

# Colorectal cancer



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Several decades ago, colorectal cancer was infrequently diagnosed. Nowadays, it is the world's fourth most deadly cancer with almost 900 000 deaths annually. Besides an ageing population and dietary habits of high-income countries, unfavourable risk factors such as obesity, lack of physical exercise, and smoking increase the risk of colorectal cancer. Advancements in pathophysiological understanding have increased the array of treatment options for local and advanced disease leading to individual treatment plans. Treatments include endoscopic and surgical local excision, downstaging preoperative radiotherapy and systemic therapy, extensive surgery for locoregional and metastatic disease, local ablative therapies for metastases, and palliative chemotherapy, targeted therapy, and immunotherapy. Although these new treatment options have doubled overall survival for advanced disease to 3 years, survival is still best for those with non-metastasised disease. As the disease only becomes symptomatic at an advanced stage, worldwide organised screening programmes are being implemented, which aim to increase early detection and reduce morbidity and mortality from colorectal cancer.

## Epidemiology

Colorectal cancer accounts for approximately 10% of all annually diagnosed cancers and cancer-related deaths worldwide.<sup>1</sup> It is the second most common cancer diagnosed in women and third most in men. In women, incidence and mortality are approximately 25% lower than in men. These rates also vary geographically, with the highest rates seen in the most developed countries (figure 1). With continuing progress in developing countries, the incidence of colorectal cancer worldwide is predicted to increase to 2·5 million new cases in 2035.<sup>1,3</sup> Stabilising and decreasing trends tend to be seen in highly developed countries only. These have been primarily attributed to nationwide screening programmes and increased uptake of colonoscopy in general, although lifestyle and dietary changes might also contribute.<sup>4</sup> In contrast, a worrying rise in patients presenting with colorectal cancer younger than 50 years has been observed, especially rectal cancer and left-sided colon cancer.<sup>5–8</sup> Although genetic, lifestyle, obesity, and environmental factors might have some association, the exact reasons for this increase are not completely understood.

## Risk factors

In epidemiological studies, male sex and increasing age have consistently shown strong associations with disease incidence. Both hereditary and environmental risk factors play a part in the development of colorectal cancer (figure 2). Positive family history seems to have a part in approximately 10–20% of all patients with colorectal cancer,<sup>9</sup> with varying risk depending on number and degree of affected relatives and age of colorectal cancer diagnosis.<sup>10</sup> Based on twin and family studies, estimates for heritability of colorectal cancer range from 12% to 35%.<sup>11,12</sup> Although several genome-wide association studies of colorectal cancer have successfully identified cancer susceptibility genes (common single-nucleotide polymorphisms) that are associated with colorectal cancer risk, most factors causing heritability are still elusive and subject to further study.<sup>13</sup> A subgroup of approximately 5–7% of the patients with colorectal cancer

is affected by a well defined hereditary colorectal cancer syndrome.<sup>14</sup> Making the diagnosis is important as it provides the patient an optimal surveillance strategy to prevent colorectal cancer, an optimal surveillance for extracolonic cancers if applicable, optimal treatment in case of incident colorectal cancer, and appropriate surveillance advice for relatives at risk. Moreover, patients with long-standing inflammatory bowel disease and those with a previous history of colorectal cancer or adenomas are at an increased risk for colorectal cancer and require adequate surveillance.<sup>15–17</sup>

Hereditary colorectal cancer syndromes can be subdivided as non-polyposis (Lynch syndrome and familial colorectal cancer) and polyposis syndromes. The polyposis syndromes are more easily recognised as the physician is alerted by the number of polyps. The type of polyps might lead directly to the appropriate diagnosis. Lynch syndrome, however, is frequently missed as those patients have few adenomas and those adenomas morphologically resemble sporadic lesions. Therefore, a systematic molecular analysis of tumour tissue in patients of any age or a subgroup of those younger than 70 years is now used to improve the diagnosis of this genetic syndrome. Lynch

