Colorectal cancer

Ernst J. Kuipers[1], William M. Grady[2,3], David Lieberman[4], Thomas Seufferlein[5], Joseph J. Sung[6], Petra G. Boelens[7], Cornelis J. H. van de Velde[7] and Toshiaki Watanabe[8]

Abstract | Colorectal cancer had a low incidence several decades ago. However, it has become a predominant cancer and now accounts for approximately 10% of cancer-related mortality in western countries. The 'rise' of colorectal cancer in developed countries can be attributed to the increasingly ageing population, unfavourable modern dietary habits and an increase in risk factors, such as smoking, low physical exercise and obesity. New treatments for primary and metastatic colorectal cancer have emerged, providing additional options for patients; these treatments include laparoscopic surgery for primary disease, more-aggressive resection of metastatic disease (such as liver and pulmonary metastases), radiotherapy for rectal cancer, and neoadjuvant and palliative chemotherapies. However, these new treatment options have had limited impact on cure rates and long-term survival. For these reasons, and the recognition that colorectal cancer is long preceded by a polypoid precursor, screening programmes have gained momentum. This Primer provides an overview of the current state of the art of knowledge on the epidemiology and mechanisms of colorectal cancer, as well as on diagnosis and treatment.

We live in an era with improved worldwide average living standards and increased access to adequate health care that has considerably improved the diagnosis and treatment of diseases. These measures have had an effect on the average life expectancy in most regions of the world. However, although death rates from communicable diseases have improved globally as a result of these medical improvements, cancer-related mortality has increased by almost 40% over the past 40 years. A further 60% increase is expected in the next 15 years, with 13 million people estimated to die of cancer in 2030 (REF. 1). The main causes of cancer-related mortality have also changed, attributable to alterations in disease incidence, the introduction of screening programmes and therapeutic improvements. Colorectal cancer was rather rare in 1950, but has become a predominant cancer in western countries, now accounting for approximately 10% of cancer-related mortality. Reasons explaining this increased incidence include an ageing population and the preponderance of poor dietary habits, smoking, low physical activity and obesity in western countries. The change in incidence is not only apparent in the rates of sporadic disease but also in some familial cancer syndromes. Indeed, given that the rates of *Helicobacter pylori* infection (a causative factor of gastric cancer) have fallen dramatically, colorectal cancer is now the predominant presentation of Lynch syndrome (a hereditary non-polyposis type of colorectal cancer), whereas carriers of this syndrome used to be predominantly affected by gastric cancer[2–4].

New treatments for primary and metastatic colorectal cancer have been developed and include: laparoscopic surgery for primary disease; resection of metastatic disease affecting, for example, the liver and lungs; radiotherapy for rectal cancer and some forms of metastatic disease; and neoadjuvant and palliative chemotherapy[5–7]. Despite advances in surgical and medical therapies, cure rates and long-term survival have changed little in the past several decades. Against this background, and given that colorectal cancer is preceded by a polypoid precursor (FIG. 1), screening programmes for early detection have gained momentum.

Indeed, screening is expected to have a substantial impact on colorectal cancer incidence and mortality in the next 15 years, an affect that is unlikely to come from lifestyle interventions or from new therapeutics. Screening will only make these improvements with high uptake; accordingly, major improvements in non-invasive screening (for example, faecal immunochemical testing and faecal DNA testing) are being investigated as alternatives to the current gold-standard, but invasive, screening methodology — colonoscopy. Alongside these advances, the quality of screening colonoscopy has undergone substantial improvement in terms of technical changes and training, and quality assurance[8,9].

In this Primer, we provide an overview of the current knowledge on the epidemiology and mechanisms underlying colorectal cancer, as well as on diagnosis and treatment, including surgical and medical approaches.

Epidemiology

Colorectal cancer is the second-most and third-most common cancer in women and men, respectively. In 2012, 614,000 women (9.2% of all new cancer cases) and 746,000 men (10% of new cancer cases) were diagnosed

Correspondence to E.J.K.
e-mail: e.j.kuipers@erasmusmc.nl
Erasmus MC University Medical Center, s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands.

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Author addresses

[1]Erasmus MC University Medical Center, s-Gravendijkwal 230, 3015 CE Rotterdam, The Netherlands.
[2]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA.
[3]Department of Medicine, University of Washington School of Medicine, Seattle, Washington, USA.
[4]Division of Gastroenterology and Hepatology, Oregon Health and Science University, Portland, Oregon, USA.
[5]Department of Internal Medicine I, University of Ulm, Ulm, Germany.
[6]Department of Medicine and Therapeutics, Chinese University of Hong Kong, Hong Kong, China.
[7]Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands.
[8]Department of Surgical Oncology and Vascular Surgery, University of Tokyo and the University of Tokyo Hospital, Tokyo, Japan.

with colorectal cancer worldwide[10]. Combined, in both sexes, colorectal cancer is the third-most common cancer and accounts for 9.7% of all cancers excluding non-melanoma skin cancer. More than half of the cases occur in more-developed regions of world. The age-standardized incidence rate (ASRi) of colorectal cancer is higher in men (20.6 per 100,000 individuals) than in women (14.3 per 100,000 individuals). The majority of patients with sporadic cancer are >50 years of age, with 75% of patients with rectal cancer and 80% of patients with colon cancer being ≥60 years of age at the time of diagnosis.

Incidence varies geographically, with the highest incidence in Australia and New Zealand (ASRi: 44.8 and 32.2 per 100,000 men and women, respectively), whereas Western Africa (ASRi: 4.5 and 3.8 per 100,000) has the lowest incidence (FIG. 2). More-developed regions (Europe, Northern America, Australia, New Zealand and Japan; combined ASRi: 29.2 per 100,000) have a higher incidence than less-developed regions (all regions of Africa, Asia (excluding Japan), Latin America and the Caribbean, Melanesia, Micronesia and Polynesia; combined ASRi: 11.7 per 100,000)[10]. The seven world regions can be ranked according to increasing ASRi: from Africa (6.3 per 100,000), Asia (13.7 per 100,000), Latin America and the Caribbean (14.0 per 100,000), Micronesia and Polynesia (15.0 per 100,000), Northern America (26.1 per 100,000), Europe (29.5 per 100,000), to Australia and New Zealand (34.8 per 100,000)[10]. Within each of these regions, the ASRi of colorectal cancer can show marked variation. In Europe, Albania (8.4 per 100,000) and Ukraine (23.4 per 100,000) have a lower incidence, whereas Slovakia (42.7 per 100,000), Hungary (42.3 per 100,000) and Denmark (40.5 per 100,000) have high incidence. Asia has the greatest diversity with regard to the ASRi of colorectal cancer. The incidence is high in South Korea (45.0 per 100,000), Singapore (33.7 per 100,000) and Japan (32.2 per 100,000), but much lower in Nepal (3.2 per 100,000), Bhutan (3.5 per 100,000) and India (6.1 per 100,000). These variations are associated with different socioeconomic levels[11].

In 2013, 771,000 people died as a result of colorectal cancer globally[12], making the disease the fourth-most common cause of cancer-related death worldwide after lung, liver and stomach cancer[12]. The age-standardized mortality rate (ASRm) of colorectal cancer in different countries reflects disease incidence, which explains why the ASRm is higher in men (10.0 per 100,000) than in women (6.9 per 100,000). Mortality also depends on the stage distribution at diagnosis, which is influenced by the availability of a population screening programme and by the level of care in each country. The ASRm is almost twofold higher in more-developed regions (11.6 per 100,000) than in less-developed regions (6.6 per 100,000). The ASRm in both sexes ranged from 3.3 per 100,000 people in Western Africa to 14.9 per 100,000 people in Central and Eastern Europe; in men, this value ranged from 3.5 per 100,000 people in Western Africa to 20.3 in Central and Eastern Europe, whereas in women, ASRm ranged from 3.0 per 100,000 people in Western Africa to 11.7 per 100,000 people in Central and Eastern Europe. That is, Western Africa showed the lowest age-standardized mortality in the world and Central and Eastern Europe exhibited the highest mortality in the world, in both men and women. Worldwide, mortality due to colorectal cancer has increased by 57% between 1990 and 2013 (REF. 12). Since the 1980s, in several countries in Europe, North America and Asia, mortality has tended to decrease. This decrease might be attributable to the introduction of colonoscopy, which has improved the detection and treatment of early lesions.

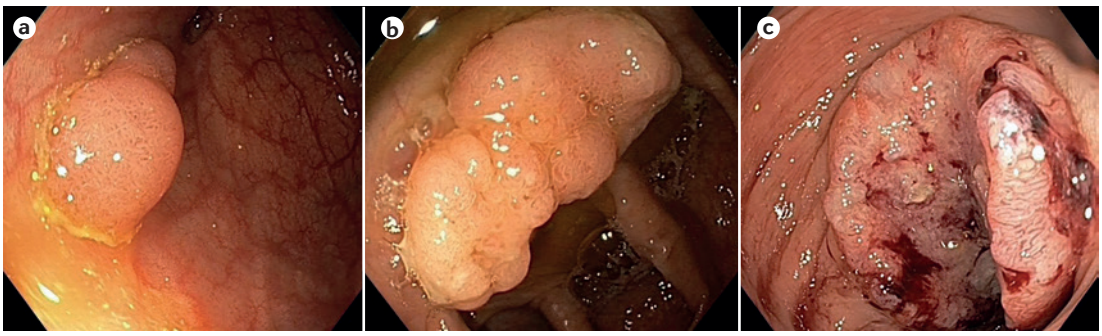

Figure 1 | **Colorectal neoplasia at different stages.** **a** | A small sessile adenoma. **b** | An advanced, larger sessile adenoma. **c** | A large, dish-shaped, ulcerating sigmoid carcinoma. The tumour covers most of the circumference, but has not yet led to substantial obstruction of the lumen.

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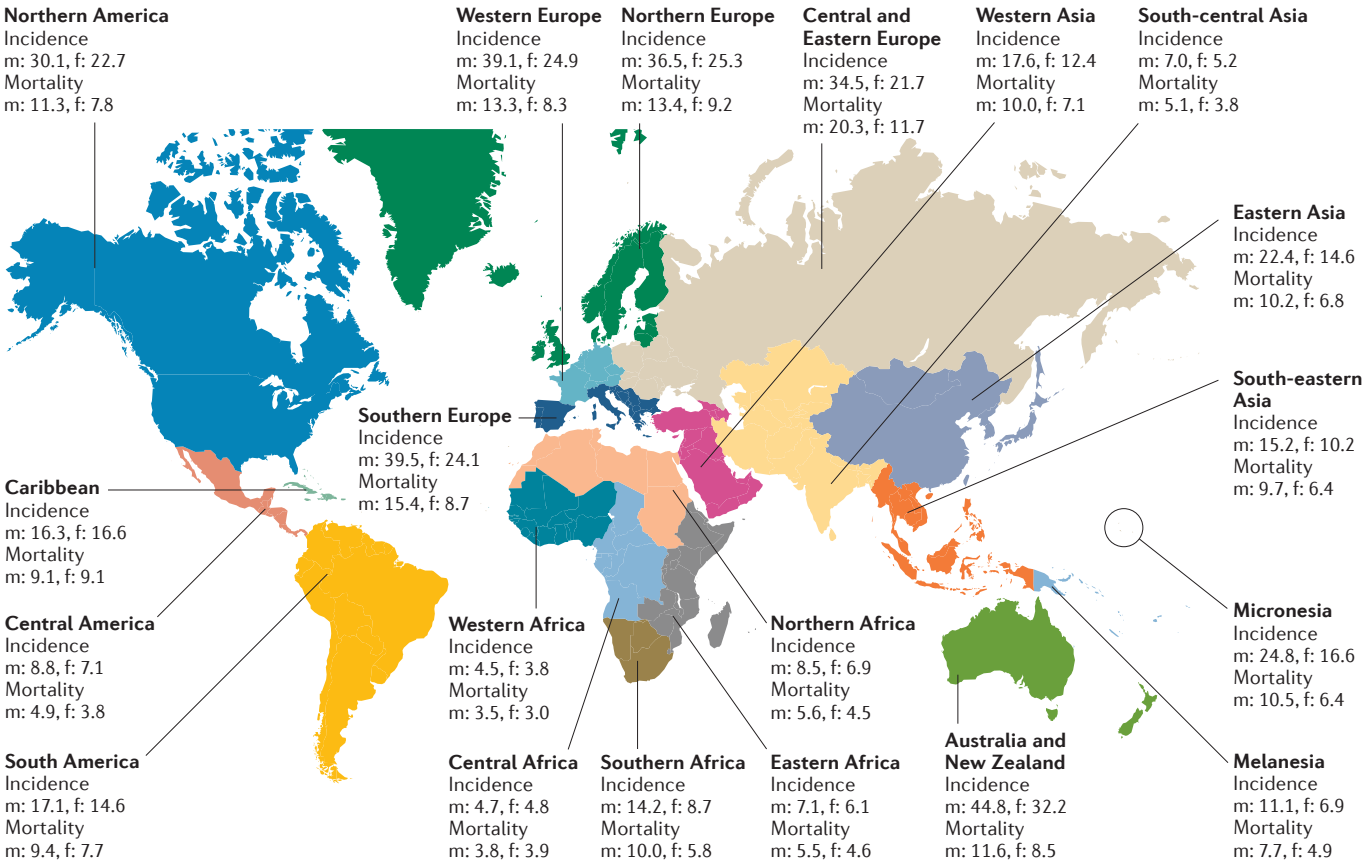

Figure 2 | **The age-standardized incidence and mortality rates in men and women (per 100,000 people) across geographical zones.** Rates are consistently higher in males (m) than in females (f), and vary considerably between regions[10]. Highest rates occur in Australia and New Zealand, Europe and Northern America.

