Colorectal cancer

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Despite decreased incidence rates in average-age onset patients in high-income economies, colorectal cancer is the third most diagnosed cancer in the world, with increasing rates in emerging economies. Furthermore, early onset colorectal cancer (age ≤50 years) is of increasing concern globally. Over the past decade, research advances have increased biological knowledge, treatment options, and overall survival rates. The increase in life expectancy is attributed to an increase in effective systemic therapy, improved treatment selection, and expanded locoregional surgical options. Ongoing developments are focused on the role of sphincter preservation, precision oncology for molecular alterations, use of circulating tumour DNA, analysis of the gut microbiome, as well as the role of locoregional strategies for colorectal cancer liver metastases. This overview is to provide a general multidisciplinary perspective of clinical advances in colorectal cancer.

Introduction

Recent developments in colorectal cancer research have substantially improved biological knowledge, treatment options, and overall survival (OS). Colorectal cancer was the third most diagnosed cancer worldwide in 2020, with 2 million new cases.[1] The estimated median age of onset is 67 years, yet approximately 10% of patients are younger than 50 years. It is our intent to provide a global multidisciplinary perspective about developments in colorectal cancer.

Incidence

Studies in high-income countries have shown decreasing incidence of colorectal cancer in older adults. However, increasing incidence is detected in emerging economies, as well as in young adults (age <50 years) worldwide. In 2018, the International Agency for Research on Cancer reported the highest incidence rates of colon cancer was found in Europe, North America, Australia, New Zealand, and eastern Asia, with similar distribution for rectal cancer.[2] According to the International Agency for Research on Cancer, by 2040, 3·2 million new cases will result in 1·6 million deaths (an increase of 63% and 73·4%, respectively, relative to 2020). Over 80% of the cases are predicted to occur in high or very high Human Development Index (HDI) countries.[1]

Geographical distribution

In 2020, the USA and China reported the highest incidence rates, followed by Japan, Russia, India, Germany, Brazil, the UK, Italy, and France.[3] The incidence rate in men is 44% greater than in women, with the highest incidence rates being in Europe (eastern Europe 20·2 per 100 000 men), Australia, and New Zealand, followed by eastern Asia. In contrast, the incidence rates in Africa and south Asia are less than ten per 100 000 men, with the lowest male mortality being in southern Asia (3·9 per 100 000 men).[1]

Search strategy and selection criteria

We searched literature using PubMed and https://www.nccn.org from Jan 1, 1976 to Dec 31, 2022. Additional records were identified through review of the reference sections of included studies and reviewed in full text if they met title and abstract review criteria. Our search terms consisted of "colon cancer", "treatment", "incidence", "ctDNA", "metastatic colorectal cancer", "molecular subtypes", "screening", "colorectal cancer", "early-onset colorectal cancer", "young onset", and "rectal cancer".

Early-onset colorectal cancer (EOCRC)

Early-onset colorectal cancer (EOCRC) refers to adults younger than 50 years. Globally, the annual percent change for EOCRC increased by 7·9% (20–29 years), 4·9% (30–39 years), and 1·6% (40–49 years) during 2004 to 2016.[4] Pivotal analysis of the USA Surveillance, Epidemiology, and End Results database (1975–2010) estimates an increase of 90% and 124·2% for colon and rectal cancers, respectively, for the cohort aged 20–30 years by the year 2030.[4] Overall, the concerning rise in EOCRC has been validated in several subsequent studies worldwide.[5,6] We recommend that all patients with EOCRC be offered fertility counselling before initiating any type of therapy.[7] Sperm, oocyte, and embryo preservation remain commonly accepted standards, but other approaches to fertility preservation should be discussed with a dedicated specialist.

Metabolic syndrome

Metabolic syndrome includes hyperglycaemia, dyslipidaemia, abdominal obesity, and hypertension. Epidemiological studies have investigated the association between metabolic syndrome and colorectal cancer risk and mortality, with inconsistent results. A meta-analysis determined that metabolic syndrome is associated with a 25% increase in incidence for both sexes and 15% increase in cancer mortality in males.[8] A nested case-control study found that metabolic syndrome was associated with EOCRC (odds ratio 1·25, 95% CI 1·09–1·43); the presence of one, two, or three or more metabolic conditions was associated with 9%, 12%, and 31% higher risk of development, respectively (p_{trend}<0·001).[9,10]

	Test preference	Screen age	Recommendations	Note
US Preventive Services Task Force and American Cancer Society	No preference	≥45 years, unless clinically indicated	Tiered approach with colonoscopy or FIT testing	NA
Canadian Task Force on Preventive Health Care	gFOBT, FIT, or a flexible sigmoidoscopy	50–74 years, unless at high risk for colorectal cancer	Either gFOBT or FIT every 2 years or a flexible sigmoidoscopy every 10 years	Does not recommend a colonoscopy
EU	gFOBT, FIT, or colonoscopy	50–74 years	Most prefer FIT or FOBT as primary screening every 1–2 years but some countries use a colonoscopy as a primary screening tool every 5–10 years	Some variation between countries on screening ages (eg, Sweden at 60–69 years *vs* France at 55–74 years)
Asia Pacific Colorectal Cancer Working Group	FIT or colonoscopy	50–75 years for average risk	FIT every 2 years or a colonoscopy every 10 years; recommends screening in regions with high incidence (>30 cases per 100 000 people)	NA
Malaysia	iFOBT	50–75 years	For average risk population iFOBT is preferred; for moderate-risk or high-risk patients a colonoscopy is recommended	NA
Middle East and North Africa	None established	None established	None established	Differences in culture and economic status among Middle East and North African countries might be responsible for absence of standard screening; the United Arab Emirates is developing a cancer control plan in line with WHO and EMRO framework; Algeria testing iFOBT screenings for average risk patients between 50 years and 74 years
Sub-Saharan Africa	None established	<50 years for high-risk patients	None established	New strategies using MAAA; use complete blood count and demographic data to identify patients at high risk of colorectal cancer; availability of endoscopic services and cost affect other screening methods
The National Bowel Cancer Screening Program, Australia	FIT	50–74 years	Government provides biennial FIT screenings	NA
Mexico	None established	None established	None established	No national standard currently but Mexico's National Institute of Cancer is one of many institutions conducting campaigns and research in the region to create standardised screening using FIT in patients ≥50 years
Colombia	FIT or colonoscopy	≥50 years	Biennial screening with FIT or screening every 10 years with colonoscopy	NA
National Cancer Institute of Argentina	FIT	50–75 years	FIT then colonoscopy	NA
Chile	iFOBT or colonoscopy	50–75 years	iFOBT every 2 years or colonoscopy every 10 years	International collaboration efforts, since 2012, between Chile and Japan have developed these guidelines as well as increased colonoscopy training

EMRO=Eastern Mediterranean Regional Office. FIT=faecal immunochemical test. FORT=faecal occult blood test. gFOBT=guaiac faecal occult blood test (chemical used for detection). iFOBT=immunological faecal occult blood test (antibodies used for detection). MAAA=multianalyte assays with algorithmic analysis. NA=not applicable.