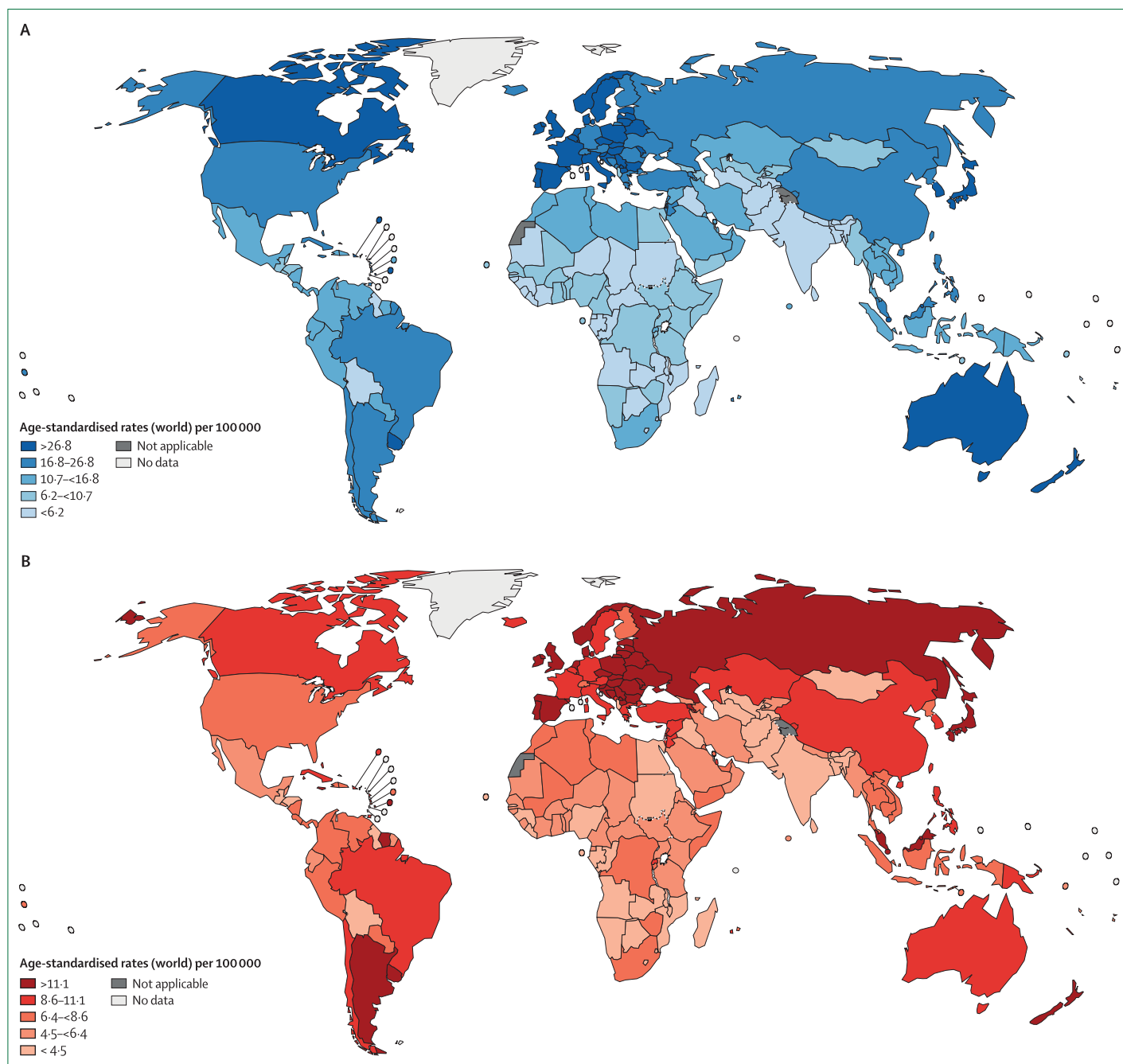
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## Search strategy and selection criteria

We identified articles for this Seminar by searches of MEDLINE, Embase, and Cochrane databases, and references from relevant articles, with various combinations of the search terms “adenoma”, “colon cancer”, “colorectal cancer”, “colorectal neoplasms”, “colorectal tumor”, “chromosomal instability”, “diagnosis”, “drug therapy”, “epidemiology”, “genomic instability”, “microsatellite instability”, “molecular pathogenesis”, “morbidity”, “mortality”, “prevention”, “prognosis”, “quality of life”, “radiotherapy”, “rectal cancer”, “risk factors”, “screening”, “serrated neoplasia”, “surgery”, “survival”, and “therapy”. We excluded articles solely reported in the form of abstracts or meeting reports. We included articles published only in English between Jan 1, 1980, and May 31, 2019.