Risk factors

Both genetic and environmental factors play an important part in the aetiology of colorectal cancer. The majority of colorectal cancers are sporadic; approximately three-quarters of patients have a negative family history. In most western populations, the average lifetime risk for colorectal cancer is in the range of 3–5%. However, this risk almost doubles in individuals with a first-degree family member with colorectal cancer who was diagnosed at 50–70 years of age; the risk triples if the first-degree relative was <50 years of age at diagnosis. Risk further increases in individuals who have two or more affected family members. For sporadic colorectal cancer, this increased risk in the presence of affected family at least in part reflects low-penetrance genetic factors. Accordingly, positive family history has a role in approximately 15–20% of patients with colorectal cancer.

Indeed, a specific subgroup of the patient population is formed by those affected by a hereditary colorectal cancer syndrome, accounting for 5–10% of all patients. The most common syndrome in this category is Lynch syndrome. This syndrome is caused by a mutation in one of the DNA mismatch-repair genes: *MLH1*, *MSH2*, *MSH6*, *PMS2* or *EPCAM*. Impaired mismatch repair during replication gives rise to the accumulation of DNA mutations, which occur, in particular, in microsatellite DNA fragments with repetitive nucleotide sequences. This microsatellite instability (MSI) can be identified by PCR testing, which compares normal and tumour DNA of the same patient. Patients with Lynch syndrome used to be identified by clinicopathological criteria, such as the Amsterdam and Bethesda criteria[4,13]. However, clinical practice is shifting towards unrestricted testing of tumour material of all patients diagnosed before 70 years of age by MSI PCR and immunohistochemistry for lack of expression of specific mismatch-repair proteins[14,15].

The second-most common hereditary colorectal cancer syndrome is familial adenomatous polyposis. This syndrome is caused by mutations in the adenomatous polyposis coli (*APC*) gene, which controls the activity of the WNT signalling pathway[4]. Most patients with familial adenomatous polyposis develop very large numbers of colorectal adenomas and subsequent colorectal cancer at a young age. Other hereditary colorectal cancer syndromes include polyposis associated with mutations in the mutY DNA glycosylase (*MUTYH*) gene, Peutz–Jeghers syndrome, serrated polyposis and juvenile polyposis; the diagnosis and management of which have been discussed elsewhere[4].

Chronic colitis due to inflammatory bowel disease (IBD) is also associated with increased risk of colorectal cancer. This risk increases with longer duration

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of IBD[16]. IBD explains only 1% of colorectal cancers in western populations, and a range of studies suggest that the incidence of colorectal cancer in those with IBD is decreasing because of effective anti-inflammatory treatments and improved surveillance[17,18], although this observation is not yet unanimous[19].

A range of environmental — largely modifiable — lifestyle factors influence the risk of developing colorectal cancer. The risk is increased by smoking, alcohol intake and increased body weight. With each unit increase of the body mass index, the risk for colorectal cancer increases by 2–3%[20]. In close conjunction, patients with type 2 diabetes mellitus also have an increased risk of colorectal cancer[21]. Moderate alcohol consumption (2–3 units per day) has been estimated to increase risk by 20%, whereas even higher alcohol consumption is associated with an up to 50% increased risk[22]. Prolonged heavy smoking has an effect of similar magnitude[23,24]. Intake of red meat and processed meat increases the risk of colorectal cancer by an estimated 1.16-fold per 100 g increase of daily intake[25]. By contrast, the consumption of milk, whole grains, fresh fruits and vegetables, as well as an intake of calcium, fibre, multivitamins and vitamin D, decrease the risk of colorectal cancer. The decrease of risk is estimated to be approximately 10% per daily intake of every 10 g of fibre, 300 mg of calcium or 200 ml of milk[25,26]. Daily physical activity for 30 minutes has a similar magnitude of effect[20,27]. Low-dose aspirin has also been associated with decreased risk of colorectal cancer[28].

The prevalence of these modifiable lifestyle factors can explain, to a considerable extent, the geographical and socioeconomic differences in colorectal cancer incidence[29]. Several studies have estimated that 16–71% of colorectal cancers in Europe and the United States are attributable to lifestyle factors[30–32]. Any benefit from lifestyle changes can be augmented by regular intake of aspirin and other NSAIDs[28]; however, this effect seems to depend on the host genotype[33,34]. Statin use might have a small preventive effect on the incidence of colorectal cancer[35,36], as does hormone therapy in postmenopausal women[37].

The various environmental factors that influence colorectal carcinogenesis is probably reflected in the heterogeneity of colorectal cancer, and has stimulated research into the field of 'molecular pathological epidemiology', which focuses on the correlation between environmental and genetic factors, and between molecular tumour characteristics and disease progression[38]. Further research into the correlation between colonic microbiota and colorectal cancer will probably provide further insights (see below).

Box 1 | **Hallmarks of cancer***

- Avoiding immune destruction: immune suppression in the tumour microenvironment by induction of local cytokines
- Evading growth suppressors: mutation and downregulation of growth-inhibiting factors and their receptors
- Genome instability and mutation: inactivation of DNA repair mechanisms
- Enabling replicative immortality: inhibition of mechanisms that induce senescence and induction of telomerase activity
- Deregulating cellular energetics: aerobic glycolysis (Warburg phenomenon) and glutaminolysis
- Tumour-promoting inflammation: induction of growth-promoting and angiogenesis-promoting factors by secreted proteins made by local inflammatory cells
- Inducing angiogenesis: induction of the formation of new blood vessels
- Resisting cell death: escape from autonomous and paracrine mediators of apoptosis and other forms of cell death (necrosis or necroptosis)
- Activating invasion and metastasis: remodelling of the extracellular matrix to promote cell motility and induction of epithelial–mesenchymal transition

*See REFS 39,40.

Mechanisms/pathophysiology

The environmental and genetic factors that cause colorectal cancer do so by promoting the acquisition of hallmark behaviours of cancer (BOX 1) in colon epithelial cells[39,40]. One way these hallmark cancer traits are acquired is through the progressive accumulation of genetic mutations and epigenetic alterations that activate oncogenes and inactivate tumour suppressor genes. The loss of genomic and/or epigenomic stability has been observed in the majority of early neoplastic lesions in the colon (namely, aberrant crypt foci, adenomas and serrated polyps) and is probably a central molecular and pathophysiological event in the initiation and formation of colorectal cancer[41,42]. The loss of genomic and epigenomic stability accelerates the accumulation of mutations and epigenetic alterations in oncogenes and tumour suppressor genes, which drive the malignant transformation of colon cells through rounds of clonal expansion that select for those cells with the most aggressive and malignant behaviour[43–45]. A prevailing paradigm is that the cell of origin of most colorectal cancers is a stem cell or stem cell-like cell that resides in the base of the colon crypts[46]. In this model, mutations in oncogenes and tumour suppressor genes in these cells lead to the formation of cancer stem cells, which are essential for the initiation and maintenance of a tumour.

In the colon, the evolution of normal epithelial cells to adenocarcinoma by and large follows a predictable progression of histological and concurrent epigenetic and genetic changes (FIG. 3). In the 'classic' colorectal cancer formation model, the vast majority of cancers arise from a polyp beginning with an aberrant crypt, which then evolves into an early adenoma (<1 cm in size, with tubular or tubulovillous histology). The adenoma then progresses to an advanced adenoma (>1 cm in size, and/or with villous histology) before finally becoming a colorectal cancer. This process is driven by the accumulation of mutations and epigenetic alterations and takes 10–15 years to occur but can progress more rapidly in certain settings (for example, in patients with Lynch syndrome)[47]. Notably, although the histology of conventional tubular adenomas is fairly homogeneous, the molecular biology of these polyps are heterogeneous, which might explain why some adenomas progress to colorectal cancer (approximately 10% of polyps) and some do not[48,49].

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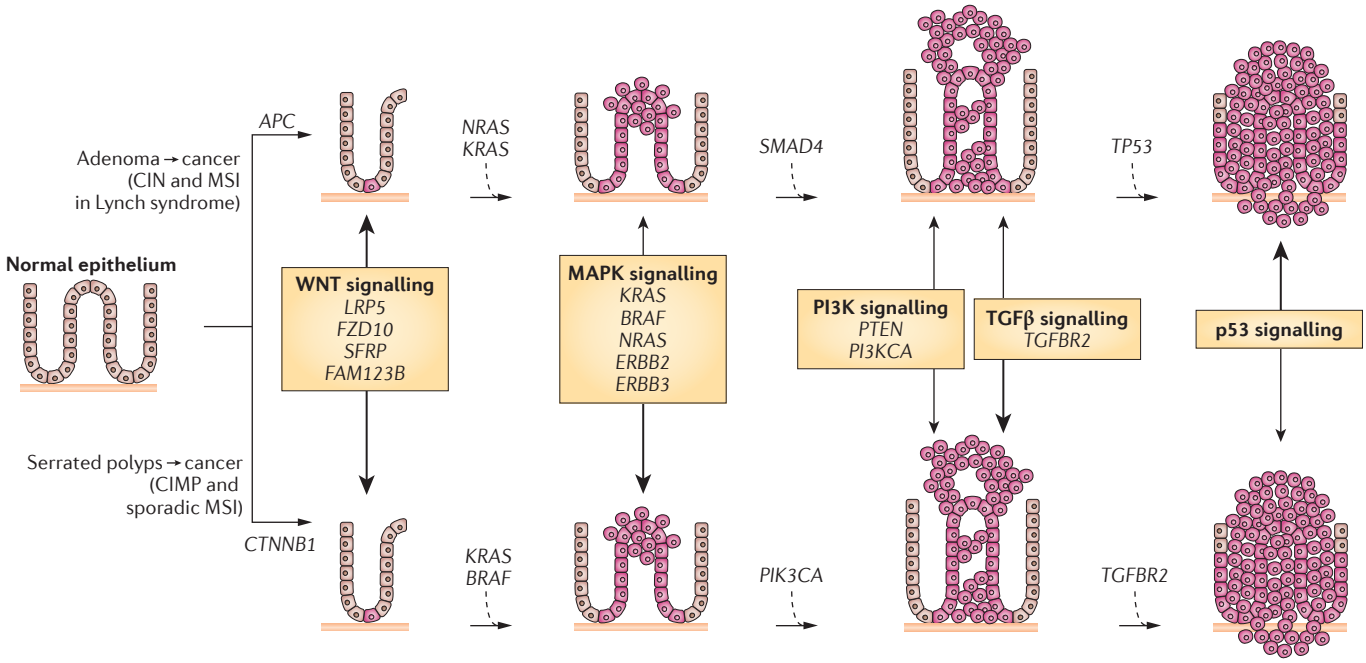

Figure 3 | **The polyp to colorectal cancer sequences.** Currently, two discrete normal colon to colorectal cancer sequences have been identified. Both sequences involve the progression of normal colon epithelial cells to aberrant crypt foci, followed by early and advanced polyps with subsequent progression to early cancer and then advanced cancer. The 'classic' or traditional pathway (top) involves the development of tubular adenomas that can progress to adenocarcinomas. An alternate pathway (bottom) involves serrated polyps, and their progression to serrated colorectal cancer has been described in the past 5–10 years. The genes mutated or epigenetically altered are indicated in each sequence; some genes are shared between the two pathways, whereas others are unique (for example, *BRAF* mutations and CpG island methylator phenotype (CIMP) only occur in the serrated pathway). The signalling pathways deregulated during the progression sequence are also shown, with the width of the arrow reflecting the significance of the signalling pathway in tumour formation. *APC*, adenomatous polyposis coli; CIN, chromosomal instability; *CTNNB1*, catenin-β1; *FAM123B*, family with sequence similarity 123B (also known as *AMER1*); *FZD10*, frizzled class receptor 10; *LRP5*, low-density lipoprotein receptor-related protein 5; MAPK, mitogen-activated protein kinase; MSI, microsatellite instability; PI3K, phosphatidylinositol 3-kinase; *PI3KCA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit-α; *PTEN*, phosphatase and tensin homologue; *SFRP*, secreted frizzled-related protein; *SMAD4*, SMAD family member 4; TGFβ, transforming growth factor-β; *TGFBR2*, TGFβ receptor 2. Figure from REF. 224, Nature Publishing Group.

Until 5–10 years ago, tubular and tubulovillous adenomatous polyps were thought to be the only lesions that were capable of progressing to cancer. However, some colorectal cancers have been shown to evolve from a subset of polyps called sessile serrated polyps, which account for approximately 5–10% of all polyps. These serrated polyps arise by molecular and histological events that are distinct from tubular adenomas[50–52] and are classified into three categories: hyperplastic polyps, sessile serrated adenomas and traditional serrated adenomas[53]. The sessile serrated polyps have the potential to transform into colorectal cancers through the following sequence: hyperplastic polyp to sessile serrated polyp to adenocarcinoma[50,54]. Furthermore, serrated polyps that arise in the right colon (which includes the caecum, ascending colon and transverse colon) commonly show MSI and a form of epigenetic instability characterized by excessive aberrant CpG island DNA methylation, termed the CpG island methylator phenotype (CIMP). By contrast, polyps that arise in the left colon (which includes the descending colon, sigmoid colon and rectum) are typically microsatellite stable but frequently carry mutations in *KRAS*, and a subset of these polyps have an attenuated form of the CIMP[51,52,55].