Table 1: **Current international screening guidelines**

Tobacco and alcohol use

History of tobacco use is linearly associated with the incidence of colorectal cancer;[11] however, the exact mechanism is unknown. Besides DNA and colorectal mucosa damage by tobacco carcinogens, a recent study showed that cigarette smoking could induce gut microbiota dysbiosis, promoting colorectal tumourigenesis.[12] Alcohol contributes to carcinogenesis by oxidative and non-oxidative metabolism, favouring genetic abnormalities, epigenetic, cell signalling, and immune processes dysregulations.[13] Alcohol consumption is dose dependent and is linked to increased risk and mortality. People consuming at least 50 g/day of ethanol had a relative risk of 1·21 (95% CI 1·01–1·46).[14]

Screening

Various screening methods are available; the most widely applied are the faecal immunochemical test and colonoscopy.[15–17] Multitarget faecal-DNA combines haemoglobin, DNA mutation analysis, and methylation. One example is Cologuard (Exact Science, USA), which is available in the USA, Puerto Rico, and the UK. Multitarget faecal-DNA has a higher single-application sensitivity for advanced precancerous lesions.[18] It is well documented that mortality from colorectal cancer is reduced through screening and early detection, and removal of preneoplastic lesions can reduce the incidence of cancer.[19] Table 1 shows international screening guidelines. In 2004, the Asian Pacific Working Group for Colorectal Cancer Screening was created, but

	Lynch (HNPCC)	Peutz-Jegher's	Familial adenomatosis polyposis	Cowden's Syndrome	Li Fraumeni Syndrome	MUYTH	CHEK2
Mutation	Mismatch repair proteins: MLH-1, MSH2, MSH6, PMS2, and EPCAM	STK-11	APC	PTEN	p53 (17p13; 1q23) CHEK2 (22q12.1)	MUYTH (*MUY* gene)	*CHEK2* gene
Incidence	1 in 279	<5000/year	1 in 8300	1 in 200 000	1 in 5000 to 1 in 20 000	1 in 100	1·4 in 100
Age	40–60 years	19–65 years	<35 years	20–30 years	At any time	>50 years	NA
Genetic	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive	NA
Presentation	Fewer than ten polyps	Hamartomas	>100 polyps	Hamartomas	Variable	NA	NA
Anatomy	Right side of the colon	NA	NA	Skin and mucous membranes	Variable	NA	NA
Associated cancers	Brain, endometrial, hepatobiliary, pancreatic, small bowel, small intestine, stomach, and urinary tract (renal pelvis, ureter, and bladder)	Cervical, gastric, and pancreatic cancer	Biliary tree, desmoid tumours, hepatoblastoma (children), medulloblastoma, pancreas, papillary thyroid tumours, small bowel, and stomach cancer	Breast cancer, colon cancer, melanoma, renal cell carcinoma, thyroid cancer, and uterine leiomyomas	Sarcomas (cancers of muscle, bone, or connective tissue), breast cancer, brain tumours, leukaemia, and adrenocortical carcinoma	Breast, duodenal, endometrial, and stomach cancer	Brain, breast, kidney, lung, kidney, papillary thyroid, osteosarcoma, and prostate cancer

HNPCC=hereditary nonpolyposis colorectal cancer.

Table 2: **Hereditary colorectal cancer syndromes**

disparities remain; low-income Asian economies often do not have the resources needed to create a cancer registry.[20] Collaborative efforts are underway with the creation of the Asian National Cancer Centers Alliance, with countries including China, India, Indonesia, Japan, South Korea, Mongolia, Singapore, Thailand, and Viet Nam.

Hereditary syndromes

An essential discussion between health-care provider, patient, and caregiver regarding family history should occur. A patient's genetics might prove to be crucial for their prognosis, treatment, and prevention of malignancy in the patient and their relatives. Hereditary syndromes might result in a diagnosis of colorectal cancer or other primary cancers (table 2). An example is Lynch syndrome, which is attributed to a germline mutation of the DNA mismatch repair genes. Immunohistochemical identification of a deficiency in a DNA mismatch repair (dMMR) is shown through loss of expression of any of the mismatch repair proteins MLH-1, MSH2, MSH6, and PMS2. This loss indicates microsatellite instability. Microsatellite instability status can be determined via PCR or next-generation sequencing. It is recommended germline testing be completed in all patients with EOCRC, dMMR, or a family history of colorectal cancer.[21,22] An exception is in the presence of loss of MLH-1 with a $BRAF^{V600E}$ (ie, Val600Glu) mutation, which is associated with MLH-1 hypermethylation and is attributed to sporadic colorectal cancer.

Clinical presentation and diagnosis

Although increases in colorectal cancer screening has reduced overall incidence, many patients with EOCRC present with advanced disease; low-income countries without the necessary infrastructure have increased mortality.[23–25] Typical signs and symptoms include: haematochezia or melena, abdominal pain, otherwise unexplained iron deficiency anaemia, or a change in bowel habits, or a combination thereof.[26,27] Less common presenting symptoms include abdominal distention, nausea, or vomiting, or a combination of these, which could indicate obstruction. Iron-deficiency anaemia from unrecognised blood loss is common in right-sided colorectal cancers.[28]

A colonoscopy is the most accurate diagnostic test to localise and biopsy lesions, detect synchronous neoplasms, and extract polyps. Synchronous colorectal cancers, defined as two or more distinct primary tumours diagnosed within 6 months, separated by normal bowel occurs in 3–5% of patients, raising the suspicion for Lynch syndrome or MUTYH-associated polyposis (table 2).[29–32] For complete staging, patients should undergo chest, abdomen, and pelvic CT before surgical resection or initiation of treatment.[33]

Serum markers are associated with colorectal cancer; however, diagnostic ability to detect primary colorectal

cancer is low.[34,35] A meta-analysis concluded that the pooled sensitivity of carcinoembryonic antigen was only 46% (95% CI 0·45–0·47).[36] False elevation in carcinoembryonic antigen could be attributed to any inflammatory state (gastritis, peptic ulcer, or diverticulitis), endocrinological disorders, and tobacco exposure.[37,38]

Pathogenesis

Prognostic classification beyond standard histology has been characterised by the creation of consensus molecular subtypes (CMSs). This international effort of transcriptome-wide analysis of primary tumours assessed the microenvironment, metabolic signatures, genomic, epigenomic, molecular aberrations, and other carcinogenesis pathways resulting in four molecular subtypes: CMS1, CMS2, CMS3, and CMS4 (figure 1). Previously published data suggested CMSs might be prognostic for OS in metastatic colorectal cancer tumours.[39–41] Initially it was suggested that CMS1 (microsatellite instability-immune) had the worst prognosis; however, these data were published before the approval for immune checkpoint inhibitors for dMMR or microsatellite instability-high (MSI-H) tumours.

An immune-based assay to assess the tumour microenvironment and immunoscore quantifies CD3 and CD8-positive T cells at the tumour centre and margin.[42] The greater the immunoscore, the lower the risk of recurrence. To date, the use of CMSs and immunoscore have not been widely adopted in the clinical setting. Pathogenic risk factors for recurrence or distant metastatic disease following surgical resection for locally advanced colon and rectal cancer include T4 tumours, N2 disease, suboptimal lymph node dissection (<12 lymph nodes), perineural or lymphovascular invasion, presence of tumour deposits or poorly differentiated histology or signet ring tumours, or a combination thereof.[43,44]

Early stage colon cancer

Approximately 37% of patients present with stage I–II disease (T1-4N0M0) and 36% of patients present with stage III disease (T1-4N1-2M0) as defined by the American Joint Committee on Cancer; there is an expected 5-year OS of 70% for patients with stage II disease and 45–65% for patients with stage III disease.[45,46] The pivotal phase 3 MOSAIC trial evaluated 6 months of adjuvant chemotherapy in patients with stage II and III colon cancer. The trial established a 3-year disease-free survival (DFS) benefit with oxaliplatin-based chemotherapy versus 5-fluorouracil–leucovorin in patients with stage III disease (72·2% *vs* 65·3%, respectively; hazard ratio [HR] 0·76, 95% CI 0·62–0·92), culminating in US Food and Drug Administration (FDA) approval.[47] In contrast, the role of adjuvant chemotherapy in all patients with stage II disease has remained controversial due to the lack of validated data. The MOSAIC investigators did not find adjuvant chemotherapy beneficial in all patients with stage II disease, but when substratified by high-risk features for recurrence, the investigators noted an improvement in 3-year DFS of 82·1% versus 74·9% (HR 0·74, 95% CI 0·52–1·06).[47] To date, consideration of adjuvant chemotherapy in patients with stage II disease remains a matter of discussion with the patient.[43]