**Figure 1: Age-standardised cancer incidence (A) and mortality (B) rates for countries in five continents according to the latest WHO International Agency for Research on Cancer figures<sup>1</sup>**

Age-standardised rates (ASR) are summary measures of the rate that a population would have if it had a standard age structure. Standardisation is necessary when comparing several populations that differ with respect to age because age has a powerful influence on the risk of being diagnosed with or dying from cancer. Dotted and dashed lines on maps represent approximate borderlines for which there might not yet be full agreement. Reproduced from Ferlay et al,<sup>2</sup> by permission of the International Agency for Research on Cancer.

syndrome is caused by a dysfunction of the DNA mismatch repair system, characterised by expansion or contraction of microsatellite regions in the tumour compared with healthy tissue, called microsatellite instability (MSI), and found at molecular analysis. Also, these tumours show deficiency of mismatch repair proteins on immunohistochemistry. However, MSI is

not specific for Lynch syndrome, and approximately 15% of sporadic colorectal cancers also demonstrate MSI. Because of the accelerated adenoma–carcinoma pathway, patients with Lynch syndrome are advised to undergo frequent, 1–2 yearly, colonoscopy from age 20 years to 25 years.<sup>14,18</sup> Besides, these patients are also at an increased risk for endometrial cancer and other malignancies (eg,

cancers of the small bowel, stomach, ovaries, renal pelvis and ureter, and hepatobiliary system).

Several, largely modifiable, environmental lifestyle factors increase colorectal cancer risk, such as smoking,<sup>19</sup> excessive alcohol intake,<sup>20</sup> increased bodyweight,<sup>21</sup> and red and processed meat intake.<sup>22</sup> Although type 2 diabetes and colorectal cancer share some of the same risk factors (such as obesity and physical inactivity), individuals with type 2 diabetes maintain their increased risk after correcting for these factors.<sup>23</sup> Colonic microbiota research suggests that infection with specific bacterial species, such as *Fusobacterium nucleatum* and *Bacteroides fragilis*, might increase the risk for colorectal cancer.<sup>24–26</sup>

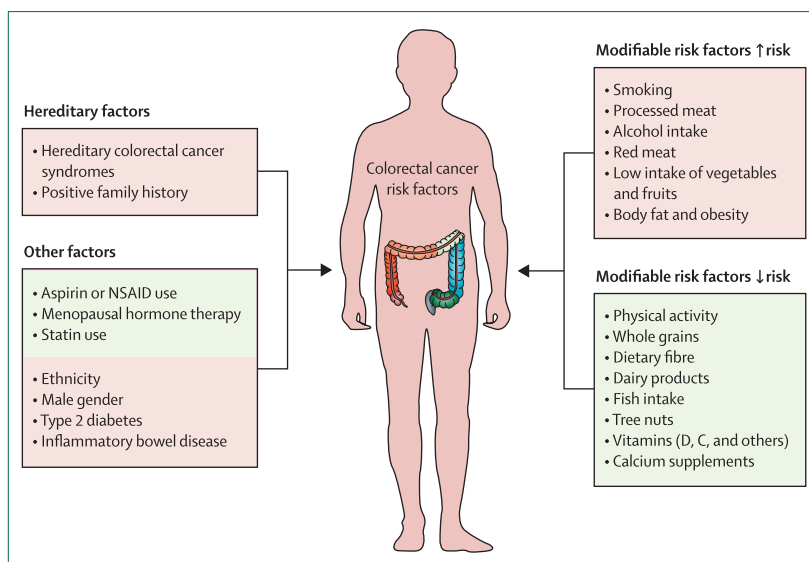
## Pathogenesis

Most cancers arise from a polyp. This process begins with an aberrant crypt, evolving into a neoplastic precursor lesion (a polyp), and eventual progressing to colorectal cancer over an estimated 10–15 year period. The cell of origin for the majority of colorectal cancers is currently assumed to be a stem cell or stem-cell-like cell.<sup>27,28</sup> These cancer stem cells are the result of progressive accumulation of genetic and epigenetic alterations that inactivate tumour-suppressor genes and activate oncogenes. Cancer stem cells reside in the base of the colonic crypts and are essential for the initiation and maintenance of a tumour.<sup>27,28</sup> Investigating the regulatory mechanisms that control the growth of these cancer stem cells is a promising area of investigation for possible therapeutic agents and preventive treatment.<sup>29,30</sup>