Given these molecular differences in the polyps and cancers they evolve into, a classification system for colorectal cancer has been proposed, with four subgroups of differing molecular features: hypermutable microsatellite unstable, hypermutable microsatellite stable, microsatellite stable or chromosome unstable, and CIMP cancers[42,56]. The frequency of specific mutations can vary dramatically between the molecular subclasses, suggesting that each has its own set of cooperating drivers[56]. However, the specific mutations and epigenetic alterations that define these molecular subgroups are still being determined. Some mutations, such as those in *APC* and SMAD family member 4 (*SMAD4*), are common among all the molecular subgroups — suggesting a central role in colorectal cancer in general — whereas others are restricted to one subgroup (for example, *BRAF* in CIMP colorectal cancers)[57].

In colorectal cancer, substantial heterogeneity in the specific mutations is evident between tumours,

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Table 1 | **Common genetic and epigenetic alterations in colorectal cancer***

Gene or biomarker	Chromosome	Function	Molecular lesion	Frequency (%)	Predictive?	Prognostic?	Diagnostic?
Tumour suppressors							
APC	5	Regulates the WNT signalling pathway	Inactivating mutations	40–70	No	No	Familial adenomatous polyposis
ARID1A	1	Member of the SWI/SNF family, and regulates chromatin structure and gene transcription	Inactivating mutations	15	No	No	N/A
CTNNB1	3	Regulates the WNT signalling pathway	Activating mutations	1	No	No	No
DCC	18	Netrin receptor; regulates apoptosis, is deleted but not mutated in colorectal cancer, and its role in primary cancer is still unclear	Deletion or LOH	9 (mutation); 70 (LOH)	No	Possible	No
FAM123B	X	Involved in the WNT signalling pathway	Inactivating mutations	10	No	No	No
FBXW7	4	Regulates proteasome-mediated protein degradation	Inactivating mutations	20	No	No	No
PTEN	10	Regulates the PI3K–AKT pathway	Inactivating mutations and loss of protein (assessed by immunohisto-chemistry)	10 (mutation); 30 (loss of expression)	Possible	No	Cowden syndrome‡
RET	10	Regulates the GDNF signalling pathway	Inactivating mutations and aberrant DNA methylation	7 (mutation); 60 (methylation)	No	No	No
SMAD4	18	Regulates the TGFβ and BMP pathways	Inactivating mutations and deletion	25	Possible	Possible	Juvenile polypsis
TGFBR2	3	Regulates the TGFβ pathway	Inactivating mutations	20	No	No	No
TP53	17	Regulates the expression of target genes involved in cell cycle progression, DNA repair and apoptosis	Inactivating mutations	50	Possible	Possible	Li–Fraumeni syndrome
Proto-oncogenes							
BRAF	7	Involved in the MAPK signalling pathway	V600E-activating mutation	8–28	Probable	Probable	Lynch syndrome
ERBB2	17	Involved in the EGF–MAPK signalling pathway	Amplification	35	No	No	No
GNAS	20	Regulates G protein signalling	Mutation	20	No	No	No
IGF2	11	Regulates the IGF signalling pathway	Copy number gain and loss of imprinting	7 (mutation); 10 (methylation)	No	No	No
KRAS	12	Regulates intracellular signalling via the MAPK pathway	Activating mutations in codons 12 or 13 but rarely in codons 61, 117 and 146	40	Yes	Possible	N/A
MYC	8	Regulates proliferation and differentiation	Amplification	2 (mutation); 10 (CNV gain)	No	No	No
NRAS	1	Regulates the MAPK pathway	Mutation in codons 12 or 13	2	Yes	No	No

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Table 1 (Cont.) | **Common genetic and epigenetic alterations in colorectal cancer***

Gene or biomarker	Chromosome	Function	Molecular lesion	Frequency (%)	Predictive?	Prognostic?	Diagnostic?
Proto-oncogenes (Cont.)							
PIK3CA	3	Regulates the PI3K–AKT pathway	Mutations in the kinase (exon 20) and helical (exon 9) domains	20	Probable	Possible	No
RSPO2 and *RSPO3*	8 and 6, respectively	Ligands for LGR family receptors, and activate the WNT signalling pathway	Gene fusion and translocation	10	No	No	No
SOX9	17	Regulates apoptosis	Copy number gain	9 (mutation); <5 (CNV gain)	No	No	No
TCF7L2	10	Regulates the WNT signalling pathway	Gene fusion and translocation	10	No	No	No
Other molecular alterations							
Chromosome instability	N/A	N/A	Aneuploidy	70	Probable	Probable	No
CpG island methylator phenotype	N/A	N/A	Methylation of >40% of loci from a selected panel of markers	15	Probable	Probable	No
Microsatellite instability	N/A	N/A	Unstable microsatellite repeats in the consensus panel	15	Probable	Yes	Lynch syndrome
Mismatch-repair genes	N/A	Regulate DNA mismatch repair	Loss of protein (as assessed by immunohisto-chemistry), methylation and inactivating mutations	1–15	Possible	Probable	Lynch syndrome
SEPT9	17	N/A	Methylation	>90	No	No	Serum-based assay for cancer detection
VIM, *NDRG4* and *BMP3*	10, 16 and 4, respectively	N/A	Methylation	75	No	No	Stool-based test for early detection
18qLOH	18	N/A	Deletion of the long arm of chromosome 18	50	Probable	Probable	No

APC, adenomatous polyposis coli; *ARID1A*, AT-rich interactive domain 1A; *BMP*, bone morphogenetic protein; CNV, copy number variation; *CTNNB1*, catenin-β1; *DCC*, DCC netrin 1 receptor; EGF, epidermal growth factor; *FAM123B*, family with sequence similarity 123B; *FBXW7*, F-box and WD repeat domain-containing 7, E3 ubiquitin protein ligase; GDNF, glial cell-derived neurotrophic factor; *GNAS*, guanine nucleotide-binding protein, α-stimulating complex locus; *IGF*, insulin-like growth factor; LGR, leucine-rich repeat-containing G protein-coupled receptor; LOH, loss of heterozygosity; MAPK, mitogen-activated protein kinase; N/A, not applicable; *NDRG4*, NDRG family member 4; PI3K, phosphatidylinositol 3-kinase; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit-α; *PTEN*, phosphatase and tensin homologue; *RSPO*, R-spondin; *SEPT9*, septin 9; *SMAD4*, SMAD family member 4; *SOX9*, SRY (sex-determining region Y) box 9; *TCF7L2*, transcription factor 7-like 2; TGFβ, transforming growth factor-β; *TGFBR2*, TGFβ receptor 2; *VIM*, vimentin. *Includes alterations in gene expression, gene deletions and amplifications, somatic mutations and aberrant promoter methylation. ‡Germline mutation, not somatic.

although the mutations seem to cluster in epistatically related groups (for example, genes involved in a certain signalling pathway)[58–60]. The most common mutations in colorectal cancer include those in *APC*, catenin-β1 (*CTNNB1*), *KRAS*, *BRAF*, *SMAD4*, transforming growth factor-β receptor 2 (*TGFBR2*), *TP53*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit-α (*PIK3CA*), AT-rich interactive domain 1A (*ARID1A*), SRY (sex-determining region Y) box 9 (*SOX9*), family with sequence similarity 123B (*FAM123B*; also known as *AMER1*) and *ERBB2*, which promote tumorigenesis by perturbing the function of key signalling pathways, including the WNT–β-catenin, epidermal growth factor (EGF)–mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K) and TGFβ signalling pathways, or by affecting genes that regulate the central behaviours of cells, such as DNA repair and proliferation[61,62] (TABLE 1). Colorectal cancer is frequently initiated by mutations that affect the WNT

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signalling pathway, and the ensuing neoplastic cells then progress upon deregulation of other signalling pathways, including the RAS–RAF–MAPK, TGFβ, and PI3K–AKT pathways[60,63].

In addition to gene mutations, epigenetic alterations commonly occur in polyps and colorectal cancers and seem to cooperate with gene mutations to drive the polyp to cancer progression[58,64,65]. DNA methylation affects CpG-rich regions (CpG islands), which are often located in the 5′ region of genes and can result in transcriptional silencing through effects on transcription factor binding and changes in the chromatin structure[66]. Modifications in DNA methylation related to the development of cancer (in general) include two fundamental changes: hypermethylation of CpG islands in gene promoters, which can silence tumour suppressor genes, and hypomethylation of repetitive genetic elements, which can lead to genomic instability or oncogene activation[67]. Hypermethylation, such as of the septin 9 (*SEPT9*) gene promoter, is also used for screening purposes (see below).

Importantly, the frequencies of many of these molecular features vary depending on the location of the tumour in the gut (from the ascending colon to the rectum)[68,69]. Some studies support a gradual gradient in change in frequency of the molecular alterations, whereas others suggest a more abrupt dichotomy. This has led to the traditional dichotomy of 'proximal' and 'distal' colorectal cancer versus adoption of a continuum model. Both models support the notion that the tumour microenvironment (the gut microbiota and the inflammatory state of adjacent tissue) modulates the way these mutations affect cancer formation and disease progression. Thus, our current understanding of the pathogenesis of colorectal cancer is that the disease results from the accumulation of mutations in genes that then drive the formation of the tumour in the context of tumour-promoting factors derived from the adjacent tissue. This paradigm formed the basis for recent recommendation to determine the *in situ* immune cell infiltrate of the tumour as a prognostic marker alongside its (standard) TNM stage[70]. In close conjunction with these data, recent research has focused on the role of the gut microbiota in colorectal carcinogenesis. Indeed, studies have shown the enriched presence of fusobacteria[71], particularly in cancers with CIMP status[72], which might be inversely related to the $CD3^+$ T cells in colorectal cancers[73]. Together, these data form a basis for further research into the role of the colon microbiota and colon carcinogenesis.

Box 2 | **Endoscopic techniques for the diagnosis of colorectal cancer**

High-definition white-light endoscopy
- Current standard for colonoscopy, combining high-definition video endoscopes with high-resolution videoscreens
- Provides detailed images of the gastrointestinal mucosa
- Advantage of routine endoscopy; disadvantage that it provides no specific contrast for the detection of neoplastic lesions

Chromoendoscopy
- The use of a dye spray during gastrointestinal endoscopy to improve visualization
- Improves the detection of neoplastic lesions
- Time-consuming to spray the complete colon
- A new technique with dye incorporated into colon preparation is under investigation

Magnification endoscopy
- Endoscope with zoom-lens in the tip, which enables 6–150-fold enlargement of the mucosa
- Can characterize and determine the extension of neoplastic lesions
- Not suitable for screening of the complete colon
- Can be combined with other methods

Narrow-band imaging
- A technique that can also be built into white-light endoscopes
- Filters light to two bands, with a wavelength of 415 nm (blue) and 540 nm (green), respectively
- Longer wavelength light is less scattered and, therefore, penetrates deeper into the mucosa
- Blue light enhances superficial capillaries, whereas green light shows deeper, subepithelial vessels
- Can characterize and determine the extension of neoplastic lesions
- Does not increase neoplasia detection rates

Intelligent colour enhancement (FICE; Fujinon) and iScan (Pentax) imaging
- Similar techniques as narrow-band imaging, but with no filtering of the outgoing light
- Instead, processes the reflected light

Autofluorescence endoscopy
- A technique that can also be built into white-light endoscopes
- Based on the principle that illumination with a specific blue wavelength light can lead to excitation of tissue, which then emits light with a longer wavelength
- Wavelength of the emitted light is longer for neoplastic tissue
- Can be used to search for neoplastic lesions

Endomicroscopy
- A technique of extreme magnification endoscopy
- Enables *in vivo* visualization of individual glands and cellular structures
- Can evaluate neoplastic lesions
- Not suitable for scanning larger mucosal surfaces

Diagnosis, screening and prevention

Diagnosis

A diagnosis of colorectal cancer either results from an assessment of a patient presenting with symptoms or as a result of screening. The disease can be associated with a range of symptoms, including blood in stools, change in bowel habits and abdominal pain. Other symptoms include fatigue, anaemia-related symptoms, such as pale appearance and shortness of breath, and weight loss. The predictive value of these symptoms for the presence of colorectal cancer in an elderly patient is limited, but they do warrant further clinical evaluation. With the widespread introduction of population screening for colorectal cancer, many individuals are diagnosed at the preclinical stage. In symptomatic patients, colonoscopy is the preferred method of investigation, but other endoscopic methods are also available or being developed (BOX 2). For population screening, a range of other methods can be used for primary assessment, followed by colonoscopy in case of a positive test.

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Colonoscopy. Colonoscopy is the gold standard for the diagnosis of colorectal cancer. It has a high diagnostic accuracy and can assess the location of the tumour. Importantly, the technique can enable simultaneous biopsy sampling and, hence, histological confirmation of the diagnosis and material for molecular profiling. Colonoscopy is also the only screening technique that provides both a diagnostic and therapeutic effect. Removal of adenomas using endoscopic polypectomy can reduce cancer incidence and mortality[9,74–77]. Indeed, the efficacy of colonoscopy for the reduction of colorectal cancer incidence and mortality was well demonstrated by the US National Polyp Study[76,78]. Recent 20-year follow-up data from this study showed a reduction in colorectal cancer-related mortality of 53%[76], which is an encouraging result that has been echoed by a more-recent study[79]. The quality of colonoscopy is a determining factor in the diagnostic yield of cancer and adenoma, which is the most certain way of avoiding interval cancers (that is, a tumour arising in between screening visits)[9,75,80,81].