The dose-limiting toxicity for oxaliplatin is cumulative peripheral neuropathy, which might be irreversible and commonly occurs at 4 months.[48,49] Exploratory studies have been unsuccessful in reducing peripheral neuropathy;[50–52] hence, consideration of reducing the duration of adjuvant chemotherapy from 6 months to 3 months was pursued.[48]

Although therapeutic options for adjuvant therapy remain unchanged, the duration of treatment has been refined. The International Duration Evaluation of Adjuvant Therapy (IDEA) was a pooled international collaboration (CALGB/SWOG 80702, IDEA France, SCOT, ACHIEVE, TOSCA, and HORG) to determine whether 3 months of oxaliplatin-based adjuvant therapy was non-inferior to 6 months in stage III colon cancer for the primary prespecified endpoint of 3-year DFS with a secondary endpoint of OS.[53] The upper limit of the two-sided 95% CI for non-inferiority 3-year DFS was 1·12; the non-inferiority upper limit for OS was HR 1·11; non-inferiority was declared if the one-sided false discovery rate adjusted (FDRadj) p value was less than 0·025. The

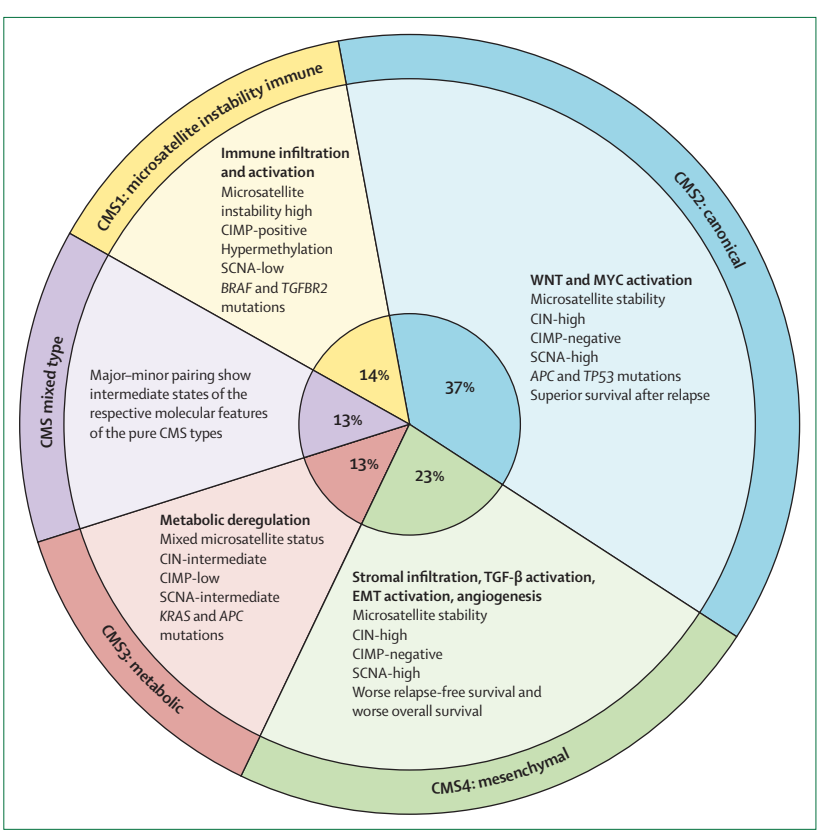

Figure 1: **CMS of colorectal cancer**
CIMP=CpG island methylator phenotype. CMS=consensus molecular subtypes. CIN=chromosomal instability.

	Phase	N	Recruiting	Eligibility criteria	Chemotherapy and radiation therapy regimen	Primary endpoints	Secondary endpoints
Approaches to organ preservation							
NCT02008656 (OPRA)	2	358	No	Stage II (T3–4, N0) or stage III (any T or ≥N)	Induction neoadjuvant chemotherapy group (group 1): chemotherapy before chemoradiation, eight cycles of FOLFOX or five cycles of capecitabine and oxaliplatin (CAPEOX) over ~15–16 weeks; after 2–4 weeks if stable or response then follow with chemoradiation with 5-FU or capecitabine; consolidation neoadjuvant chemotherapy group (group 2): 6 weeks of chemoradiation therapy with either 5-FU or capecitabine; after 2–4 weeks if stable or response then follow with eight cycles of FOLFOX or six cycles of CAPEOX	3-year DFS 76% for groups 1 and 2 (not significant; p=0·98)	LRFS 94% for groups 1 and 2 (not significant; p=0·78); DMFS 84% (group 1) and 82% (group 2), p=0·67; 3-year TME-free survival 41% (group 1) and 53% (group 2), p=0·01; sphincter preservation overall 60% (group 2) and 47% (group 1), p=0·02
NCT02505750 (OPERA)	3	141	No	cT2–cT3b, cN0, or cN1 <8 mm adenocarcinoma of the low to mid rectum; tumour <5 cm in diameter	All patients first received neoadjuvant chemoradiotherapy with EBRT 45 Gy in 25 fractions for 5 weeks with concurrent capecitabine	3-year organ preservation group A 59%	OS pending
NCT 02514278 (GRECCAR12)	3	Pending	No	cT2–3, N0–N1, M0 adenocarcinoma of the middle and lower rectum (<10 cm from anal verge); primary tumour <4 cm	Group 1: neoadjuvant FOLFIRINOX for four cycles (oxaliplatin intravenously, irinotecan intravenously, folinic acid intravenously, and 5-FU intravenously) followed by long-course chemoradiotherapy with 50 Gy in 25 fractions over 5 weeks, with capecitabine daily; group 2: long-course chemoradiotherapy with 50 Gy in 25 fractions over 5 weeks, with capecitabine daily; 8–-10 weeks post therapy, those who were considered to have good response (residual tumour ≤2 cm per pelvic MRI) underwent local excision; poor responders (residual tumour >2 cm) underwent TME with adjuvant capecitabine	1 year organ preservation; results pending*	Rate of cCR, rate of radiological response, rate of pCR, rate of R0 resection, 3-year LRRR, 3-year OS, 3-year DFS; results pending*
NCT04095299 (WW3)	3	Pending	Yes	cT1–3, M0 adenocarcinoma of the rectum, ≤4·5 cm, with lowest tumour edge located at or below the peritoneal reflection	Group A: long-course chemoradiotherapy with 50·4 Gy given over 28 fractions, with concomitant capecitabine twice per day; group B 62 Gy to the clinical tumour volume and 50·4 Gy to the elective volume, given over 28 fractions with concomitant capecitabine twice per day	2-year rectal preservation; results pending*	Rate of cCR at 4 months, RFS, OS, CFS; results pending*
NCT05646511 (ENSEMBLE)	3	608	Yes	T3–4 or ≥N	Group A: five fractions of 5 Gy then 12 weeks CAPOX then evaluate for NOM; group B: five fractions of 5 Gy then 12 weeks CAPOXIRI then evaluate for NOM	3-year rectal preservation	cCR pending, clinical response pending, NOM pending, LRR pending, OS pending, DMFS pending, TME-free survival pending, TME-free DFS pending
NCT04246684 (ACO/ ARO/AIO-18.1)	3	702	Yes	Must meet one of the following: any cT3 (if the distal extent of the tumour is <6 cm from the anocutaneous line) or cT3c or d in the middle third of the rectum (≥6–12 cm) with MRI evidence of extramural tumour spread into the mesorectal fat of more than 5 mm (>cT3b) or cT3 with clear ≥cN based on strict MRI criteria or cT4 tumours or any middle or low third of rectum with clear MRI criteria for ≥N	Group A (control): five fractions of 5 Gy followed by nine cycles of consolidation chemotherapy of mFOLFOX6 (or six cycles of CapeOx) followed by re-staging at week 22–24; groupB (experimental): fluoropyrimidin or oxaliplatin-based chemoradiotherapy (1·8–45 Gy to the primary tumour and pelvic lymph nodes; followed by sequential boost of 9 Gy to the gross tumour volume) followed by consolidation chemotherapy with six cycles of mFOLFOX6 (or four cycles of CAPOX) followed by re-staging at week 22–24; in both groups, for patients achieving a cCR, a watch and wait option with close follow-up is scheduled; in case of non-complete response, immediate TME surgery is performed	Organ preservation; defined as survival with sphincter intact, no major surgery, no stoma	DFS, rate of cCR after TNT, rate of immediate TME after TNT, cumulative incidence of locoregional regrowth after cCR, short and long-term toxicity, OS, and QoL