Globally, there are two major distinct precursor lesion pathways (figure 3): the traditional adenoma–carcinoma pathway (also referred to as the chromosomal instability sequence) leading to 70–90% of colorectal cancers, and the serrated neoplasia pathway (10–20% of colorectal cancers). These pathways represent distinct multiple genetic and epigenetic events in a rather sequential order.<sup>32</sup> Chromosomal instability phenotypes typically develop following genomic events initiated by an APC mutation, followed by RAS activation or function loss of TP53. Conversely, the serrated neoplasia pathway is associated with RAS and RAF mutations, and epigenetic instability, characterised by the CpG island methylation phenotype, leading to microsatellite stable and unstable cancers. Further genome-wide studies have also identified newer markers and phenotypic subtypes on the basis of mutations present (eg, presence of polymerase-ε or POLE mutations or mismatch repair deficiency [dMMR]) leading to a hypermutated phenotype.

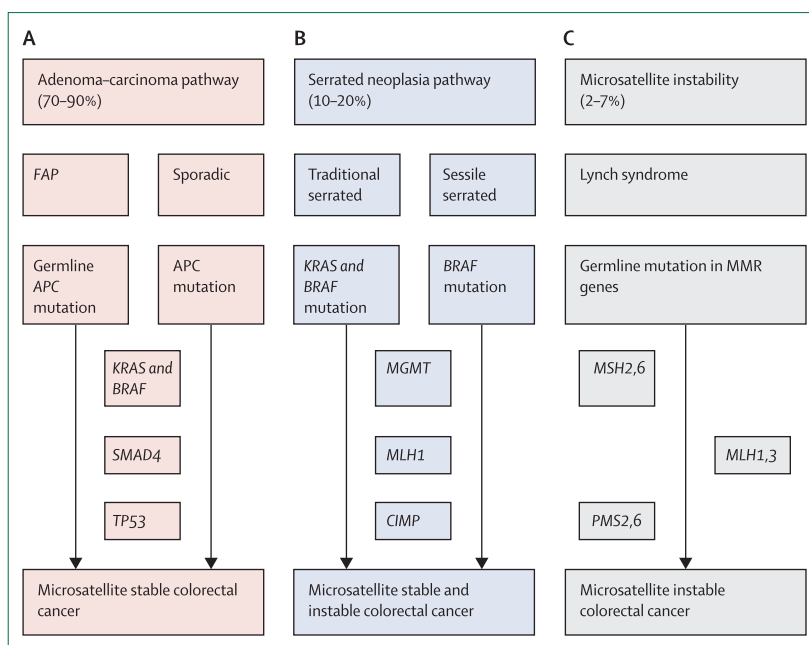
## Left-sided versus right-sided disease

Molecular features of right-sided (proximal) colon cancers are different when compared with left-sided (distal) colon cancers and rectal cancers (figure 4). Apart from molecular differences, embryological, biological, and anatomical differences exist between left-sided and



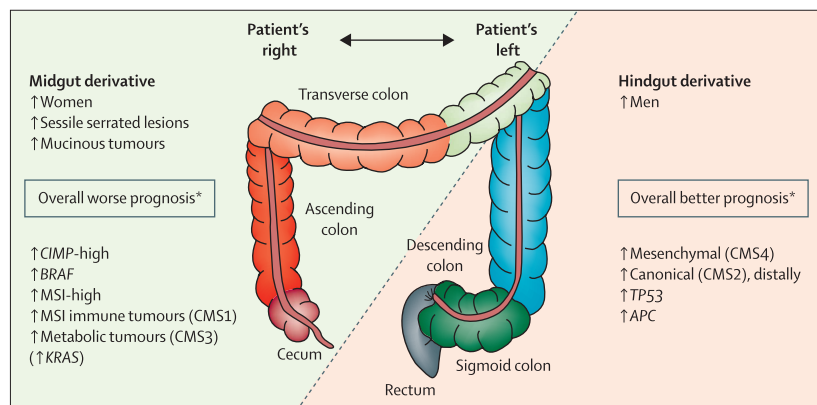
**Figure 2: List of modifiable and non-modifiable risk factors for colorectal cancer**

Although data for some risk factors (eg, smoking and processed meat consumption) are convincing, other factors (eg, menopausal hormone therapy) exist, for which data are more suggestive. NSAIDs=non-steroidal anti-inflammatory drugs.