The image quality of colonoscopy has markedly improved over the past 20 years, from original fibre-optic to videochip endoscopes. Videochip endoscopes were further improved over the years, leading to higher resolution and wider angle of view. The current standard combines high-power endoscopes with high-resolution videoscreens to yield high-definition white-light endoscopy (hWLE). Although various technologies for further image enhancement in colonoscopy have been introduced over the past decade, none of them have been shown to improve the diagnosis of polyps and colorectal cancer compared with hWLE[82]. Only chromoendoscopy (BOX 2) has proven to be superior to hWLE in the identification of adenomas[83]. Narrow-band imaging, imaging with the Fujinon Intelligent Colour Enhancement system (Fujinon Corporation, Saitama, Japan) and autofluorescence endoscopy are not advantageous over hWLE in the detection of adenomas or carcinomas[82]. The Third Eye Retroscope® device (Avantis Medical Systems, California, USA) was designed to address the fact that lesions behind mucosal folds in the gut are often missed. This endoscope provides a simultaneous retrograde view of the colon that complements the forward view of a standard colonoscope. Several pilot studies have indicated that it might be useful[84–86], but more data are needed. The invasive nature of colonoscopy poses a burden to screenees and patients, which might affect participation in screening programmes. In recent years, several alternative diagnostic methods have been introduced, such as capsule endoscopy and biomarker tests.

Capsule endoscopy. Capsule endoscopy uses a wireless capsule device that is swallowed by the screenee and enables examination of almost the entire gastrointestinal tract without the use of conventional endoscopy[87–90]. Capsule endoscopy is useful in diagnosing adenomas and colorectal cancer. The first-generation capsule endoscopy was found to be able to detect polyps >6 mm in size with a sensitivity of approximately 60% and specificity of >80%[87]. Cancer detection was achieved in 74% of patients with colorectal cancer[87]. With the development of the second-generation capsule endoscopy for the colon (PillCam® Colon2 (Given Imaging Ltd, Yokne'am Illit, Israel)), the frame speed was increased from a fixed speed of four pictures per second to a variable 4–35 pictures per second depending on capsule movement. The angle of view was widened from 156° to 172° on both ends of the capsule, providing a 344° view. A large trial in the United States and Israel assessed the accuracy of this new capsule to diagnose colorectal neoplasia. With 884 patients included, sensitivity was shown to be 88% and specificity 82% for the detection of adenomas >6 mm in size[91].

The European Society for Gastrointestinal Endoscopy guideline for colon capsule endoscopy recommends capsule endoscopy as a feasible and safe tool for the visualization of the colonic mucosa in patients who have undergone no or incomplete colonoscopies[90]. This recommendation was then also incorporated in the Asia–Pacific guidelines on colorectal cancer screening[92]. The indications for capsule endoscopy are at this moment limited to patients who refuse conventional colonoscopy and to those in whom a complete colonoscopy is not possible for anatomical reasons. The presence of a stenosis is a contraindication for capsule endoscopy as it could lead to capsule retention.

CT colonography. CT colonography uses low-dose CT scanning to obtain an interior view of the colon. The technique is well established as a diagnostic modality for colorectal cancer[93]. In a systematic review and meta-analysis that included >11,000 people from 49 centres, CT colonography was shown to have a sensitivity of 96% for the detection of colorectal cancer[94]. This performance is similar to that of conventional colonoscopy. A recent study reported similar performance of CT colonography and capsule endoscopy in patients with previous incomplete colonoscopy[95]. A large trial in 411 patients with obstructive cancers showed excellent performance of CT colonography for the evaluation of proximal synchronous lesions[96]. An observational study based on data from England of 2,731 people with a positive guaiac faecal occult blood test (gFOBT, see below) showed that the detection rate of advanced neoplasia was significantly lower for subsequent CT colonography than for subsequent colonoscopy[97]. Furthermore, the detection and accuracy rates for advanced neoplasia were better in high-volume centres. These findings underline the need for adequate quality assurance similar to measures implemented for colonoscopy screening.

CT colonography requires full bowel preparation (that is, clearance of the bowel), air inflation and a change in position of the patients during the examination. The discomfort to the screenee undergoing CT colonography is similar to colonoscopy in experienced hands, particularly because of the need for substantial bowel insufflation[98], but it has the advantage of obviating the use of sedation and can be used as part of the staging procedure in a confirmed case of colorectal cancer. However, CT colonography has low sensitivity for

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small (6–9 mm) and flat lesions[99]. The technique is associated with high colonoscopy referral rates (up to 30%) and high rates of extra-colonic findings in non-cancer cases, which translate to unnecessary investigations and increased anxiety for individuals[100,101]. The costs of CT colonography and the need for further investigation in a subset of screenees limit the usefulness of this method for population screening in most countries.

CT colonography has been recommended as one of the options for colorectal cancer screening in guidelines in the United States and Europe[102,103]. In many countries, CT colonography has replaced double-contrast barium enema examination (the conventional X-ray-based imaging modality for the colon) and is increasingly being used as an alternative to conventional colonoscopy. However, CT colonography has not readily been accepted in Europe because of radiation exposure, costs, burden to patients and high colonoscopy referral rates. In the Asia–Pacific region, CT colonography is not recommended for colorectal cancer screening, except in those for whom total colonoscopy is not possible[92].

Biomarkers of colorectal cancer. Molecular detection of colorectal cancer offers a non-invasive test that is appealing to patients and clinicians as samples of multiple patients can be analysed in batch. The ideal molecular marker should be highly discriminating between cancer and advanced adenomas from other lesions, be continuously released into the bowel lumen or circulation, and disappear or reduce after the lesion is removed or treated. Indeed, assays using proteins, RNA and DNA in the blood, stool and urine have been developed but with varying degrees of success (TABLE 1). Stool tests are based on the fact that early cancers as well as advanced pre-malignant lesions can bleed and shed cells into the bowel lumen, which can be detected. Blood tests obviate the handling of stool and urine and can be performed alongside routine checking of blood sugar and cholesterol in the elderly population.

SEPT9 belongs to a class of GTPases, and hypermethylation of its promoter region is associated with colorectal cancer; aberrant methylation of *SEPT9* at the tissue level discriminates colorectal neoplasia from normal mucosa. Early case–control studies from referral centres showed that *SEPT9* methylation testing yielded a moderate sensitivity of 50–70% for colorectal cancer, with a specificity of 85–90%[104]. However, a more-recent larger scale study in the population with average risk of developing the disease suggested a colorectal cancer detection rate of <50% when using *SEPT9* methylation testing[105]. The reported detection of advanced colonic adenoma by *SEPT9* methylation status is only approximately 10%. As such, *SEPT9* assays are outperformed by current quantitative faecal immunochemical tests (FITs).

Mutations of *APC* and *KRAS* have been tested in DNA shed by epithelial cells and isolated from stool samples. The first-generation faecal DNA tests only gave satisfactory results with fair sensitivity for the detection of colorectal cancer but low sensitivity for the detection of advanced colonic adenomas[106]. Since then, several technological improvements have been made, including the use of a stabilizing buffer, the addition of other more-discriminating markers (*KRAS* mutations, aberrant NDRG family member 4 (*NDRG4*), bone morphogenetic protein 3 (*BMP3*) methylation and the presence of β-actin), the use of more-sensitive analytical methods and the optimization of the determining algorithm — all of which have improved the accuracy of the assay (see further description below)[107]. Other potentially useful markers under investigation include circulating tumour mRNA, microRNA and circulating cytokeratins[108].

Screening and prevention

Colorectal cancer is more suitable for population screening than any other malignancy owing to a combination of factors[1]. First, the incidence of the disease is high, and outcome for a significant proportion of affected patients is poor despite intense, burdensome and often very costly treatments[109]. Colorectal cancer also has a long preclinical stage. For instance, 7,151 Dutch men 55–75 years of age were newly diagnosed with colorectal cancer in 2012 (see the Dutch Cancer Registry: www.cijfersoverkanker.nl), which corresponds to approximately 0.2% of the 3.5 million people in that age group. Such an incidence is in line with similar annual incidences in other western European countries. However, colonoscopy screening studies generally tend to find prevalent colorectal cancer in 0.5–0.9% of the participants in the same age group[53,62,63]. Although an increased willingness of symptomatic screenees might confound this difference, these data indicate that colorectal cancer on average progresses for several years before becoming symptomatic. Furthermore, colorectal cancer is preceded by colorectal adenoma. In individuals with sporadic (non-hereditary) disease, the progression from adenoma to cancer takes at least 5–10 years[110]. The long preclinical stage of the disease offers a large window of opportunity for screening.

Second, colorectal cancer is also suitable for screening because adenomas and early cancers are detectable and treatable entities, which is in contrast to precursors of other highly common cancers of the breast, prostate and lung.

Last, both endoscopic removal of adenomas and treatment of early-stage cancers have a profound effect on colorectal cancer mortality. After a 20-year follow-up of the US National Polyp Study cohort, colorectal cancer-specific mortality was approximately 50% lower among subjects who at baseline had undergone endoscopic removal of adenomas than in an unscreened control cohort[76]. Furthermore, the 5-year survival rates for patients with early-stage cancer are approximately 90%, compared with 10% for patients diagnosed with advanced-stage metastatic disease. Together, these factors form the background for various international guidelines on colorectal cancer screening. Screening in most countries aims to capture men and women who are 50–75 years of age, although different age ranges are being used in various programmes depending on the available resources[111]. Adoption of lifestyle measures can also substantially affect colorectal cancer incidence.

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Table 2 | **Key performance indicators for organized screening with different modalities**

Test	Advantages	Disadvantages	Refs
gFOBT	• Cheap • Low screenee burden • Reasonable uptake	• Limited sensitivity for advanced neoplasia • Need for short screening intervals • No effect on the incidence of colorectal cancer • Qualitative, not automated • Multiple sampling • Moderate positive predictive value	123,124, 225
FIT	• Cheap • Low screenee burden • Quantitative, automated • Single sample • Sensitive for colorectal cancer • Highest uptake • Effect on incidence and mortality	• Limited sensitivity for advanced adenoma • Moderate positive predictive value • Repeated screening needed (interval can be longer than for gFOBT) • Temperature-dependent performance*	124,126, 127,131, 226
Sigmoidoscopy	• Sensitive for distal advanced neoplasia • Long screening interval • Effect on incidence and mortality	• Low uptake • Expensive • Moderately sensitive for proximal advanced neoplasia	115–117, 227
Colonoscopy	• Sensitive and specific • Long screening interval • Effect on incidence and mortality	• Low uptake • Expensive • Burdensome • Associated with complications	75,76,80, 135,228
CT colonography	• Sensitive and specific • Long screening interval • Likely effect on incidence and mortality	• Low uptake • Expensive • Need for repeated lavage in case of advanced neoplasia • Radiation exposure • Burdensome	93,94, 96–98, 101,103, 229
Multi-target faecal DNA test	• Sensitive and specific	• Uptake unknown • Expensive • Lack of prospective data	107,108

FIT, faecal immunochemical test; gFOBT, guaiac faecal occult blood test. *Less problematic with newer-generation tests.

Endoscopy. Given that imaging of the colon can confirm a diagnosis or exclude colorectal neoplasia, clinicians often favour these methods for screening purposes. Colorectal adenomas and early-stage cancers can directly be visualized by endoscopy, CT colonography or capsule endoscopy[76,88,94,101]. A randomized comparison between CT colonography and colonoscopy for primary population screening has shown a slightly higher uptake of CT colonography, counterbalanced by a slightly lower sensitivity for advanced neoplasia[101]. Capsule endoscopy screening might in the near future provide an alternative visualization method for primary screening[88]. Overall, colonoscopy has the highest accuracy, is generally considered the gold standard for screening and is associated with several advantages (TABLE 2). Recent large observational studies showed that screening colonoscopy reduced the risk of colorectal cancer by approximately 80%, and had a similar effect on related mortality[112,113]. This preventive effect of colonoscopy strongly depends on procedural quality, which can be measured in terms of adenoma detection rate of the performing endoscopist[75]. Other measures for procedural quality include the level of bowel preparation, caecal intubation rates, complication rates, average sedative medication dose and patient burden scores[9]. In a study from the United States, adenoma detection rates per colonoscopist ranged from 7% in the lowest quintile of detection to 50% in the highest quintile — a difference that is associated with an almost twofold risk in interval cancer[80]. The correlation between risk of post-colonoscopy cancer and adenoma detection rates was also reported in a study from Poland[75]. Training and quality-assurance measures, and adherence to surveillance guidelines also have an effect on the rate of post-colonoscopy cancers[74,114].

Sigmoidoscopy, which images the rectum and sigmoid colon and can include the descending colon, has been shown in several randomized prospective trials to reduce the incidence of colorectal cancer by approximately 33% and reduce related mortality by 38–59%[1,115–117]. This effect was obtained by single sigmoidoscopy screening, with further colonoscopy in those with signs of advanced polyps — a finding that formed the basis for the current roll-out of nationwide primary sigmoidoscopy screening in England. The wide use of colonoscopy and sigmoidoscopy for primary screening in various countries supports the introduction of non-physician endoscopists who can perform diagnostic endoscopy according to international standards[118]. Further studies are needed to assess performance and cost efficacy[119].

Population screening. Given the considerable rise in treatment costs, colorectal cancer screening is a cost-saving exercise in many countries[120]. Screening can

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be carried out using a range of methods, both invasive and non-invasive (TABLE 2). Most programmes are based on a single primary screening test, followed by colonoscopy in those who test positive[111]. In other settings, screenees are offered a choice between different screening methods, which might increase or decrease participation rates depending on the local setting[121,122].

Population screening must consider more than just test accuracy, but should take test uptake and the demand on resources into account. Accordingly, screening results must be reported in terms of identification of subjects with advanced neoplasia per 1,000 invited and in numbers needed to scope. A very accurate test by definition has no effect on cancer incidence and mortality in a population if not widely applied[1,109]. Similarly, limitations in endoscopy capacity preclude the use of colonoscopy for primary screening. For these reasons, many countries prefer a two-step approach in population screening, first using a non-invasive screening test to select a subgroup of screenees who are at high risk of cancer for subsequent colonoscopy. Typically, a faecal occult blood test is this primary screen[1], either using gFOBTs or FITs. FITs are now more widely used than gFOBTs because of easier handling, resulting on average in approximately 10% higher uptake, higher sensitivity for advanced neoplasia and automated analysis[123,124]. Indeed, quantitative FITs offer the additional advantage that their cut-off points can be adjusted to match colonoscopy capacity[125]. For an optimal impact on the population level, adequate quality assurance is needed over the full range of the screening programme, as is organized active call–recall screening[1].