(Table 3 continues on next page)

	Phase	N	Recruiting	Eligibility criteria	Chemotherapy and radiation therapy regimen	Primary endpoints	Secondary endpoints
(Continued from previous page)							
NCT05610163 (JANUS)	2	312	Yes	≤12 cm from the anal verge: T4 N0 or any T, ≥N, or T3 N0 requiring abdominal perineal resection or coloanal anastomosis	Group 1: long-course chemoradiation therapy then either FOLFOX regimen (consisting of leucovorin intravenously, fluorouracil intravenously, and oxaliplatin intravenously) or CapeOx (consisting of capecitabine orally, and oxaliplatin intravenously); patients undergo CT scan, MRI, biospecimen collection and sigmoidoscopy throughout the trial and a biopsy during screening; group 2: long-course chemoradiation therapy then FOLFIRINOX regimen (consisting of leucovorin intravenously, fluorouracil intravenously, irinotecan intravenously, and oxaliplatin intravenously); patients undergo CT scan, MRI, biospecimen collection, and sigmoidoscopy throughout the trial and a biopsy during screening	cCR rates	DFS, organ preservation time, time to distant metastasis, OS, incidence of adverse events
Neoadjuvant approaches to rectal cancer							
NCT01804790 (PROIDGE/ Néofirinox)	3	461	No	Stages cT3 with risk of local recurrence or cT4, M0 and for which a multidisciplinary meeting recommend preoperative chemoradiotherapy	Group A (control) chemoradiotherapy 5 weeks (50 Gy, 2 Gy/session; 25 fractions) + capecitabine (800 mg/m² twice per day for 5 days in 7 days, excluding weekends), then 6–8 weeks after chemoradiation, surgery with TME, followed by adjuvant chemotherapy for 6 months, either mFolfox6* or capecitabine; group B (experimental): neoadjuvant mFolfirinox* for six cycles; followed by 5 weeks of chemoradiotherapy 50 Gy + capecitabine (800 mg/m² twice per day for 5 days in 7 days); surgery with TME 6–8 weeks after chemoradiation followed by 3 months of adjuvant chemotherapy (either mFolfox6 or capecitabine)	3-year DFS 76% (group B) and 69% (group A), p=0·034	3-year OS 91% (group B) and 88% (group A), p=0·0773; 3-year metastasis-free survival 79% (group B) and 72% (group A), p=0·17; local regional recurrence rate 4% (group B) and 6% (group A); 3-year cancer-specific survival rates: 92% (group B) and 89% (group A)
NCT01558921 (RAPIDO)	III	920	No	Locally advanced tumour fulfilling at least one of the following criteria on pelvic MRI indicating high risk of failing locally or systemically: T4a, cT4b, or N2; positive MRF; or enlarged lateral nodes (>1 cm)	Group A (control): standard long course chemoradiotherapy; arm B (experimental): short course five fractions of 5 Gy radiation scheme; followed by 6 cycles of combination chemotherapy CAPOX (or FOLFOX4) and surgery	3-year disease-related treatment failure: group A (30·4%) and group B (23·7%), p=0·019	OS group A (88·8%) and group B (89·1%), p=0·59; 3-year locoregional failure group A (6 %) and group B (8·3%), p=0·12; toxicity of grade 3 or worse occurred in 48% (group B) and 25% (group A) during preoperative treatment; 35% of all participants had toxicity in postoperative chemotherapy
NCT02533271 (STELLAR)	3	599	Yes	cT3–4 or regional LN, or both positivity without distant metastasis; primary tumour located in the distal or middle third of the rectum	Group 1: short-course radiation (5 Gy in five fractions over 1 week) followed by CapeOX for four cycles starting 7–14 days post radiation; TME was performed 6–8 weeks after preoperative treatment, followed by two cycles of CapeOX; group 2: chemotherapy and radiation therapy with 50 Gy in 25 fractions over 5 weeks, with concurrent capecitabine; TME was performed 6–8 weeks after preoperative treatment, followed by six cycles of CapeOx	3-year DFS: 64·5% (group 1) and 62·3% (group 2), p<0·002 for non-inferiority	3-year OS 86·5% (group 1) and 75·1% (group 2), p=0·033; 3-year DMFS 77·1% (group 1) and 75·3% (group 2)
NCT04928807 (UNION)	3	230	Yes	T3–4 or ≥N	Group A: five fractions of 5 Gy followed by camrelizumab and CAPOX twice (preoperatively), TME, followed by six cycles of adjuvant camrelizumab and CAPOX; group B: long-course concurrent chemoradiotherapy, followed by CAPOX for two cycles (preoperatively) followed by TME and then CAPOX for six cycles	pCR 39·8% *vs* 15·3%, p<0·001	3-year EFS pending, OS pending, R0 resection rate pending, 3-year DFS pending

(Table 3 continues on next page)

	Phase	N	Recruiting	Eligibility criteria	Chemotherapy and radiation therapy regimen	Primary endpoints	Secondary endpoints
(Continued from previous page)							
Omission of radiation							
NCT01515787 (PROSPECT)	3	1194	No	Stage II or III T2 N1, T3 N0, or T3 N1	Group A: FOLFOX chemotherapy for six cycles then MRI scan or endorectal ultrasound to examine the tumour; if the tumour has not decreased by ≥20%, the patient will have chemotherapy and radiation therapy; if the tumour has decreased in size by ≥ 20%, then the patient will proceed directly to surgery; if R0, then FOLFOX for six cycles postoperatively; if R1, then the patient proceeds to adjuvant chemoXRT; arm B: standard chemoradiotherapy followed by TME and adjuvant FOLFOX for eight cycles	Pelvic R0 resection rate: arm A (99%) *vs* arm B (97%); DFS: arm A (80·8%) *vs* arm B (78·6%), HR 0·92 (95% CI 0·74–1·14)	Path CR: arm A (24%) *vs* arm B (22%); OS: arm A (89·5%) *vs* group B (90·2%), HR 1·04 (95% CI 0·74–1·44)

5-FU=5-fluorouracil. cCR=clinical complete response. CFS=cancer-free survival. CR=complete response. DFS=disease-free survival. DMFS=distant metastasis-free survival. EBRT=external beam radiation therapy. EFS=event-free survival. LN=lymph node. LRFS=local recurrence-free survival. LRRR=locoregional recurrence rate. NOM=non-operative management. OS=overall survival. pCR=pathologicAL complete response. QoL=quality of life. RFS=relapse-free survival. TME=tumour microenvironment. TNT=total neoadjuvant therapy. *mFolfirinox=oxaliplatin (85 mg/m^2 in 2 h at day 1), irinotecan (180 mg/m^2 in 90 min at D1), folinic acid (400 mg/m^2 simultaneously in 2 h at day 1). During the irinotecan infusion add 5-FU continuous infusion for 48 h (1200 mg/m^2 at day 1 and day 2), every 14 days for four cycles.

Table 3: **Rectal total neoadjuvant chemotherapy trials**

primary endpoint of DFS (HR 1·07, 95% CI 1·00–1·15) for the full analysis was not met. Non-inferiority for 3 months of capecitabine–oxaliplatin (CAPOX; HR 0·95, 0·85–1·06) was met but not for FOLFOX (HR 1·16, 1·06–1·26). In an exploratory analysis when tumours were stratified as low risk (T1-3N1M0) versus high risk (T4 or N2, or both), 3 months was non-inferior to 6 months for the low-risk tumours, with a 3-year DFS of 83·1% and 83·3%, respectively (HR 1·01, 0·90–1·12). For high-risk tumours, the 3-year DFS rate for 6 months of therapy was superior regardless of treatment (64·4% *vs* 62·7%, respectively; HR 1·12, 1·03–1·23). A reduction in treatment-related toxicities of grade 2 or more was noted for 3 months (16·6% with FOLFOX and 14·2% with CAPOX) versus 6 months (47·7% with FOLFOX and 44·9% with CAPOX) of adjuvant therapy.