**Figure 3: Colorectal cancer development pathways**

Conventional adenomas progress by the sequential accumulation of genetic mutations and chromosomal instability causing microsatellite stable tumours (A). The sessile serrated neoplasia pathway is often, but not always, initiated by genetic mutation of BRAF or KRAS genes but then progresses by methylation of tumour suppressing genes (CpG island methylator phenotype [CIMP]; B). Both microsatellite stable and unstable tumours can result, depending on the genes epigenetically silenced as the lesions progress. Microsatellite instability is the result of defective DNA repair through inactivation of mismatch repair genes and is epitomised by the germline mutation of mismatch repair genes that is also seen in Lynch syndrome (C). There is some overlap between microsatellite stable and unstable pathways. Comparatively, little is known about the traditional serrated pathway, but evidence is accumulating that this is a distinct molecular subtype. Adapted from reference 31, by permission of East and colleagues. FAP=familial adenomatous polyposis.



**Figure 4: Differences in right-sided versus left-sided colon and rectum**

Simplistic schematic representation of right-sided colon (cecum, ascending colon, hepatic flexure) versus left-sided colon (splenic flexure, descending colon, sigmoid, rectosigmoid) and rectum representing a continuum of changes secondary to different embryological origin. Arbitrarily, two thirds of transverse colon are considered right-sided. The figure is a simplistic cartoon reflecting the heterogeneity and the continuum of changes seen in patients with colorectal cancers. \*Please note that the prognosis of overall being worse for right-sided colon cancers does not apply to all stages of cancers and is primarily seen in metastatic setting with respect to response to anti-EGFR and anti-VEGF therapies. With more of the right-sided tumours being MSI-high, although historically these tumours had worse prognosis because of being relatively resistant to chemotherapy, they now have immunotherapy as an option. Therefore, the outcomes for these tumours are evolving and changing. CMS=consensus molecular subtypes. MSI=microsatellite instability.

right-sided colorectal cancer. Sidedness has a key role, particularly in the metastatic setting and is increasingly being recognised as a predictive marker of response to anti-EGFR drugs.<sup>33,34</sup>

### Consensus molecular subtypes

In 2014, on the basis of gene expression, colorectal cancer was classified into four molecular subtypes (consensus molecular subtypes [CMS] 1–4).<sup>35</sup> The genes or pathways implicated are unique to each CMS (MSI immune [CMS1], canonical [CMS2], metabolic [CMS3], and mesenchymal [CMS4]). Right-sided colorectal cancers are more often MSI-immune and metabolic tumours.<sup>36</sup> Although the sidedness and mutation status (*RAS* or *RAF*) of tumours are factors that help to choose systemic treatments, the CMS classification is being explored in clinical trials as a prognostic or predictive marker.

## Diagnosis

### Clinical symptoms

Patients can present with a wide range of signs and symptoms such as occult or overt rectal bleeding, change in bowel habits, anaemia, or abdominal pain. However, colorectal cancer is largely an asymptomatic disease until it reaches an advanced stage. By contrast, rectal bleeding is a common symptom of both benign and malignant causes, and therefore additional risk factors might be needed to help identify those people who should undergo further investigation by colonoscopy. New onset rectal bleeding should generally prompt colonoscopy in individuals aged 45 years or older. In younger patients, additional factors are used to identify those at highest risk for colorectal cancer

(eg, having a family history of colorectal cancer, change in bowel habits, unexplained weight loss, and blood mixed with the stool as opposed to blood on the surface of the stool).<sup>37</sup>

