despite unfavourable morphology and more advanced-stage disease. *Eur J Cancer* 2015; **51**: 1675–1682.

7 Rodriguez L, Brennan K, Karim S, Nanji S, Patel SV, Booth CM. Disease characteristics, clinical management, and outcomes of young patients with colon cancer: a population-based study. *Clin Colorectal Cancer* 2018; **17**: e651–e661.

8 Kolarich A, George TJ Jr, Hughes SJ, Delitto D, Allegra CJ, Hall WA *et al.* Rectal cancer patients younger than 50 years lack a survival benefit from NCCN guideline-directed treatment for stage II and III disease. *Cancer* 2018; **124**: 3510–3519.

9 Abdelsattar ZM, Wong SL, Regenbogen SE, Jomaa DM, Hardiman KM, Hendren S. Colorectal cancer outcomes and treatment patterns in patients too young for average-risk screening. *Cancer* 2016; **122**: 929–934.

10 Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK *et al. AJCC Cancer Staging Manual*, eighth edition. Springer: New York, 2017; 252–254.

11 Ryan R, Gibbons D, Hyland JM, Treanor D, White A, Mulcahy HE *et al.* Pathological response following long-course neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *Histopathology* 2005; **47**: 141–146.

12 Vuik FE, Nieuwenburg SA, Bardou M, Lansdorp-Vogelaar I, Dinis-Ribeiro M, Bento MJ *et al.* Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut* 2019; **68**: 1820–1826.

13 Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS *et al.* Colorectal cancer incidence patterns in the United States, 1974–2013. *J Natl Cancer Inst* 2017; **109**.

14 Antelo M, Balaguer F, Shia J, Shen Y, Hur K, Moreira L *et al.* A high degree of LINE-1 hypomethylation is a unique feature of early-onset colorectal cancer. *PLoS One* 2012; **7**: e45357.

15 Chang DT, Pai RK, Rybicki LA, Dimaio MA, Limaye M, Jayachandran P *et al.* Clinicopathologic and molecular features of sporadic early-onset colorectal adenocarcinoma: an adenocarcinoma with frequent signet ring cell differentiation, rectal and sigmoid involvement, and adverse morphologic features. *Mod Pathol* 2012; **25**: 1128–1139.

16 Boardman LA, Johnson RA, Petersen GM, Oberg AL, Kabat BF, Slusser JP *et al.* Higher frequency of diploidy in young-onset microsatellite-stable colorectal cancer. *Clin Cancer Res* 2007; **13**: 2323–2328.

17 Chan TL, Curtis LC, Leung SY, Farrington SM, Ho JW, Chan AS *et al.* Early-onset colorectal cancer with stable microsatellite DNA and near-diploid chromosomes. *Oncogene* 2001; **20**: 4871–4876.

18 You YN, Xing Y, Feig BW, Chang GJ, Cormier JN. Young-onset colorectal cancer: is it time to pay attention? *Arch Intern Med* 2012; **172**: 287–289.

19 O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Do young colon cancer patients have worse outcomes? *World J Surg* 2004; **28**: 558–562.

20 Wang MJ, Ping J, Li Y, Adell G, Arbman G, Nodin B *et al.* The prognostic factors and multiple biomarkers in young patients with colorectal cancer. *Sci Rep* 2015; **5**: 10645.

21 Kneuertz PJ, Chang GJ, Hu CY, Rodriguez-Bigas MA, Eng C, Vilar E *et al.* Overtreatment of young adults with colon cancer: more intense treatments with unmatched survival gains. *JAMA Surg* 2015; **150**: 402–409.

22 Peeters KC, Marijnen CA, Nagtegaal ID, Kranenbarg EK, Putter H, Wiggers T *et al.* The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* 2007; **246**: 693–701.

23 Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L *et al.* Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; **355**: 1114–1123.

24 Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C *et al.* Preoperative *versus* postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012; **30**: 1926–1933.

25 Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. *N Engl J Med* 1985; **312**: 1465–1472.

26 Krook JE, Moertel CG, Gunderson LL, Wieand HS, Collins RT, Beart RW *et al.* Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 1991; **324**: 709–715.

27 Petersen SH, Harling H, Kirkeby LT, Wille-Jørgensen P, Mocellin S. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. *Cochrane Database Syst Rev* 2012; (3)CD004078.

28 Glynne-Jones R, Counsell N, Quirke P, Mortensen N, Maraveyas A, Meadows HM *et al.* Chronicle: results of a

randomised phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomising postoperative adjuvant capecitabine plus oxaliplatin (XELOX) *versus* control. *Ann Oncol* 2014; **25**: 1356–1362.
29 Breugom AJ, van Gijn W, Muller EW, Berglund Å, van den Broek CB, Fokstuen T *et al.* Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. *Ann Oncol* 2015; **26**: 696–701.
30 Bosset JF, Calais G, Mineur L, Maingon P, Stojanovic-Rundic S, Bensadoun RJ *et al.* Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomised study. *Lancet Oncol* 2014; **15**: 184–190.
31 Sainato A, Cernusco Luna Nunzia V, Valentini V, De Paoli A, Maurizi ER, Lupattelli M *et al.* No benefit of adjuvant fluorouracil leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): long term results of a randomized trial (I-CNR-RT). *Radiother Oncol* 2014; **113**: 223–229.
32 Jover R, Zapater P, Castells A, Llor X, Andreu M, Cubiella J *et al.* The efficacy of adjuvant chemotherapy with 5-fluorouracil in colorectal cancer depends on the mismatch repair status. *Eur J Cancer* 2009; **45**: 365–373.
33 Ribic CM, Sargent DJ, Moore MJ, Thibodeau SN, French AJ, Goldberg RM *et al.* Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. *N Engl J Med* 2003; **349**: 247–257.
34 Sargent DJ, Marsoni S, Monges G, Thibodeau SN, Labianca R, Hamilton SR *et al.* Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. *J Clin Oncol* 2010; **28**: 3219–3226.
35 Goel A, Nagasaka T, Spiegel J, Meyer R, Lichliter WE, Boland CR. Low frequency of Lynch syndrome among young patients with non-familial colorectal cancer. *Clin Gastroenterol Hepatol* 2010; **8**: 966–971.
36 Mork ME, You YN, Ying J, Bannon SA, Lynch PM, Rodriguez-Bigas MA *et al.* High prevalence of hereditary cancer syndromes in adolescents and young adults with colorectal cancer. *J Clin Oncol* 2015; **33**: 3544–3549.
37 Pearlman R, Frankel WL, Swanson B, Zhao W, Yilmaz A, Miller K *et al.* Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. *JAMA Oncol* 2017; **3**: 464–471.
38 Stoffel EM, Koeppe E, Everett J, Ulintz P, Kiel M, Osborne J *et al.* Germline genetic features of young individuals with colorectal cancer. *Gastroenterology* 2018; **154**: 897–905.e1.
39 Lynch HT, Snyder CL, Shaw TG, Heinen CD, Hitchins MP. Milestones of Lynch syndrome: 1895–2015. *Nat Rev Cancer* 2015; **15**: 181–194.
40 Jacobs D, Zhu R, Luo J, Grisotti G, Heller DR, Kurbatov V *et al.* Defining early-onset colon and rectal cancers. *Front Oncol* 2018; **8**: 504.
41 Peterse EFP, Meester RGS, Siegel RL, Chen JC, Dwyer A, Ahnen DJ *et al.* The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: Microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. *Cancer* 2018; **124**: 2964–2973.
42 Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ *et al.* Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. *CA Cancer J Clin* 2018; **68**: 250–281.