After a median follow-up of 72·3 months, the secondary endpoint of OS for non-inferiority was not met (5-year OS was 82·4% [95% CI 81·4–83·3] *vs* 82·8% [81·8–83·8] for 3 months and 6 months, respectively; HR 1·02 [0·95–1·11]; non-inferiority FDRadj p=0·058), with an absolute difference in OS of only 0·4%.[54] For patients treated with CAPOX, 5-year OS was 82·1% (95% CI 80·5–83·6) versus 81·2% (95% CI 79·2–82·9; HR 0·96, 95% CI 0·85–1·08) for 3 months and 6 months, respectively; non-inferiority FDRadj p=0·033), with an absolute difference in OS of 0·9%. However, in patients treated with FOLFOX, 5-year OS was 82·6% (95% CI 81·3–83·8) versus 83·8% (82·6–85·0; HR 1·07, 0·97–1·18; non-inferiority FDRadj p=0·34), with an absolute difference in OS of –1·6%. Based on these findings, 3 months of CAPOX is reasonable. However, if FOLFOX is the preferred regimen, a 6 month duration is recommended. When making these decisions, the patients' existing comorbidities must also be considered. Despite not meeting the primary endpoint for full analysis, providers in the USA have widely adopted the 3 months of CAPOX regimen.[55]

A novel approach is the consideration of neoadjuvant chemotherapy before colon resection.[56] The phase 3 FOxTROT trial randomly assigned patients with T3-4, N0-2, M0 colon cancer to 6 weeks of modified FOLFOX preoperatively plus adjuvant chemotherapy versus adjuvant chemotherapy alone (2:1).[57] The objective was to determine a 25% proportional reduction in 2-year recurrence with neoadjuvant chemotherapy with 80% power at p less than 0·05. The investigators noted an improvement of reduced residual disease or recurrence within 2 years of 16·9% (neoadjuvant chemotherapy) versus 21·5% (adjuvant chemotherapy; HR 0·72, 95% CI 0·54–0·98; p=0·037), corresponding to a 28% lower recurrence rate with neoadjuvant chemotherapy. In contrast, the phase 3 OPTICAL trial provided 3 months of neoadjuvant oxaliplatin chemotherapy versus standard adjuvant chemotherapy and noted no statistical difference in 3-year DFS.[58] At this time neoadjuvant systemic therapy is exploratory.

Early stage rectal cancer

Management of non-metastatic rectal cancer has become increasingly complex over the last decade. Because rectal cancers are below the peritoneal reflection, dedicated pelvic MRI is crucial to delineate the tumour, mesorectal fascia, and the circumferential resection margin.[59,60] Surgical approach to total mesorectal excision (TME) has been explored extensively. Laparoscopic surgery has been found to be equivocal to open surgery for locoregional recurrence, DFS, and OS.[61,62] The use of robotic surgery when compared with open laparotomy does not significantly reduce the risk of conversion to open laparotomy.

Historically, neoadjuvant chemoradiation therapy has been a standard of care, but can cause chronic bowel and bladder toxicity, as well as sexual dysfunction. Therefore, selection of treatment strategies is influenced by oncological and functional outcomes, location of the tumour, sphincter preservation, and the possibility of deferring surgery. Following standardised implementation of TME, the risk of locoregional recurrence is less of a concern with negative margins (R0).[63,64] Thus, patients with a threatened circumferential resection margin on preoperative MRI are optimal candidates for neoadjuvant chemoradiation treatment.[65] Historically, adjuvant chemotherapy is offered following TME but with modest compliance rates.[66] Thus, new strategies incorporating neoadjuvant systemic chemotherapy to increase compliance, reduce toxicity, and improve distant metastases-free survival are being explored.[67–69] Such modifications include induction chemoradiation therapy (before chemotherapy) or consolidative chemotherapy (following chemoradiation), before consideration of TME.[70] Collectively named total neoadjuvant therapy, this is an accepted new standard of care. Multiple studies using short-course or long-course radiation have shown the benefits of local disease control, including complete resolution of the primary tumour (complete pathological response), with sphincter preservation and possibly deferring TME (table 3).[33,71,72]

Additional risk factors include extramural venous invasion, tumour deposits, extensive nodal metastases (cN2), and advanced T stage (T3 or T4). Although there might be subtle differences in the various approaches or the sequence of therapy (table 3), one notable difference is that induction chemoradiation therapy (before chemotherapy) might achieve sphincter preservation for clinical or near complete response but must be followed using a stringent programme of clinical, endoscopic, and radiological surveillance.[73–77] In the USA, JANUS is a phase 2/3 randomised trial investigating the role of dose intensification with an investigational group of fluoropyrimidine plus oxaliplatin plus irinotecan (FOLFOXIRI). An ongoing German phase 3 trial (NCT04246684) is exploring the role of organ preservation as a primary endpoint when providing induction short-course versus long-course radiation followed by consolidative chemotherapy.

Early stage (T1–2, N0) rectal cancers are a distinct entity, where TME alone could result in excellent outcomes. However, there is now an interest in total neoadjuvant therapy and sphincter preservation with or without local excision, with additional studies in development.[74,78–80] In contrast, the phase 3 PROSPECT trial (NCT01515787) determined non-inferiority of DFS for the omission of radiation therapy when patients have had adequate tumour response (defined as >20% clinically) following 3 months of neoadjuvant oxaliplatin-based chemotherapy in mid to high lying tumours.[81] Lastly, exploration of the use of immune checkpoint inhibition in dMMR or MSI-H rectal cancer (<5%) has been pursued. Promising early single-institution data suggest 6 months of single-agent PD1 blockade (NCT05723562) in dMMR or MSI-H tumours might result in high clinical complete response with sphincter preservation and is being validated in a multicentre phase 2 trial (NCT05723562).[82] EA2201 (NCT04751370) is an ongoing multicentre phase 2 trial exploring the role of combination immunotherapy (nivolumab plus ipilumumab).

Metastatic colorectal cancer

General principles

The life expectancy of patients with metastatic colorectal cancer (mCRC) has increased in the last decade, with a median OS of 32–40 months, attributable to effective systemic therapy, treatment selection, locoregional treatment options, and novel approaches due to clinical trial developments.[83–86] For patients with surgically unresectable mCRC, the expected 5-year OS is 15·6%.[46] The increased adoption of parenchyma-sparing liver surgery enables repeated surgical intervention.[87] With optimal integration of systemic and locoregional approaches, cure is feasible in a small percentage of patients with mCRC.[88] The expected 5-year OS for a patient with resected liver metastases is 35–65%.[89,90] Local ablative techniques (eg, thermal ablation or stereotactic body radiotherapy) can also be considered and could contribute to DFS and potentially OS.[91–94] Therefore, multidisciplinary management is imperative to individualise therapeutic strategies for optimal outcomes, with repeat diagnostic imaging at 2-month and 3-month intervals to determine degree of response.[90]

For initially unresectable metastases, resection of the primary tumour has not been proven to improve the 5-year OS in an asymptomatic patient.[95–97] In the phase 3 SYNCHRONOUS trial, patients were randomly assigned to systemic chemotherapy or surgical resection of the primary tumour. No improvement in OS (18·6 months *vs* 16·7 months; not siginificant) following surgical resection of the primary tumour was achieved and this is not recommended unless clinically indicated;[95] 24·1% of patients randomly assigned to the surgical group never received systemic chemotherapy.