### Endoscopy

For diagnosing colorectal cancer, colonoscopy is the method of choice. Colonoscopic identification of advanced lesions is relatively straightforward, but early colorectal cancers might appear as very subtle mucosal lesions (eg, an innocuous flat laterally spreading polyp; figure 5). To ensure detection, these lesions require careful and complete mucosal inspection and optimal bowel preparation. These and other factors, like adenoma detection by an endoscopist, have been associated with the risk of developing colorectal cancer after colonoscopy (postcolonoscopy colorectal cancers) and are used as quality indicators for colonoscopy.<sup>38–40</sup>

### Imaging

CT colonography is used as a complementary imaging method for the diagnosis of polyps and colorectal cancer (eg, after incomplete or inadequate colonoscopy). Imaging methods however are mostly used for accurate locoregional and distant staging. In rectal cancer, locoregional staging is routinely done by MRI, and guides further treatment decisions.<sup>42</sup> Locoregional staging for colon cancer has become more important as neoadjuvant systemic therapy has the potential to downsize locally advanced tumours. CT scans are routinely used for this purpose, although with restrictive accuracy.<sup>43</sup> Distant staging of liver and lungs is routinely done with CT, with an increasing role of MRI for further determination of liver lesions. PET-CT imaging is increasingly being used but its exact role for staging and assessment of disease burden in advanced cases is still debated.<sup>44</sup>

### Laboratory

In addition to obtaining a complete blood count, all guidelines recommend checking carcinoembryonic antigen concentrations at the time of diagnosis.<sup>45</sup> An elevated baseline carcinoembryonic antigen concentration is associated with worse prognosis, and concentrations that do not normalise in the postoperative phase might indicate residual disease.

### Pathology

Histology is still the basis for pathological staging and subsequent management. Besides the classic TNM staging, histological subtyping, grading, and histological assessment of lymphatic, perineural, and venous invasion, the value of a multitude of tumour-based markers (including mismatch-repair testing and immunoscore) is increasingly being recognised.<sup>44,46–48</sup> Universal mismatch-repair testing is being adopted not only for the identification of Lynch syndrome, but also because of implications for adjuvant fluoropyrimidine-based therapy,



and the potential of identifying patients with metastatic colorectal cancer who would benefit from immunotherapy.<sup>48</sup> Mismatch–repair testing is done by immunohistochemistry, and most institutions resort to PCR-based MSI testing only if the results are equivocal. *RAS* and *RAF* mutations regulate proliferation, apoptosis, and angiogenesis and have an evolving role as prognostic and predictive markers in the treatment of colorectal cancer.<sup>49–51</sup>

## Management

### Endoscopic treatment

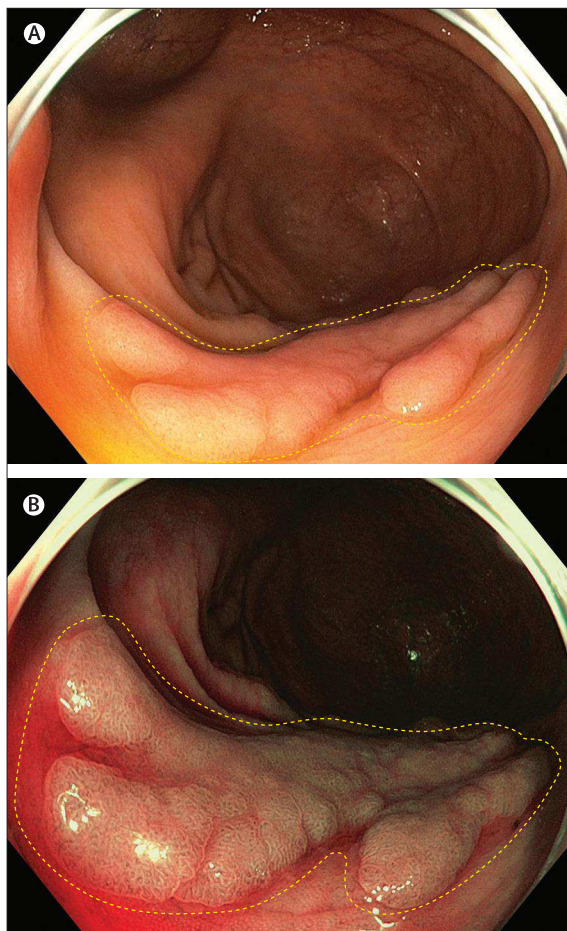
Some early cancers are amenable to local treatment only. The incidence of these early colorectal cancers have increased because of colorectal cancer screening programmes. Upon diagnosis, malignant polyps might be resected endoscopically in an en-bloc manner, thus allowing for a precise assessment of high-risk features (submucosal invasion depth, differentiation, lymphatic invasion, and tumour budding) and deep and lateral margins by the pathologist. The decision on adjuvant surgery with mesenteric lymphadenectomy is challenging and depends on the estimated oncological and operative risk, and the preferences of the patient.