The effect of uptake on the yield of screening was shown by a randomized study comparing primary colonoscopy and FIT screening in Spain[126]. The cancer detection rate was similar in both groups, but a considerable proportion of cancers in the colonoscopy group were actually detected by primary FIT screening after screenees first refused primary colonoscopy. Similarly, in a range of screening trials in the Rotterdam area, the highest detection rate was observed with repeated FIT screening[1,127]. This detection rate can be further increased with the use of two samples per screening round, especially in the first screening round[128], although this approach is less cost effective than screening with one sample[129]. gFOBT screening routinely makes use of a 1–2-year interval, and the higher accuracy of FIT screening can allow for extension of the screening interval to 3 years[130].

The performance of the aforementioned multi-target faecal DNA test plus FIT was compared with FITs alone for the detection of colorectal neoplasia[107]. All participants in the study underwent each of the 'experimental' screening methods and a confirmatory colonoscopy. The combined tests identified 60 out of 65 patients (92%) with colorectal cancer and 321 out of 757 patients (42%) with advanced adenomas; FITs alone detected 48 patients with colorectal cancer (74%; $P = 0.002$) and 180 patients with advanced adenomas (24%; $P < 0.001$)[107]. These results provide evidence for the accuracy of the DNA test in asymptomatic average-risk individuals, and led to US FDA approval of the multi-target faecal DNA test plus FIT. However, the positive predictive value of the multi-target faecal DNA test was low (24%) for a non-invasive test, and the DNA test plus FIT yielded a 16.1% positivity rate versus 7% for FIT alone, thus necessitating 2.3-fold more colonoscopies in the DNA test plus FIT arm. If both tests were compared at the same positivity rate — a crucial determinant in countries with limited colonoscopy resources — the actual diagnostic yield and positive predictive value could have been approximated. This assumption is supported by previous studies that reported a similar number needed to screen to detect advanced neoplasia[131]. Finally, study design did not include a component to examine uptake of either test. For these reasons, further studies are needed to position the DNA test as a population-screening method.

Surveillance after resection

Patients who have adenomatous polyps or colorectal cancer continue to be at risk for new neoplastic lesions after these have initially been removed — either because of biological or environmental factors, or both[132]. These patients could benefit from surveillance to detect and remove new lesions. Most evidence supporting this hypothesis is based on surveillance studies that have documented higher rates of tubular adenomas >10 mm in size, adenomas with villous histology, high-grade dysplasia or cancer in patients with neoplasia at the baseline colonoscopy examination; the risk of developing subsequent tumours also depends on the size and histology of polyps at the index examination[132–134]. Furthermore, there is a relationship between the index lesion and subsequent risk of death from colorectal cancer[135]. Together, this body of data provides a strong justification for surveillance, but does not prove with certainty that surveillance will actually prevent recurrent cancer or reduce mortality.

Guidelines for surveillance in patients without hereditary syndromes vary in the United States and Europe[133,136,137]. The underlying premise of all such recommendations is that the baseline examination must be complete (including the caecum), with adequate bowel preparation, and that any detected lesions are removed completely. If the completeness of the resection or quality of the examination comes into question, early re-examination is recommended. The guidelines stratify risk based on the findings of the index examination (BOX 3). The US guidelines endorse a 10-year interval if the baseline examination is negative or if the patient only has hyperplastic polyps in the rectum or sigmoid colon. New evidence adds further support for this recommendation[79,138]. Interval faecal blood testing is generally not recommended, owing to a lack of evidence of benefit[133,136].

Several longitudinal studies of patients after adenoma removal have provided some guidance for the optimal intervals for surveillance examinations[132,134]. Surveillance intervals are based on the findings at the last colonoscopy (BOX 3). If the patient has an adenoma

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with high-risk features at baseline but no polyp or an adenoma with low-risk features at surveillance, the next examination is recommended at 5 years. If the patient has an adenoma with low-risk features at baseline and at surveillance, the next examination interval is recommended at 5 years; if there is no polyp at surveillance, the next examination interval is at 10 years. Finally, if a high-risk adenoma is found at surveillance, the next examination is recommended at 3 years. These recommendations are designed to reduce the frequency of surveillance for many individuals with low-risk lesions and are based on findings using high-quality colonoscopy. Complete examinations with good bowel preparation[9] are required, but the role of other mitigating factors during surveillance such as lifestyle, sex and race are unknown. Surveillance should be discontinued when the risks of performing the bowel preparation and/or colonoscopy could outweigh any potential benefit. These factors should also be considered in elderly patients with co-morbid conditions that might limit life expectancy, diminish any potential benefit of polyp removal and increase the risk of complications during the colonoscopy procedure[139,140].

Box 3 | **Surveillance guidelines**

Colorectal cancer

- Patients with colorectal cancer should have intensive follow-up care
- If a complete colonoscopy was not possible before surgical resection, colonoscopy should be offered within 3–6 months to detect synchronous lesions
- If a complete colonoscopy was performed at baseline, patients with colorectal cancer should have colonoscopy at 1 year; if negative, every 3–5 years thereafter

High-risk adenoma

- High-risk features include adenomas with high-grade dysplasia, villous histology, tubular adenoma >10 mm in size, serrated lesions >10 mm in size, serrated lesions with dysplasia or ≥3 adenomas
- The risk of advanced neoplasia during surveillance is 15–20%, which is approximately 2–3-fold higher than individuals with 1–2 small (<10 mm) tubular adenomas and 5–6-fold higher than individuals with no polyps at baseline colonoscopy[133]
- The US Multi-Society Task Force on Colorectal Cancer (USMSTF)[133] and European Society of Gastrointestinal Endoscopy (ESGE)[136] guidelines recommend a 3-year interval for surveillance
- The UK guidelines define highest-risk features as >5 small adenomas or >3 adenomas, in which at least one is >10 mm in size, and recommends annual surveillance[137] based on data indicating a high likelihood of finding additional high-risk adenomas at 1 year[221]
- The UK guidelines define intermediate-risk features as 3–4 small (<10 mm) adenomas or ≥1 large (>10 mm) adenomas, irrespective of histology, and suggest a 3-year screening interval

Low-risk adenoma

- Individuals with 1–2 tubular adenomas <10 mm in size represent a low-risk group
- A statistically insignificant increase in risk, relative to patients with no polyps at baseline colonoscopy, are attributed to these patients
- The UK guidelines recommend no specific follow-up[137]; the ESGE guidelines recommend follow-up at 10 years[136]; the USMSTF guidelines recommend surveillance at 5–10 years, with evidence supporting the 10-year interval if the index examination preparation was adequate[133]
- Serrated lesions <10 mm in size with no dysplasia might also represent a low-risk lesion, but evidence is weak; the USMSTF recommends a 5-year interval for surveillance and the ESGE recommends a 10-year interval

How to conduct surveillance of patients with serrated lesions is under debate. Understanding the natural history of these lesions requires accurate histological definition, endoscopic detection and longitudinal follow-up[141]. Furthermore, inter-observer variability in histological interpretation, wide variation in detection rates and virtually no longitudinal follow-up study of these patients have hindered surveillance assessment[142]. Nevertheless, some evidence suggests that this pathway accounts for >20% of colorectal cancers, and patients may be at risk for recurrent disease and, therefore, require surveillance after resection. Further studies have to substantiate the risk for recurrent polyps and define optimal surveillance schedules.

In addition to endoscopic surveillance after cancer resection, follow-up surveillance by measuring carcinoembryonic antigen (CEA) levels in the plasma and/or CT imaging might detect curatively treatable metastatic recurrence[143]. There have been concerns about the cost, benefit and number needed to test to achieve a survival benefit. A randomized study found that CEA testing resulted in 6.7% of patients receiving treatment with curative intent and CT resulted in 8% receiving treatment, which was significantly more than a group receiving minimum follow-up care that involved only targeted diagnostic assessment if symptomatic[144]. The actual survival benefit was probably small. The cost-effectiveness is also uncertain, but CEA testing is likely to be more cost effective than CT, depending on the cost in different countries.

Management

Although the molecular drivers of colorectal cancer have been described, where in the gut a tumour occurs has implications for treatment. That is, colon cancer and rectal cancer are two distinct cancers requiring different approaches, also depending on their stage. Cancer registries from different countries show huge differences in outcomes after treatment for colorectal cancer, although a trend for improvement is emerging[145]. Fortunately, increasing attention is being paid to quality assurance in cancer care[146]. Indeed, unravelling the effects of treatment on outcome is of utmost importance and, for this, population-based registries and audits are used to critically assess practice.

Surgery

Surgery is the mainstay curative treatment for patients with non-metastasized colorectal cancer. However, outcome is strongly related to the quality of surgery[147,148], the quality of preoperative staging and treatment selection. The dissection should ideally follow the embryological anatomical planes to ensure that the tumour and its principle zone of lymphatic spread are removed. Special attention should be given to the circumferential surgical resection margins[148,149] (FIG. 4). In more-advanced cases of rectal cancer, neoadjuvant treatment (for example, preoperative chemotherapy for T4 colon cancer, and chemoradiotherapy or radiotherapy for locally advanced cancer) can reduce tumour load and even tumour stage, and might be necessary to

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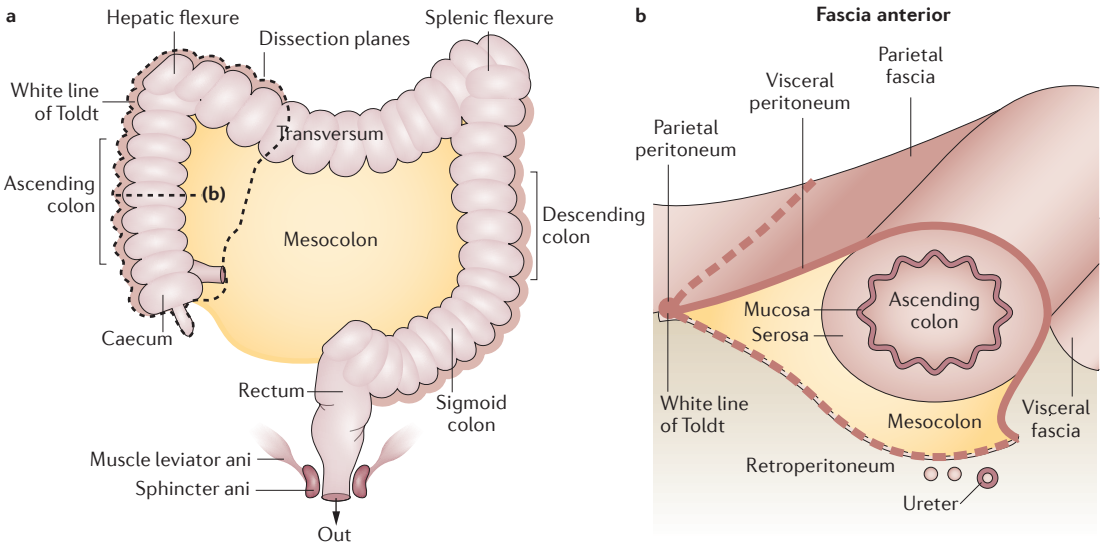

Figure 4 | **Surgical planes for right colon surgery.** **a** | The mesocolon harbours the main blood vessels and draining lymph nodes; surgical planning involves considering the large blood vessels and the resection lines. For the caecum and the ascending colon (before the hepatic flexure), the main vessels are the ileocolic and right colic artery. The transverse colon begins at the hepatic flexure and ends at the splenic flexure; important vessels to consider in this region are the middle colic artery (via the superior mesenteric artery) arcading on the left side, with branches of the left colic artery (inferior mesenteric artery). The descending colon 'bends' at the sigmoid colon (at the left iliac crest) before continuing to the rectum. **b** | In the paracolic grooves, the parietal peritoneum is attached to the lateral border of the visceral peritoneum that overlies the colon and forms the surgical planes referred to as the White line of Toldt, which gives access to the avascular plane above the fascia of Gerota — the fascia on top of the retroperitoneum covering the kidney and ureter — without interfering with the perirenal space or ureters.

optimize the chances for a successful resection[146,148,150]. Thus, a multidisciplinary approach before beginning treatment, based on adequate staging information, is mandatory[147,149,151,152].

Preoperative assessment. When considering a patient for surgery, several factors such as their age, fitness, the perioperative management plan, tumour staging, type of surgery (including resection planes and reconstruction) and quality assurance are important. In terms of age, elderly patients with colorectal cancer have lower overall survival rates than their younger counterparts[145]. Indeed, postoperative mortality rates increase in elderly patients in the immediate postoperative period (that is, the first 30 days) and can double in the first 6–12 postoperative months[153–156]. However, 'elderly patients' as a group are heterogeneous, with varying co-morbidities, degrees of fitness for surgery and risks for postoperative complications. Accordingly, age alone should not be a reason not to operate.