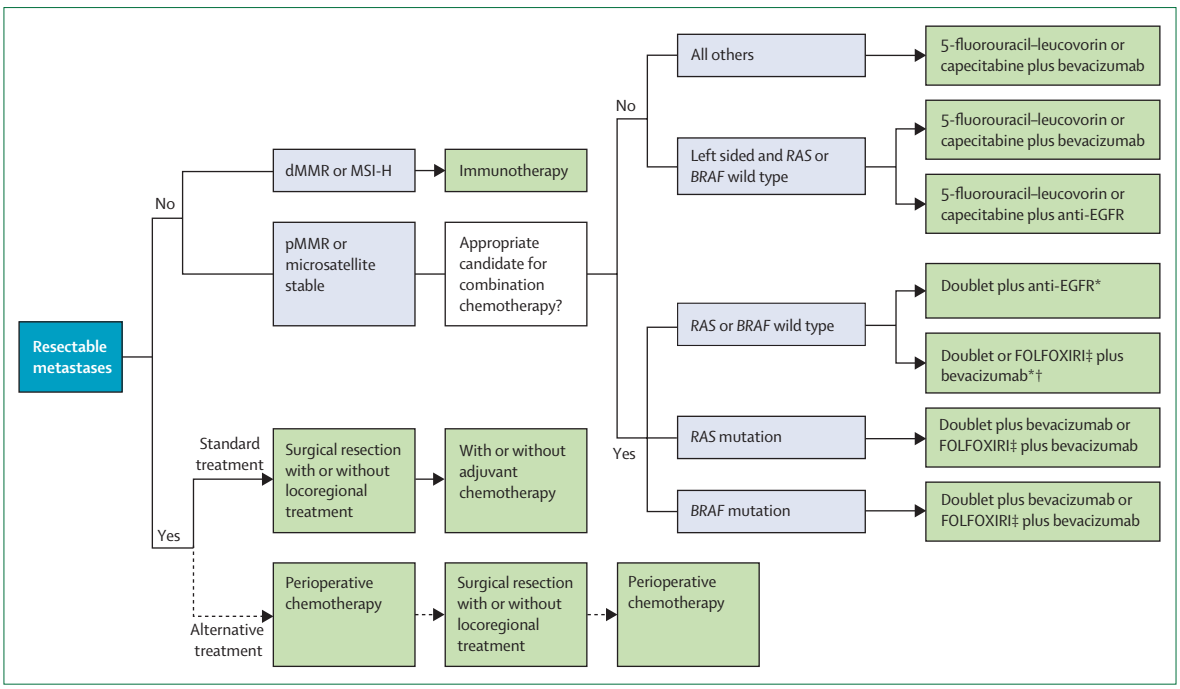

Figure 2: **Multidisciplinary tumour board encourages therapeutic algorithm for first-line treatment in mCRC**
Blue box indicates the starting point for treatment. Lavender boxes indicate molecular alteration. Green boxes indicate treatment options. A clinical trial should always be considered if available. EGFR=epidermal growth factor receptor. dMMR=deficient mismatch repair. mCRC=metastatic colorectal cancer. MSI-H=microsatellite instability high. pMMR=proficient mismatch repair. *Mainly if left-sided tumours. †Mainly if right-sided tumours. ‡Only if younger than 75 years (age 71–75 years with Eastern Cooperative Oncology Group performance status 0).

First-line therapy for metastatic colorectal cancer

Determining the first-line systemic therapy used in initially unresectable mCRC is based on molecular and clinical drivers commonly determined by next generation sequencing. Approximately 5% of all patients have dMMR or MSI-H tumours and can achieve a clinically relevant benefit from the use of immune checkpoint inhibitors.[98] The randomised KEYNOTE-177 trial established the anti-PD-1, pembrolizumab as a new standard of care versus standard chemotherapy in treatment-naive patients.[99] Additional promising data were noted for the combination of the anti-CTLA4, ipilimumab, and the anti-PD-1, nivolumab, in the single arm phase 2 Checkmate-142 study.[100] The magnitude of the benefit with the addition of an anti-CTLA4 remains under investigation.[101]

In unresectable proficient mismatch repair (pMMR) or microsatellite-stable mCRC, morbidity, molecular mutation status, and primary tumour location are major drivers for treatment choice (figure 2). Comorbidity, age, and Eastern Cooperative Oncology Group performance status influence the intensity of the chemotherapy backbone, ranging from monotherapy with fluoropyrimidines to the addition of oxaliplatin-based (FOLFOX or CAPOX) or irinotecan-based (FOLFIRI) doublets versus the triple combination of 5-fluoruracil, oxaliplatin and irinotecan (FOLFOXIRI).[102,103] S1 (tegafur/gimeracil–oteracil) is an oral fluoropyrimidine used in Asia yet received European Medicines Agency approval as monotherapy or in combination for patients intolerant of 5-fluoropyrimidine.[103]

RAS mutations are well established predictors of resistance to anti-epidermal growth factor receptor (EGFR) agents (cetuximab and panitumumab) providing minimal benefit in $BRAF^{V600E}$ mutated tumours.[104–106] In addition, *HER2* (also known as *ERBB2*)-amplified tumours are also resistant to anti-EGFR therapy.[107] Right-sided pMMR or microsatellite-stable colon tumours have a reduced OS as well as intrinsic resistance to anti-EGFR agents even if *RAS* and *BRAF* are wild-type.[108] The phase 3 PARADIGM study prospectively showed prolonged OS in combination with FOLFOX–panitumumab versus FOLFOX–bevacizumab alone in left-sided *RAS* wild-type mCRC and is a preferred regimen.[86,109]

In patients fit for intensified chemotherapy, FOLFOXIRI with bevacizumab provides substantial benefit over doublets or bevacizumab in terms of OS, progression-free survival (PFS), overall response rate, and resection rate.[110] However, the TRIPLETE study showed no benefit from a modified schedule of FOLFOXIRI plus panitumumab versus FOLFOX–panitumumab in an *RAS* and *BRAF* wild-type primarily left-sided treatment-naive cohort.[111]

For patients with surgically unresectable pMMR or microsatellite-stable tumours, first-line combinations are generally administered for up to 4–6 months, followed by maintenance chemotherapy with a fluoropyrimidine and the same targeted agent until disease progression or

intolerance to provide a continuum of care to improve OS.[102] Although age is not an absolute contraindication to any treatment, a complete geriatric assessment is recommended to assess treatment tolerance and compliance in all patients.[112]

Peritoneal disease

Development of peritoneal metastases might occur in up to 17% of colorectal cancers with isolated peritoneal disease in up to 2% of patients.[113] These tumours commonly have multiple poor prognostic features: right-sided colonic origin; *BRAF*^{V600E} mutation tumour type; and poorly differentiated histology with mucinous or signet ring features.[114] Additional challenges exist due to the reduced sensitivity of diagnostic imaging in assessing the degree of tumour burden.[115] A meta-analysis of 14 randomised phase 3 trials noted that patients with isolated and non-isolated peritoneal disease fared worse for OS than patients with non-peritoneal metastases.[116] Three recent phase 3 trials evaluated the role of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC): PRODIGE-7 was specifically in mCRC with peritoneal disease and COLOPEC and PROPHYLOCHIP-PRODIGE-15 were conducted in high-risk recurrent patients.[117–119] PRODIGE-7 suggested there might be a potential role for cytoreductive surgery but no role for HIPEC in patients with stage IV disease. Unfortunately, COLOPEC and PROPHYLOCHIP did not show any benefit for HIPEC in patients with high-risk stage III disease. Current treatment recommendations are systemic chemotherapy with shared decision making involving multidisciplinary management and the consideration of cytoreductive surgery in select cases; the role of HIPEC remains investigational.[102,113,120]

Progression or intolerance after first-line therapy

Following first-line chemotherapy, if there is evidence of progression or intolerance of therapy, normal laboratory values, and adequate Eastern Cooperative Oncology Group performance status, consideration of second-line therapy is initiated. Commonly, the alternate regimen is then provided (oxaliplatin-based therapy will transition to irinotecan-based therapy and vice versa). The choice of the treatment is mainly driven by the patients' comorbidities, previous treatment outcome and tolerance, and *RAS* mutational status. As a general principle, switching to the alternate doublet chemotherapy is common, but the reintroduction of the same chemotherapy backbone is reasonable if there is previous prolonged PFS or chemotherapy-free interval.[121] Continuation of anti-vascular growth factor agents (bevacizumab, aflibercept, and ramucirumab) is associated with improved OS,[122–124] whereas the continuation of anti-EGFR agents did not improve OS.[125]