Depending on its size, appropriate endoscopic resection techniques for T1 cancers (figure 6) are en-bloc endoscopic mucosal resection, endoscopic submucosal dissection, and endoscopic full-thickness resection. The last two techniques should be considered when there is a high suspicion of superficial submucosal invasion, to be assessed on the basis of mucosal pit pattern analysis, polyp morphology, and other endoscopic aspects of the colorectal lesion.<sup>52–54</sup> These resection techniques require substantial technical skills<sup>55</sup> and should be done in centres with such expertise.<sup>56</sup> Doctors and patients should be aware that endoscopic resection is a viable option for many large polyps and T1 cancers. Several studies have suggested that endoscopic removal is both safer and less expensive than surgery.<sup>57–60</sup> Unfortunately, many patients with such a lesion are still referred for surgery without discussion of endoscopic resection options.<sup>61,62</sup>

### Surgical treatment

Surgery is the cornerstone of curative intent treatment. Quality of colorectal cancer resection is crucial and can be assessed with objective parameters. Postoperative imaging studies have shown that surgical quality could be further optimised,<sup>63</sup> stressing the importance of training and specialisation of surgeons.

Surgery for colon cancer has been optimised by the use of sharp dissection along the embryological planes within the mesofascial interface, according to the so-called complete mesocolic excision principle. A still controversial topic is the extent of lymphadenectomy, because no evidence shows the beneficial impact of extensive (D3) versus more limited (D2) dissection on

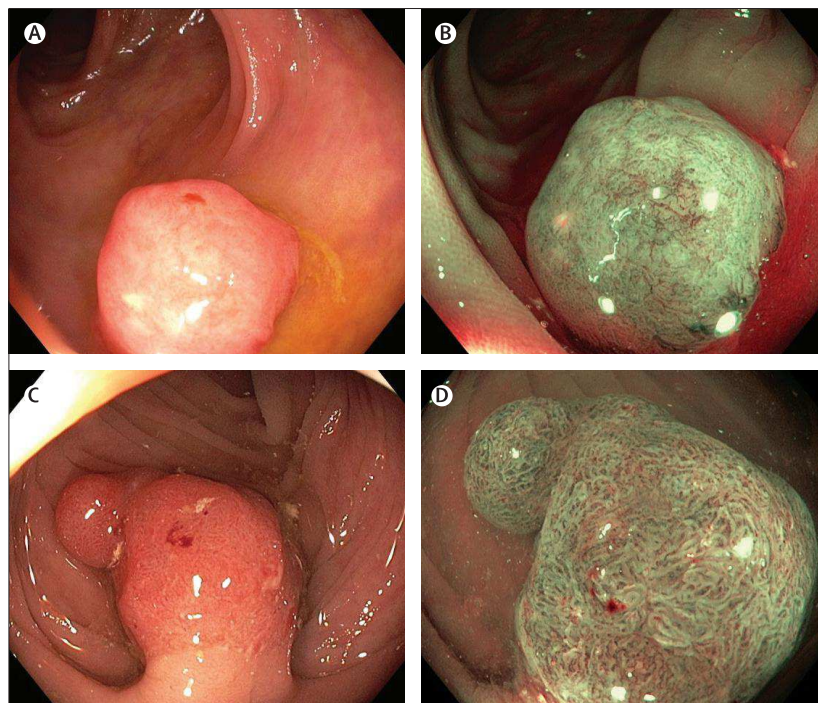


**Figure 5: High-definition images of a flat, lateral-spreading polyp**  
(A) High-definition white light image. (B) Close-up view, using narrow band imaging—an endoscopic imaging technique that highlights the mucosal surface and can help with detection and differentiation of colonic lesions. The yellow dotted lines indicate the borders of the lesion.

oncological outcome and it might increase morbidity.<sup>64</sup> Laparoscopy has become the standard technique for colon cancer in many countries worldwide, with proven short-term benefits in randomised trials and population studies.