Before patients undergo surgery for colorectal cancer, it is important to be informed about the whole colon to rule out synchronous cancers, which occur in approximately 4% of patients[157]. If preoperative endoscopy was incomplete owing to tumour obstruction, visualization of the colon should either be completed before surgery by CT colonography or endoscopy should be performed in the 3 months following surgical resection[96,157]. Active search for distant metastases in the lungs and liver by means of a chest and abdominal CT is also recommended before surgery[151]. CEA levels are preferably obtained before colorectal cancer surgery to provide a baseline value for postoperative surveillance. Genetic counselling is advised in young patients with a positive family history of colorectal cancer. Fast-track protocols and laparoscopy should be considered to minimize the surgical trauma. In those with obstructive colorectal disease, abdominal CT imaging can also assess for T4. In patients with rectal cancer, preoperative MRI of the pelvis is further recommended for planning purposes, as well as to distinguish the tumour in relation to the mesorectal fascia, and to assess T stage[158]. This information is necessary to select patients with T3c, T3d and T4 tumours for preoperative chemoradiotherapy or radiotherapy.

Colon surgery. Laparoscopic resection of colorectal cancer (FIG. 5) has been shown to be as safe as open surgery[159–161]. As with any surgical procedure, the team needs to be skilled in laparoscopic colorectal surgery and adequately select patients. Contraindications for laparoscopic approach are obesity, previous abdominal surgeries and advanced-stage disease[147,148,160]. If, during the laparoscopic procedure, conversion to open surgery is necessary, the earlier this is done the better the outcomes.

In colon surgery, anatomical planes of the mesocolon with the parietal cavity wall and retroperitoneum should be followed to avoid damage of the ureters, duodenum, pancreas and spleen. Moreover, the mesenteric margins are planned accurately, ensuring proficient

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vascularization of the remnant bowel loops for the anastomosis. A tension-free and torsion-free anastomosis must be created to avoid the feared complication of an anastomotic leakage.

Some patients might require perioperative placement of a stoma, in which the faeces are diverted into a bag on the outside of the body. Loop ileostomy or loop colostomy (FIG. 6), or permanent colostomies, are an essential part of surgery for rectal and sigmoid cancers, either to protect the anastomosis or when the distal rectum is resected. In cases of a rectal obstruction, a loop colostomy is placed on the right (ascending) side; a permanent stoma is placed in cases of an abdominoperineal excision (that is, removal of the anus, rectum and part of the sigmoid colon along with the associated lymph nodes). Each stoma has its advantages and disadvantages; there is no strong argument for superiority of one over the other[162]. Complications of stomas are numerous and cumbersome for the patient, and include prolapse, retraction, dermatitis, leakage, parastomal hernia, obstruction and anastomotic leakage after stoma closure.

In patients presenting with subtotal or total obstruction due to a left-sided (descending) tumour, temporary preoperative stenting can be considered to reduce perioperative morbidity and risks of surgery, but the risk of perforation must be considered[147,148,163]. Colostomy versus stent for palliation could be considered in patients presenting with obstruction and multiple distant metastases[147,148,164].

Rectal surgery. There are several surgical approaches for patients with rectal cancer, depending on the tumour stage. Each technique aims for adequate oncological treatment with complete tumour and local node resection to minimize locoregional and distant recurrence, and optimize disease-free and overall survival. In addition, sphincter preservation and avoidance of a permanent stoma are important additional goals of rectal cancer treatment. Accordingly, a careful, balanced choice of treatment is needed for each individual patient.

For early-stage rectal cancer, advances in minimally invasive techniques have reduced the number of open rectal resections and have improved functional outcome dramatically. Transanal endoscopic microsurgery (TEM) is just such a minimally invasive technique for local tumour excision of well-differentiated T1N0 tumours[165–167]. TEM is associated with better functional outcomes and is performed through the anus (and, therefore, does not leave an abdominal scar or require a stoma), but has the trade-off of higher local recurrences. Thus, TEM is not recommended for tumours that are unlikely to be completely resected, as well as for poorly differentiated tumours given their high risk of local recurrence. The technical complexity of TEM and the high costs of the apparatus led to the introduction of new transanal techniques, in particular transanal minimally invasive surgery. This technique makes use of a disposable multichannel port that is positioned transanally and provides access for conventional laparoscopic equipment[168].

Total mesorectal excision (TME) is the gold-standard surgical technique for rectal tumours staged T1, T2 and favourable T3 (that is, T3 with negative nodal status (T3N0M0) and excluding low-seated rectal cancers, and T3c and T3d disease). In patients with the unfavourable rectal tumours, TME surgery is only recommended after neoadjuvant therapy to reduce the risk of local recurrences. For tumour resection, the anatomical plane

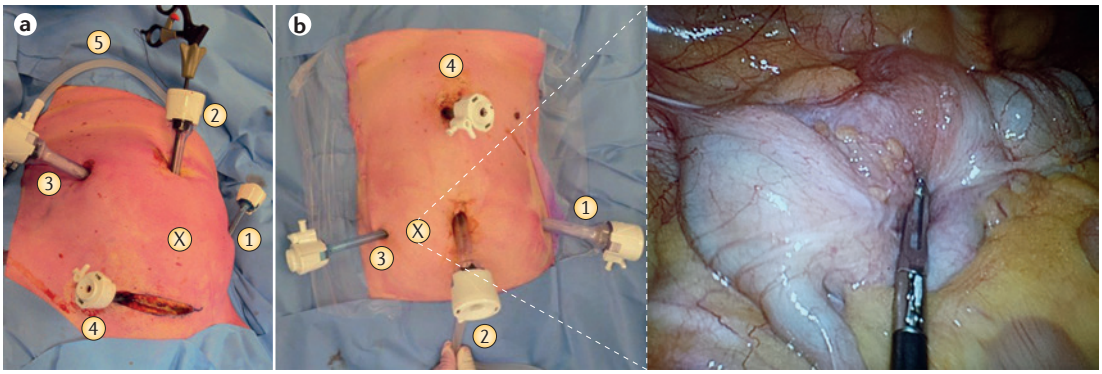

Figure 5 | **Laparoscopic surgery for colorectal cancer.** **a** | A sigmoidectomy can be performed using three to six trocars. The laparoscopic exploration via the supraumbilical trocar (2) is a guide for the location of the other operating trocars. X indicates the tumour location. (1) A 5 mm trocar in the left hypochondrium, for retracting the descending colon. (2) The first trocar to be introduced is a 12 mm trocar through the umbilical port. (3) A 12 mm trocar is used as an optical and operating port. (4) A 5 mm trocar is used for retracting tissue. (5) Carbon dioxide insufflation: pneumoperitoneum. **b** | The number of trocar ports for right colectomy varies depending on the surgeon and operative difficulties. Trocar positioning is also variable, but our standard for a tumour in the caecum (shown in insert; X) is to place: (1) a 12 mm trocar in the left hypochondrium as an optical or operating port. (2) The umbilical port side can be extended to a small laparotomy to extract the dissected colon and perform the extracorporeal anastomosis. (3) A 5 mm trocar is placed for operating and retracting the tissue (ascending colon or caecum). (4) A 5 mm trocar is used to retract the hepatic flexure, to expose the ileocolic and right colic vessels, and perform the division. In both images, the patient's head is at the top, their feet are at the bottom.

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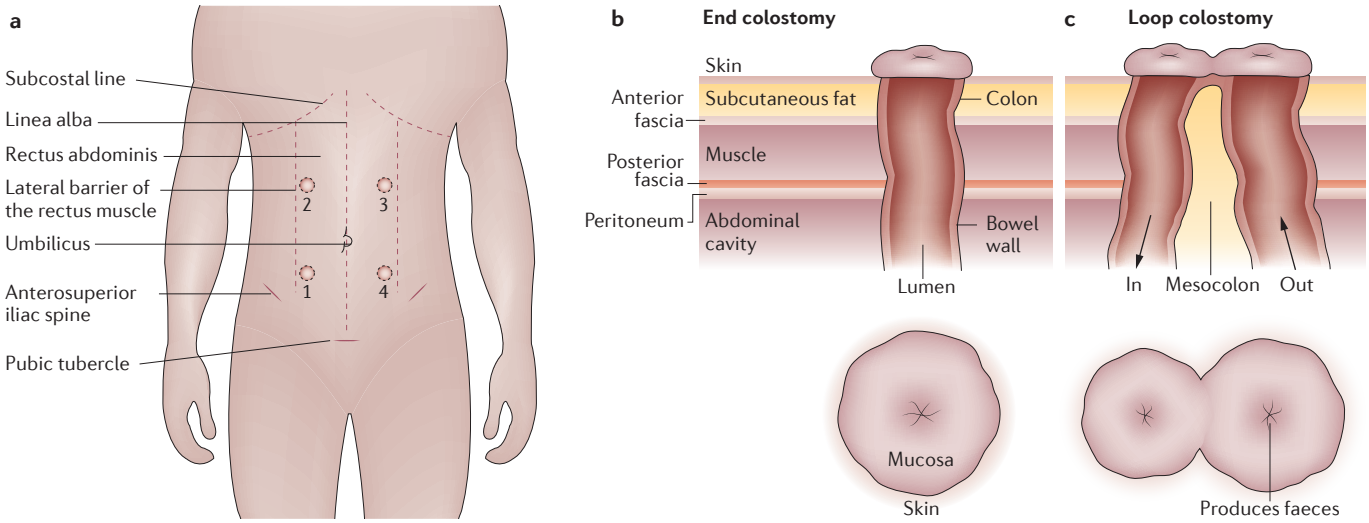

Figure 6 | **Stoma surgery for colorectal cancer.** A colostomy is a surgical procedure in which a stoma (from the Greek for 'mouth' or 'opening') is formed by drawing the healthy end of the colon through an incision in the anterior abdominal wall and suturing it into place. **a** | For stoma positioning (sites 1–4), the subcostal line, lateral border of the rectus abdominus muscle, anterosuperior spine of the ilium, shape of the abdomen and abdominal creases (for example, when trousers and belt are worn, and while sitting) are considered. Ill-placed ostomies result in invalidating leakage and dermatitis. The position of an end ileostomy or a loop ileostomy is preferable in the right hypochondria (site 1); a loop transversostomy is preferred in the right upper quadrant (site 2) to preserve the upper and lower quadrants of the left-side (site 3 and site 4, respectively) for a definitive end colostomy if necessary. **b** | In end stoma formation, the inside of the intestinal loop with the mucosa is placed at the abdominal wall. End stomas provide only one lumen, commonly formed to stay. A well-placed ostomy is about 2–3 cm above the skin, which ensures that the faeces are not in contact with the skin. **c** | In loop stoma formation, two openings are sewn into the skin: afferent (in) and efferent (out). The afferent limb produces the stool and the efferent limb enables the passage of flatus from the distal portion of the bowel.

is the mesorectal fascia and the circumferential resection margin is just outside of this fascia[169–171] (FIG. 7). The intact mesorectum — the fatty envelope that surrounds the rectal bowel wall — includes the draining lymph nodes. Complete resection involves removal of the bowel wall and these nodes. TME can be performed by an open approach as well as laparoscopically; both have similar rates of locoregional recurrence and disease-free and overall survival[160]. Rectal cancer surgery in locally advanced stages is associated with more blood loss; longer operation duration; more concomitant organ resections; and more postoperative complications, such as anastomotic leakage, pelvic floor dysfunction, incontinence and genitourinary problems. However, robotic rectal resection may improve perioperative outcomes, such as reduction of perioperative blood loss, and is being explored[172].

Local recurrences after rectal surgery can be minimized using short-course radiotherapy[173–175], although long-term data (12-year follow-up) showed no effect on overall survival for this approach[176]. The timing of surgery after short-course radiotherapy is important. Surgery after a longer waiting period is associated with fewer complications than immediate surgery after radiotherapy[177]. Importantly, neoadjuvant radiotherapy (that is, before surgery) is associated with an increased risk for low anterior syndrome (a complex of symptoms that include frequent and urgent stools, numerous bowel movements over a few hours, stool incontinence and sexual dysfunction)[178].

Neoadjuvant radiotherapy (or chemoradiotherapy) can be proposed for patients with unfavourable T3 (upper and mid T3c, T3d and low T3b) rectal tumours: those that invade >5 mm into the mesorectal fat and/or approach within 2 mm of the mesorectal fascia as visualized on MRI. T4 and lymph node-positive rectal cancer need short-course fractionated radiotherapy or chemoradiotherapy depending on the patient and tumour characteristics[179]. After the primary radiotherapy or chemoradiotherapy, restaging by means of endoscopy and MRI is recommended for these patients. TME surgery can be possible when the tumour has been downsized sufficiently. In patients with advanced and recurrent rectal cancer, surgery should aim for complete resection and conventional surgical planes may not be adhered to[180]. In some patients, a clinical complete response can be achieved after chemoradiation alone. This raises the question whether surgery can be omitted in these patients. In the largest series of patients treated non-surgically, high response rates were reported[181]. Other series had lower response rates[182,183]. Prospective research will be necessary for this group of patients. Indeed, in 2015, the prospective International Watch & Wait Database (http://www.iwwd.org) for rectal cancer was launched; this initiative aims to assess whether non-surgical approaches are valuable alternatives to surgery.

Finally, a prospective multicentre randomized trial in Japan comparing TME alone versus TME with dissection of lateral nodes was recently completed[184].

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In this study, approximately 10% of patients had pathological pelvic sidewall lymph nodes. Given that preoperative radiotherapy on lateral nodes might not completely eradicate nodal metastases, TME surgery with lateral lymph node clearance might be justified.

Quality assurance. The resected tumour specimen can be used to judge the quality of surgery; if the margin around the specimen is free of cancer cells in both colon and rectal cancer, the surgery is considered high quality[169,170]. The removal and assessment of the lymph nodes is another guide for determining whether the mesocolic or mesorectal resection is adequate[149]. Internationally, removal of 12 lymph nodes is viewed as the cut-off value needed to provide adequate histopathological staging; the lymph nodes can also be used to prognosticate patients. However, the role of procedures to remove the sentinel node (the first lymph node or group of nodes draining the cancer) in colorectal cancer is still unclear.