Advanced lines of treatment: precision oncology

mCRC is now fragmented in several molecular entities with potentially actionable targeted options varying based on local regulatory approvals (figure 3).[126–128] For *NTRK* rearranged tumours (<0·5%), larotrectinib and entrectinib received agnostic approval both in Europe, Japan, and the USA.[129,130] Patients with *BRAF*^{V600E} mutated tumours (<10%) are recommended to receive the *BRAF*^{V600E} inhibitor encorafenib with cetuximab after receiving at least one line of therapy, showing improved OS over conventional treatment.[131] Several phase 2 trials have investigated anti-*HER2* strategies (trastuzumab plus lapatinib, pertuzumab, or tucatinib, trastuzumab–deruxtecan) in previously treated mCRC *HER2*-positive (3–5%) tumours.[132–134] The MOUNTAINEER trial evaluated the combination of tucatinib and trastuzumab in *HER2*-positive refractory mCRC with a response rate of 38·1% (95% CI 27·7–49·3), progression-free survival of 8·2 months, and overall surival of 24·1 months.[134] The benefit of therapy was in the *HER2* equivocal

A

	Matched treatment	ESCAT score[126–128]	OncoKb level
RAS mutation	..	..	..
KRAS Gly12Cys mutation	Adagrasib or sotorasib with or without cetuximab	..	3A
BRAF^{V600E} (ie, Val600Glu) mutation	Encorafenib plus cetuximab	I-A	1
dMMR or microsatellite instability high	Pembrolizumab or dostarlimab (dMMR)	I-A	1
dMMR or microsatellite instability high	Nivolumab plus ipilimumab	I-A	1
BRAF$^{non\text{-}V600E}$ mutation	BRAF blockade (eg, PLX8394)	..	4
MET amplification or fusion	MET blockade	IIIA*	4†
HER2 or *ERBB2* amplification	HER2 blockade‡	II-B	2
NTRK gene fusion	Entrectinib	I-C	1
NTRK gene fusion	Larotrectinib	I-C	1
ATM mutation	Olaparib	IIIA	..
PIK3CA mutation	Alpelisib	IIIA	4
POLE mutation	Anti-PD1 or anti-PD-L1	IIIA	..
RET or ALK fusions	Selpercatinib§	IIIA	1
RET or ALK fusions	ALK blockade¶	IIIA	..
No genomic alterations	..	..	..

B

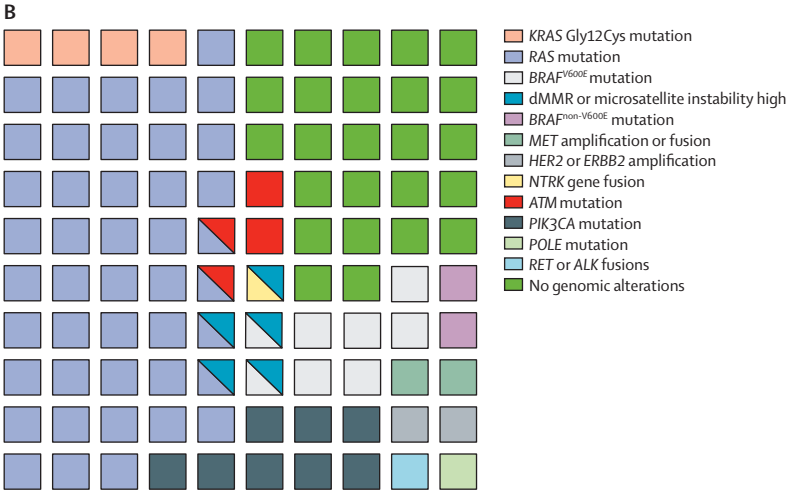

***Figure 3*: Clinical actionability (A) and distribution (B) of genomic alterations in mCRC**
Boxes represent prevalence in 100 patients. For example, RAS mutation makes up approximately 43% of mutations, of which 4% are KRAS Gly12Cys mutation. dMMR=deficient mismatch repair. ESCAT=ESMO Scale of Clinical Actionability for molecular Targets. *Savolitinib for MET amplification. †Crizotinib for *MET* fusions. ‡Trastuzumab plus lapatinib, trastuzumab plus pertuzumab, trastuzumab–deruxtecan, or trastuzumab plus tucatinib. §Selpercatinib for *RET* fusions. ¶ALK inhibitors for ALK fusions.

immunohistochemical or fluorescence in situ hybridisation or *HER2*-positive immunohistochemical tumour types. Tucatinib is the first FDA-approved drug anti-*HER2* regimen in refractory mCRC. The MOUNTAINEER-3 trial (NCT05253651) is an ongoing frontline trial of FOLFOX with or without tucatinib plus trastuzumab. The *KRAS* Gly12Cys mutation is rare (5%) with promising data when combined with anti-EGFR therapy.[135] Codebreak 300 (NCT05198934) randomly assigned mCRC patients to two different doses of sotorasib plus panitumumab or the treating physician's choice of trifluridine–tipiracil or regorafenib.[136] The investigators fulfilled their primary endpoint of PFS of 5·6 months (960 mg; 95% CI 4·2–6·3) and 3·9 months (240 mg; 3·7–5·8) versus the control group of 2·2 months. The phase 3 trial KRYSTAL-10 (NCT04793958) is ongoing, which is evaluating the combination of the *KRAS* Gly12Cys inhibitor, MRTX849, and cetuximab with co-primary endpoints of OS and PFS.

For chemorefractory patients not bearing any targetable molecular alteration, trifluridine–tipiracil, fruquintinib, and regorafenib have been shown to improve OS.[137–144] In combination, trifluridine–tipiracil and bevacizumab has been determined to be superior for OS versus trifluridine–tipiracil alone, resulting in its new FDA and European Medicines Agency indication.[140] The highly selective oral VEGFR-1, VEGFR-2, and VEGFR-3 inhibitor, fruquintinib, showed OS benefit over placebo in two phase 3 randomised trials (FRESCO and FRESCO2).[143,144] FRESCO2 fulfilled the primary endpoint of OS independent of previous exposure to regorafenib or trifluridine–tipiracil, or both (HR 0·662, 95% CI 0·549–0·800), as well as the secondary endpoint of PFS (HR 0·321, 95% CI 0·267–0·386).[144] Fruquintinib subsequently received FDA approval. Pembrolizumab is agnostically approved in the USA and Japan for patients with tumours, with tumour mutational burden of more than ten mutations per DNA megabase, although the benefit is limited in microsatellite-stable and tumour mutational burden-high mCRC.[145]

Surveillance

Patients with localised colorectal cancer, following curative surgery and adjuvant chemotherapy, are under close surveillance for 5 years since it is expected that 30–50% of patients will relapse, most occurring within this timeframe.[146] It should be noted surveillance guidelines might vary by medical society, region, or country. Below is a general overview of the National Comprehensive Cancer Network, the European Society for Medical Oncology, and pan-Asian guidelines with some slight variability.[147–149]

For patients with stage I disease, a colonoscopy is recommended at years 1, 3, and 5 after surgery. For patients with stage II or III disease, clinical assessment and review of blood *carcinoembryonic antigen* levels are recommended at baseline and every 3–6 months for 2–3 years, then biannually until 5 years. Colonoscopy is recommended at 1 year, then every 3–5 years after surgery. Chest-abdominal and pelvic CT scans is recommended every 6–12 months for 5 years. Monitoring with PET-CT is not recommended.[33,148] For patients with stage IV disease who have undergone metastatic resection, close surveillance is recommended with sequential diagnostic imaging due to the high risk of recurrence.