Furthermore, quality assurance in colorectal cancer care has been defined for several aspects of the care continuum: performing trials, working in multidisciplinary teams, integrated care pathways, shared decision making, auditing cancer care, centralization of complex procedures and international comparison of cancer outcomes. Auditing is a powerful instrument to improve cancer care. Especially for rectal cancer, survival and local recurrences have been shown to drastically improve with national auditing initiatives[146,185,186]. To reduce the differences in Europe, an international, multidisciplinary, outcome-based quality improvement project — European Registration of Cancer Care (EURECCA) — was launched in 2007 (REF. 152). EURECCA aims to capture the best practices and promote uniform structured data collection and analysis to study outcomes of all patients with cancer. Although these analyses are used for feedback for surgeons on the best techniques at hand, volume is another issue that has been shown to improve patient outcome in colorectal cancer management[187].

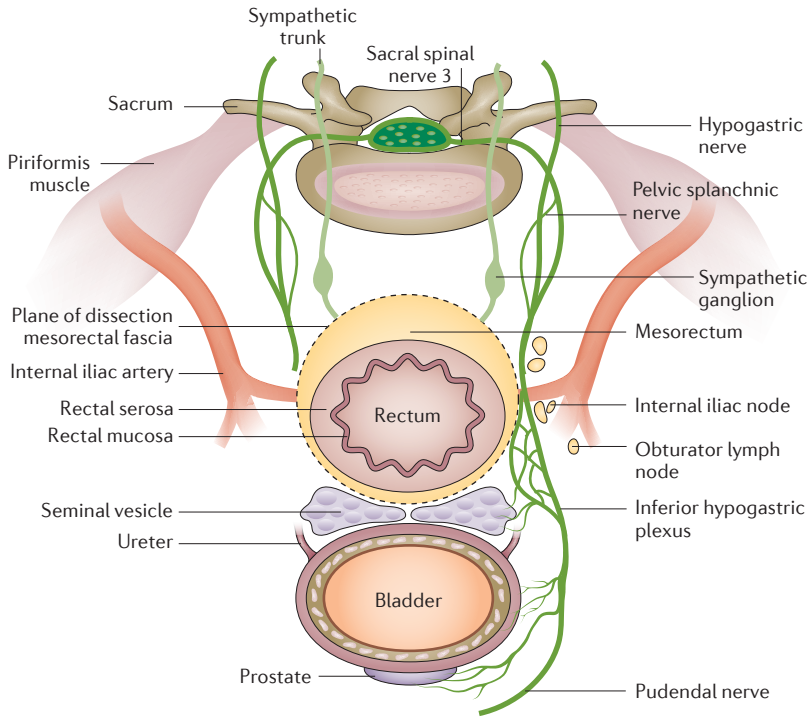

Figure 7 | **Surgical planes for rectal surgery.** The plane between the urogenitoury structures (the prostate, urethra and seminal vesicle in men, and the vagina, uterus and ovaries in women) and the rectum is called Denonvilliers' fascia. The dissection plane of the total mesorectal excision is sharp around the mesorectal fascia and surrounds the mesorectal fat, in which the draining lymph nodes and the rectum are located. The plane is avascular, and avoids the parasympatethic and sympathetic nerves in the pelvic lateral space, which coordinate sexual and urinary function. The superior hypogastric plexus is formed at the level of the sacral promontory, distally dividing in the hypogastric nerves. Together with the parasympathetic erigente nerves, these form the inferior hypogastric (pelvic) plexus, which should not be clamped during surgery to avoid damage. The pudendal nerve innervates the external sphincter, puborectalis muscle and external genitalia, among other structures.

Recovery after surgery. Perioperative protocols such as fast-track protocols and Enhanced Recovery After Surgery have been designed to minimize surgical complications[188,189]. The protocol describes the perioperative care pathway and lists elements of care for patients at various steps in the perioperative process. Considering these elements are supported by evidence to improve recovery time after surgery, Enhanced Recovery after Surgery was first implemented for patients undergoing colectomy[190] and includes elements such as preoperative counselling and bowel preparation, perioperative fluid management and the prevention of ileus (that is, obstipation and intolerance to oral intake), and postoperative glucose control and early mobilization. Indeed, for patients at high risk of postoperative ileus, enteral nutrition should be anticipated even before surgery[191].

Systemic treatments for primary disease

The systemic treatment of patients with colorectal cancer has substantially developed over the past two decades, with major improvements in the neoadjuvant setting for rectal cancer and the adjuvant setting for cancer of the colon.

Neoadjuvant treatment. There is no accepted neoadjuvant treatment for colon cancer. However, for rectal cancer, neoadjuvant radiotherapy or chemoradiotherapy are recommended for intermediate-stage and advanced-stage cancer (for example, very low-tract anteriorly located cT2 lesions, most T3 lesions, some T4a lesions with limited peritoneal involvement, N^+ lesions, cT3 lesions that invade the mesorectal fascia, and cT4a and cT4b lesions with positive lateral nodes) to reduce the rate of local recurrence. The neoadjuvant treatment can either be given as short-course radiotherapy followed by surgery or as chemoradiotherapy with 5-fluorouracil or capecitabine (an oral fluoropyrimidine). Although preoperative radiotherapy or chemoradiotherapy is more effective than postoperative treatment in reducing local recurrence, it does not improve overall survival[176,192]. Strategies that aimed to improve neoadjuvant treatment by intensifying the

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chemoradiotherapy regimen (for example, by combining 5-fluorouracil and oxaliplatin with radiotherapy instead of using 5-fluorouracil with radiotherapy) did not exhibit clear survival benefit, but increased toxicity[193]; more research is needed.

Adjuvant treatment. The cure rate by surgery alone for T3, T4a, T4b and N0M0 colon cancers (Union for International Cancer Control (UICC) stage II) is high, and only approximately 5% of patients benefit from adjuvant chemotherapy. However, guidelines endorsed by European and Japanese societies recommend considering adjuvant therapy in high-risk cases (that is, poorly differentiated tumours; when <12 lymph nodes were resected; in cases with vascular, lymphatic or perineural tumour invasion; in cases with obstructive or perforated tumours; or with pT4 stage tumours)[194]. By contrast, adjuvant treatment is standard for UICC stage III tumours (any T, N1–2 (3 or more positive nodes) and M0); a combination of 5-fluorouracil plus oxaliplatin is used (orally, as in the XELOX protocol (capecitabine and oxaliplatin), or intravenously as in the FOLFOX4 protocol (leucovorin**,** 5-fluorouracil and oxaliplatin)). Currently, no data support that the addition of targeted therapies (such as epidermal growth factor receptor (EGFR)-specific or vascular endothelial growth factor (VEGF)-specific monoclonal antibodies) improves the outcome for patients in the adjuvant setting[194]. Data from pooled analyses suggest that patients >70 years of age might not benefit profoundly from oxaliplatin-based chemotherapy combinations in the adjuvant setting. These patients may benefit from fluoropyrimidine chemotherapy, similar to younger patients[195]. For rectal cancer, postoperative chemoradiotherapy can be applied if no preoperative treatment was given and if certain risk factors (including positive resection margins, perforation in the tumour area or defects in the mesorectum) are present; adjuvant chemotherapy typically uses fluoropyrimidines.

Metastatic disease

The survival of patients with metastatic disease has substantially improved over the past two decades, and a median overall survival of 30 months has been achieved in clinical trials. This improvement in survival can be attributed to the use of chemotherapeutics such as oxaliplatin and irinotecan, the introduction of targeted therapies that address specific properties of the tumour or its microenvironment and the incorporation of multidisciplinary approaches, including surgical resection of liver metastases.

Chemotherapy combinations. The chemotherapy backbone for first-line treatment of metastatic disease is typically a combination of leucovorin, 5-fluorouracil and either oxaliplatin (FOLFOX protocol) or irinotecan (FOLFIRI protocol). 5-Fluorouracil in the FOLFOX regimen can be replaced by capecitabine, but the combination of capecitabine with irinotecan is more toxic than FOLFIRI. Doublet (two chemotherapeutic agents) and triplet (three chemotherapeutic agents) chemotherapy regimens comprising leucovorin, 5-fluorouracil, oxaliplatin and irinotecan (the FOLFOXIRI protocol) have been shown to be efficacious[196]. As compared with single-agent fluoropyrimidine, combination chemotherapy achieves better tumour growth control. However, elderly and frail patients in particular might benefit from a sequential approach with initial single-agent fluoropyrimidine chemotherapy or combined fluoropyrimidine with VEGF-A-targeted therapy (for example, bevacizumab; see below).

Targeted therapies. Alongside these combined chemotherapy regimens, targeted agents are used for metastatic colorectal cancer treatment. In particular, these include three main groups of drugs: monoclonal antibodies against EGFR (cetuximab and panitumumab), monoclonal antibodies against VEGF-A (bevacizumab), and fusion proteins that target multiple pro-angiogenic growth factors (for example, aflibercept) and small-molecule-based multikinase inhibitors (for example, regorafenib).

Approximately 80% of all colorectal cancers express or overexpress EGFR; overexpression correlates with reduced survival and increased risk of metastases. The EGFR tyrosine kinase can be blocked by monocloncal antibodies specific to the extracellular domain of the receptor, decoy receptors that bind to and block the soluble ligand, or small molecules that inhibit receptor dimerization or fit into the ATP-binding pocket of its cytoplasmic tyrosine kinase domain. Most clinical data in colorectal cancer are available for receptor-blocking antibodies, such as cetuximab, which is a recombinant chimeric monoclonal IgG1 antibody, and panitumumab, which is a human EGFR-specific antibody. These antibodies show efficacy in chemotherapy-naive patients, as well as in patients whose tumours are refractory to chemotherapy by improving the overall response rate of the tumours. These strategies also improve progression-free survival (PFS) and even overall survival in patients with metastatic colorectal cancer. However, a prerequisite for the efficacy of these agents is that the tumours do not harbour activating mutations in *KRAS* and *NRAS*[197,198].

RAS is mutated in about half of all patients with colorectal cancers, with codons 12 and 13 being the most commonly affected; codons 61 and 146 of *KRAS* and codons 12, 13 and 61 of *NRAS* are affected to a lesser extent. *HRAS* mutations have so far not been described in colorectal cancer. The mutations render the RAS GTPase constitutively active; active RAS induces a plethora of tumorigenic intracellular signalling pathways. Thus, the RAS status of the tumour must be examined before treatment with EGFR-specific antibodies.

Tumours establish a vascular network of their own once they reach a critical size[199]. Accordingly, a key effector of tumour angiogenesis is the secreted glycoprotein VEGF-A, which binds to VEGF receptor 1 (VEGFR1) and VEGFR2. VEGF-A is produced by many tumour and stromal cells, promotes proliferation and migration of endothelial cells and increases vessel permeability. VEGF is also a growth factor

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Box 4 | **Supportive palliative care for patients with colorectal cancer**

Maintenance of adequate nutrient intake
Surgery and chemoradiotherapy can impair energy intake temporarily or for prolonged periods. Nutritional counselling and dietary monitoring can improve nutritional status, which benefits physical condition.

Pain relief
A substantial proportion of patients with advanced-stage disease require opioid treatment in the last months of their life. In a large UK study[222], approximately 20% of patients received intense opioid combination therapy. Such pain relief requires adequate patient monitoring, physician training and access to a dedicated pain treatment team[222].

Physical condition maintenance
Various studies focusing on patients with advanced-stage colorectal as well as other cancers have reported that exercise programmes can improve the patient's physical condition, mobility and sleep, and reduce fatigue[27,223].

Prevention of avoidable hospital admission
A considerable proportion of hospital admissions in patients with advanced-stage colorectal cancer are potentially avoidable by adequate support at home and hospice access. Potentially avoidable admissions seem to occur more often in elderly patients and those with end-stage disease.

Psychosocial support
Routine assessment at outpatient clinic visits or visits at home can help to identify patients who need specific psychosocial support in a timely manner.

for various tumour cells. VEGF-specific therapies are used in metastatic colorectal cancer, but the precise mechanisms of action are not fully understood. These compounds might act by normalizing the dysregulated tumour vasculature, which would lead to improved tumour oxygenation and delivery of chemotherapy[200]. There are as yet no predictive biomarkers for anti-angiogenic agents.

Bevacizumab has demonstrated efficacy in combination with chemotherapy in the metastatic setting; combined with 5-fluorouracil and irinotecan, bevacizumab significantly improved median PFS and median overall survival of patients in a Phase III trial compared with chemotherapy alone[6]. The addition of bevacizumab also significantly improved median PFS in patients receiving a combination of fluoropyrimidine and oxaliplatin. Interestingly, the combination of bevacizumab and 5-fluorouracil or oxaliplatin also yielded a significant improvement in tumour response, median PFS and median overall survival compared to chemotherapy alone in patients with chemorefractory metastatic disease[201]. Bevacizumab is also one of the few compounds that confer a survival benefit to patients when treatment is continued even after disease progression[202].

Aflibercept also targets angiogenesis. This drug is a recombinant fusion protein that consists of the VEGF-binding portions from the extracellular domains of human VEGFR1 and VEGFR2 fused to the Fc portion of human IgG1. Aflibercept also binds to the placenta growth factor and, therefore, has a somewhat broader anti-angiogenic activity than bevacizumab. Aflibercept has been shown to improve PFS and overall survival when used in combination with FOLFIRI in the second-line setting for treatment of metastatic disease[203].

Metastatic resection. For patients with colorectal cancer who have isolated liver and/or lung metastases that are technically R0 resectable, surgery should be considered — particularly when the metastases are limited in number and size. The 5-year overall survival rate in this group is about 20%[204,205], an impressive figure for metastatic disease. One clinical trial has used a perioperative FOLFOX protocol in this group of patients and has shown an improvement in PFS, but no significant difference in overall survival compared with surgery alone[196].

In the majority of patients with isolated liver and/or lung metastases, a R0 resection cannot be primarily achieved. However, if the metastases can be downsized and combined with adjuvant chemotherapy, the 5-year overall survival rate is similar to R0 resections[206]. In this situation, the most active chemotherapy should be employed to 'convert' the disease to a resectable state; FOLFOXIRI triplet chemotherapy regimen confers high response rate (approximately 60%)[207]. In a *RAS* wild-type population, chemotherapy doublets plus EGFR-specific treatment also results in high response rates. According to data from the FIRE3 study, EGFR-specific antibodies in combination with FOLFIRI seem to induce more pronounced tumour shrinkage than FOLFIRI plus bevacizumab. Thus, this combination is an option if the tumour is *RAS* wild-type[208].

If a more-active treatment with the intent to downsize metastases for secondary resectability is used, it is important to ensure that the tumour is regularly re-evaluated by a multidisciplinary team and resection of metastases is performed at the earliest time point when an R0 resection is possible. In doing so, chemotherapy toxicity is reduced and perioperative morbidity is minimized. The 'disappearance' of the metastases on CT imaging does not necessarily indicate a complete destruction of the metastases in most patients, and makes it difficult for the surgeon to completely resect all lesions[209].

Further considerations. Patients with symptomatic or more-aggressive metastatic disease without chance of secondary metastatic resection benefit from active first-line treatment to achieve optimal tumour control. This can generally be achieved using doublet chemotherapy in combination with a targeted agent such as bevacizumab. In patients with *RAS* wild-type tumours, doublet chemotherapy together with an EGFR-specific antibody treatment can also be used. For those who respond to this 'induction' treatment, or who have a stable disease after 4–6 months of the treatment, the intensity of the treatment should be reduced to avoid excessive toxicity. This is particularly important if a FOLFOX protocol is used to avoid the cumulative neurotoxicity of oxaliplatin. A Phase III trial showed that, after FOLFOX plus bevacizumab induction therapy, a maintenance strategy with fluoropyrimidine chemotherapy plus bevacizumab prolonged PFS without significantly improving overall survival compared to a complete treatment break[210]. Thus, active maintenance, but also treatment discontinuation, can be considered when tumours respond to or are stable during a 4–6-month induction treatment and the tumour burden is not high.

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In the palliative setting, a less-aggressive approach with monotherapy with fluoropyrimidine chemotherapy or a combination of fluoropyrimidine chemotherapy with bevacizumab is possible. Such a strategy requires the patient to be at low risk for rapid deterioration. Upon disease progression, treatment should be escalated and combination chemotherapy (together with bevacizumab) should be used. However, recent data from the FIRE3 and CALGB trials suggest that using a more-intensive treatment in the first-line setting can achieve a median overall survival of about 30 months in a *RAS* wild-type population. Such survival rates have so far not been reported in a sequential setting when treatment starts with just fluoropyrimidine chemotherapy with or without bevacizumab[196].

In the second-line palliative setting, upon further disease progression, chemotherapy should be changed to a regimen that is not used in the first-line setting (either FOLFOX/XELOX or FOLFIRI). A recent study showed that bevacizumab can be given after disease progression and improves overall survival in the second-line setting[202]. Apart from bevacizumab, aflibercept can be used in the second-line setting (in combination with FOLFIRI). Cetuximab or panitumumab can also be used if not previously used and if the tumour is *RAS* wild-type. For these compounds, efficacy beyond progression has not been demonstrated.

In cancers that are refractory to two lines of chemotherapy, EGFR-specific antibodies can be used if the tumour is *RAS* wild-type and an EGFR-specific antibody has not been used previously[197]. Regorafenib is an orally available multikinase inhibitor that has shown efficacy in patients who had previously been treated with all available therapies. Accordingly, it has become the standard in pre-treated patients[211].

Quality of life

Colorectal cancer can manifestly impair quality of life through, for example, direct consequences of the

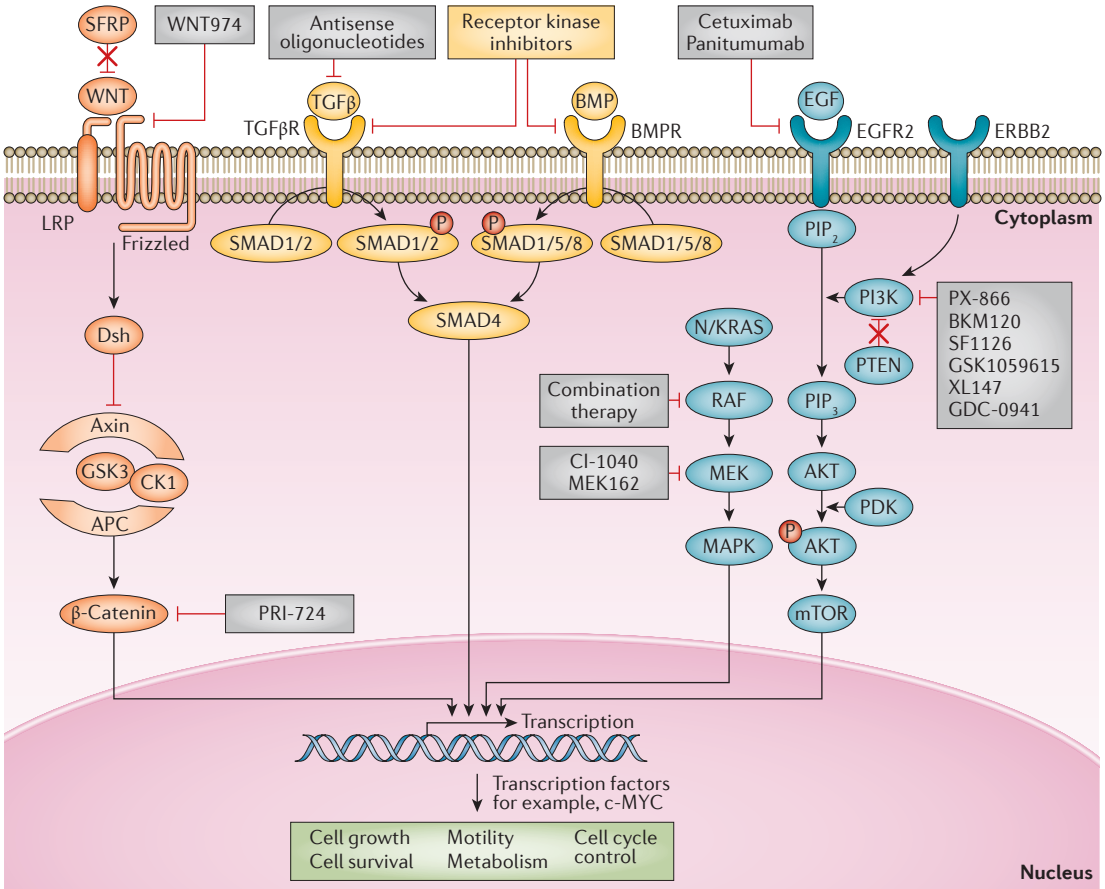

Figure 8 | **Emerging drug targets and drug candidates in colorectal cancer.** The Cancer Genome Atlas and various other genomics projects have identified several novel potential molecular targets and markers in colorectal cancer that might be used to guide specific treatments for subgroups of patients. These targets include the WNT, transforming growth factor-β (TGFβ) and epidermal growth factor receptor (EGFR) signalling pathways. Experimental agents that target these molecules are included in grey boxes. APC, adenomatous polyposis coli; BMP, bone morphogenetic protein; BMPR, BMP receptor; CK1, casein kinase 1; Dsh, Dishevelled; GSK3, glycogen synthase kinase 3; LRP, low-density lipoprotein receptor-related protein; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; P (in a red circle), phosphate; PDK, 3-phosphoinositide-dependent protein kinase; PI3K, phosphatidylinositol 3-kinase; PIP_2, phosphatidylinositol-4,5-bisphosphate; PIP_3, phosphatidylinositol-3,4,5-trisphosphate; PTEN, phosphatase and tensin homologue; SFRP, secreted frizzled-related protein; SMAD, SMAD family member; TGFβR, TGFβ receptor.

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disease, such as abdominal pain, change in bowel movements, blood loss and anaemia, fatigue and weight loss. Furthermore, treatment incurs a burden to quality of life by means of surgery, chemotherapy and radiotherapy, which can be associated in the short term with impaired nutrient intake and physical activity[212]. Indeed, weight loss and reduced physical condition is particularly relevant for elderly patients and those with co-morbidities, and should be adequately monitored during treatment and follow-up care.

Each treatment modality can be associated with further specific adverse effects and complications. One of the most feared surgical complications is the occurrence of leakage of the anastomosis, at the suture line of the intestinal loops after removal of the tumour. This event usually requires further surgical or radiological intervention and is associated with significant morbidity, lengthening of hospital stay and mortality. Other more-common complications of surgery are wound dehiscence (that is, rupture of the wound along a surgical suture) and abdominal scar herniation. Overall, the effect on quality of life does not differ between open and laparoscopic surgery[130]. A range of stoma-related complications can also substantially impair social functioning and quality of life; these can sometimes be managed conservatively, but may require surgical revision of the stoma.

Treatment for rectal cancer is frequently associated with long-term complications. These include faecal incontinence and increased numbers of stools. These complications are well defined in the validated low anterior resection syndrome score[213]. Pelvic floor problems are more frequent in patients with rectal cancer receiving neoadjuvant chemoradiotherapy or radiotherapy[214]. Toxicity is higher after chemoradiotherapy in comparison to radiotherapy alone[215]. Moreover, erectile dysfunction in men and dyspareunia in women are common after rectal cancer treatment[216,217].

With respect to chemotherapy, 5-fluorouracil is usually well tolerated, but oxaliplatin or irinotecan more often give rise to adverse effects, such as neutropenia and diarrhoea. Targeted therapies have important adverse effects that must be considered. For the EGFR-specific antibodies, papulopustular rash and paronychia (infection of the nail) occur within days of treatment, followed by skin atrophy after several weeks and alopecia that occurs within a few months. High-grade skin toxicity can involve pain and secondary infections. Anti-angiogenic agents cause bleeding, arterial thromboembolic events, impaired wound healing, hypertension and proteinuria[6]. Aflibercept increases (to some extent) chemotherapy-induced adverse events, such as diarrhoea, neutropenia and asthenia[203].

Metastatic disease can give rise to a range of additional symptoms that affect quality of life, such as cachexia, loss of appetite, anaemia, liver failure, biliary obstruction and impaired pulmonary function[218]. These symptoms relate to duration of survival to some extent[218]. A range of interventions, with focus on the management of pain, improvement of food intake and maintenance of physical activity benefit individual patient groups. For example, a systematic review of three studies reported that increased physical activity improved quality of life in patients with colorectal cancer[219]. Clinicians are aware of the potential major impact of colorectal cancer on many aspects of quality of life, and individualized options to improve this should be given[220] (BOX 4).

Outlook

Over the past several decades, colorectal cancer has become one of the most common cancers, and its incidence is expected to continue to increase in coming years. Despite major advances in treatment, mortality from colorectal cancer remains high and 40–50% of patients eventually die because of their disease. As discussed above, colorectal cancer arises as a result of environmental factors and genetic factors cooperating to generate colon polyps that progress to colorectal cancer. The polyp to cancer progression sequence is primarily driven at the cellular level by gene mutations and epigenetic alterations, and is now recognized to be a heterogeneous process. It is widely anticipated that insights into the unique gene mutations will lead to more-precise and individualized care for people with polyps and cancers, which will be guided by the molecular characterization of the individual's colon tumour.

The future of cancer surgery for colorectal disease is aimed at minimizing surgical trauma and preserving organ function. Population-based studies to unravel the effects of multimodal strategies for elderly patients and those with co-morbidities need to be undertaken. High-precision imaging will lead to image-guided techniques. Each patient is unique and surgery needs to be tailor-made, aimed at complete removal for cure. Feedback on performance is required to keep on improving our efforts.

Chemotherapy has made substantial progress in recent years. We can now individualize the treatment according to the type of metastases (isolated liver or lung metastases, resectable or primarily not resectable), the *RAS* mutation state of the tumour and the response to a given treatment (for maintenance strategies or therapeutic breaks). The Cancer Genome Atlas and various other genomic projects have identified several novel potential molecular targets and markers for colorectal cancer that might be used to guide more-specific treatments for subgroups of patients (FIG. 8).

These developments in surgery and chemoradiotherapy or radiotherapy will improve and further individualize treatment in the near future, which should prolong the survival of patients. However, the largest impact on incidence and mortality will come from widespread organized population screening. Screening programmes should aim for optimal uptake and smart use of available resources. Opportunistic screening programmes must be replaced by organized screening, together with the incorporation of strict quality-assurance measures. With such an approach, the foreseen rapid rise in colorectal cancer incidence and mortality could be reversed in the coming decade.

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Author contributions

Introduction (E.J.K.); Epidemiology (T.W. and E.J.K.); Mechanisms/pathophysiology (W.M.G.); Diagnosis, screening and prevention (J.J.S., E.J.K. and D.L.); Management (P.G.B., C.J.H.v.d.V., T.S. and E.J.K.); Quality of life (E.J.K.); Outlook (All authors); Overview of the Primer (E.J.K.).

Competing interests

T.S. has received honoraria for lectures or advisory boards from Roche, Merck-Serono, Amgen and Bayer. All other authors declare no competing interests.

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