Outstanding research questions

Role for circulating tumour DNA

The value of diagnostic circulating tumour DNA (ctDNA) analysis remains uncertain. Technologies such as plasma-based assays of ctDNA are being developed with the goal of detecting multiple types of cancers. However, these tests are pending validation and are not currently recommended for cancer screening.[150] The potential role of ctDNA for minimal residual disease was originally noted following surgical resection in patients with stage II colon cancer and correlated with minimal residual disease and likelihood of recurrent disease.[151] The Australian phase 3 DYNAMIC trial indicated that a postoperative ctDNA-guided approach to stage II colon cancer reduced the use of adjuvant chemotherapy without compromising recurrence-free survival.[152] Ongoing prospective phase 3 clinical trials are underway internationally, including CIRCULATE-US (NCT05174169), CIRCULATE-Japan (consisting of three clinical trails: GALAXY, ALTER, and VEGA), and DYNAMIC III (ACTRN12617001566325). These trials aim to clarify clinical outcomes by reducing or intensifying therapy on the basis of minimal residual disease.[153,154]

To monitor the emergence of acquired mutations, randomised interventional studies are required to assess whether dynamic changes in treatment based on ctDNA assessment can improve outcomes to a change in the subsequent therapy or the intensification of therapy.[155]

Screening asymptomatic populations

Studies show high specificity and encouraging sensitivity findings with error-corrected sequencing, which might be combined with protein biomarkers, genome-wide fragmentation patterns, and methylation-based ctDNA assays.[156–159] Large studies are ongoing, with results pending.

Other points of discussion

EGFR rechallenge

Rechallenging with anti-EGFR monoclonal antibodies has shown promising initial outcomes in patients with wild-type *RAS* in small non-randomised studies.[160–162] However, secondary resistant genomic alterations such as *EGFR* extracellular domain, *BRAF* gene, and amplification of *ERBB2, RAS,* or *MET* are also associated with efficacy outcomes; therefore, refinement of eligible patients who are more likely to benefit from EGFR rechallenge using multiple genotypes is required.[163,164] Further investigation is warranted to determine the optimal timing of molecular testing by

ctDNA assays in this patient population. Several studies are ongoing.[165,166]

Microbiome

Abundant evidence links the gut microbiome to colorectal cancer development.[167] Gut microbes interact with the host immune system and influence anti-tumour immune responses. Patients with colorectal cancer have reduced bacterial diversity compared with healthy individuals, and studies indicate that Firmicutes, Bacteroidetes, enterotoxigenic *Bacteroides fragilis*, and the oral anaerobe *Fusobacterium nucleatum* are enriched in colorectal cancer.[168,169] However, there is no clear understanding regarding the function of each bacterial strain, its mechanism of action in anti-tumour immunity, and the therapeutic effect on cancer treatment. Encouraging data have been reported on the role of faecal microbiome transplant (FMT) in patients with melanoma for overcoming drug resistance.[170] However, a broader role for FMT is unknown. FMT is being explored in patients with MSI-H or dMMR mCRC initially resistant to anti-PD-1 therapy (NCT04729322).

EOCRC

Although it is presumed patients with EOCRC are more likely to have a hereditary syndrome, the majority of EOCRC are sporadic with no obvious cause. Approximately 30% are related to family history but the exact cause of EOCRC is unknown.[171–175] Earlier analyses show EOCRC is characterised by different clinicopathological features compared with average-onset CRC, but others note no difference in molecular alterations;[176–178] microbiome work is ongoing.[179] The prognosis of EOCRC is controversial; some studies suggest favourable OS, whereas others suggest reduced OS.[180]

Artificial intelligence

There is burgeoning interest in the use of artificial intelligence (AI) and its effect on cancer care. Computational data integration and synthesis might predict the response to systemic therapy and patient prognosis.[181,182] AI might also be used at the molecular level, for example in genomics, proteomics, metabolomics, and transcriptomics. AI is currently being used for colorectal cancer screening and to improve detection of adenomas.[183] Caution is still warranted since data consistency and interpretation continues to be refined.[184] There are approximately 50 FDA-approved AI-associated or AI-associable equipped medical devices for clinical oncology.[185]

Controversies and uncertainties: addressing liver metastasis

EORTC 40983 was a phase 3 randomised trial in resectable colorectal liver metastases designed to evaluate the role of perioperative FOLFOX4 for six cycles before surgery followed by adjuvant therapy versus surgery alone.[186] The investigators reported improved DFS, but no statistical benefit in OS.[187] Similarly, JCOG0603 was a randomised phase 2/3 trial that allowed unlimited hepatic metastases and noted improved DFS with adjuvant mFOLFOX6 following hepatic resection versus hepatic resection alone, but no difference in OS.[188] Therefore, the role of neoadjuvant and adjuvant chemotherapy following liver resection remains a matter of discussion between the provider and patient. Resurgence for the role of hepatic arterial infusion for colorectal cancer liver metastases has been generated. Earlier data were criticised for largely being retrospective. The role of hepatic arterial infusion is currently being investigated in newly diagnosed patients (PUMP; EA2222; NCT05863195). ERASur is a phase 3 trial evaluating the role of systemic chemotherapy with and without stereotactic radiation therapy, ablation, and surgery for the primary endpoint of OS rate (NCT05673148). Similarly, a concept of neoadjuvant systemic therapy followed by repeat local liver directed therapy is being investigated for OS versus upfront liver directed therapy (Collision Relapse; NCT05861505).

Liver transplantation is an aggressive treatment for patients with colorectal cancer with liver metastases. Three decades ago, the European Liver Transplant Registry reported a summary that showed 1-year and 5-year OS rates of 62% and 18%, respectively. Systemic therapy for mCRC was not adequately effective during this period, making liver transplantation unfeasible. Over the past two decades, the efficacy of systemic therapy for mCRC has substantially improved, and the outcomes of liver transplantation for colorectal cancer with liver metastases have also increased. The NORDIC group conducted a single-arm prospective clinical trial with revised selection criteria. They reported that the 2-year DFS was 44% in the SECA II study.[189,190] These results indicate that liver transplantation could have a promising role, although additional validation is warranted. Several randomised trials (NCT01479608, NCT0259734, and NCT03494946) are ongoing. These trials are trying to determine whether there is any benefit to having liver transplantation for OS. Large-scale prospective randomised controlled trials with long-term follow-up is necessary to elucidate the effectiveness of such an approach for OS.

Conclusion

Colorectal cancer remains a common malignancy globally. Prevention through screening techniques is crucial to reducing its incidence, especially in developing countries, where the highest incidence rates are expected to occur. Colorectal cancer screening techniques are further complicated by a lack of uniform international guidelines. Colorectal cancer screening reduces associated morbidity and would decrease mortality if a sufficient fraction of individuals were screened appropriately. Of the growing concern is the unknown cause of EOCRC due to the rising incidence in young patients.

The field of colorectal cancer is evolving, and not just in novel therapeutic agent development. Unique tumour characteristics must be considered in the treatment of mCRC: molecular alterations, presence or absence of microsatellite instability, anatomic primary tumour sidedness, previous therapy, or extent of tumour involvement to guide treatment decisions. In rectal cancer, sequence of therapy and consideration of organ preservation is paramount. On an exploratory level, ctDNA is currently being evaluated as a diagnostic tool in early and advanced colorectal cancer to monitor for minimal residual disease, risk of recurrence, drug resistance, as well as dynamic changes to determine intensification of therapy. If validated and adopted into standard practice, ctDNA will impact existing surveillance guidelines.

Contributors

CE: conceptualisation; writing, original draft; validation; and writing, review, and editing. TY: writing, original draft. ER-G: writing, original draft. NM: writing, original draft. CGC: writing, revised draft. BO'B: writing, review, and editing; all figures; and administrative. AB: writing, review, and editing. ROP: writing, original draft. CC: writing, original draft; and conceptualisation of figures 2 and 3.

Declaration of interests

We declare no competing interests.

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