Surgery for rectal cancer is more complex related to the accessibility and intricate anatomy of the pelvis. Total mesorectal excision is the standard oncological approach to rectal cancer, and extent of resection further depends on involvement of the sphincter complex and other surrounding structures. In rectal cancer, the role of conventional multiport laparoscopy is still debated.<sup>65</sup> Transanal minimally invasive total mesorectal excision and robot-assisted laparoscopic total mesorectal excision might improve results for mid-rectal and distal rectal cancer, but these techniques require a high degree of expertise and still have to prove additional value.<sup>66,67</sup>

Colorectal cancer can also present as an emergency with obstruction or perforation. Colonic obstruction can be relieved by a decompressing colostomy or endoscopic



**Figure 6: White light and narrow band imaging of T1 colorectal cancer**  
Corresponding photographs of T1 colorectal cancers with white light (A and C) and narrow band imaging (B and D). Narrow band imaging can help with differentiating between the different subtypes of colonic lesions (adenomas, hyperplastic polyps), and can also help with finding areas within polyps that are suspicious for invasive growth (eg, T1 cancer).

stenting, after which staging and patient status can be optimised. Decision for stenting should be multidisciplinary since it can limit the later use of anti-VEGF drugs due to risk of perforation.

### Radiotherapy for rectal cancers

As opposed to postoperative radiotherapy, several historical trials have shown the benefit of preoperative radiotherapy in reducing the risk of local recurrence.<sup>68</sup> The absolute risk reduction that is achieved by preoperative radiotherapy depends on the clinical stage and quality of surgery. This evidence has informed a tailored approach, with radiotherapy reserved for intermediate to high-risk cancers on the basis of MRI staging.<sup>69</sup>

Chemoradiotherapy is the most used therapy, with a dose of 45–50 gray in 25–28 fractions, and with a fluoropyrimidine as radiation sensitiser.<sup>70</sup> Downsizing is achieved in most patients and complete response occurs in at least 15–20%. Time interval to surgery is still a subject of debate, but is generally 8–10 weeks.<sup>71,72</sup> Dose intensification of radiotherapy is the subject of studies, including addition of a local boost (NCT01951521). Short-course radiotherapy (5×5 Gy) has been a popular schedule in Europe for resectable rectal cancer. Although historically followed by immediate surgery, a 4–8 week interval with the advantage of downsizing is a valid alternative; also for selected patients with locally advanced tumours or oligometastatic disease.<sup>73,74</sup>

The observation of complete clinical response after chemoradiotherapy has initiated rectal preserving treatment approaches, with omission of radical surgery and close surveillance—the so-called watch-and-wait strategy. Concerns have been expressed about the oncological safety, but data support such a strategy in selected patients with sustained complete clinical response.<sup>75</sup> Patients are increasingly asking for rectal preserving options, and the explicit patient preferences hamper conduct of randomised trials. If regrowth is detected in a timely way with an intensive surveillance programme with rectal examination, endoscopy, and MRI, salvage surgery is often achievable. Nevertheless, patients should know about uncertainty of recurrence during surveillance and functional impairment of the preserved rectum by chemoradiotherapy.

There is a paradoxical trend towards application of radiotherapy for early stage rectal cancers, otherwise being treated with total mesorectal excision surgery alone. This approach results in preservation of the rectum in about 50–60%.<sup>76,77</sup> However, the remainder of patients who ultimately need radical surgery are overtreated with radiotherapy.<sup>78</sup>

### Local treatment options for metastatic disease

One of the important developments in stage IV colorectal cancer is the increasing number of available local therapies for an increasing number of patient categories, aiming at long-term disease control and possible cure. Technical innovations have resulted in better local salvage of metastatic tumour localisations at acceptable morbidity.<sup>78</sup> Although never proven in randomised trials, the value of eradicating or ablating restricted metastatic tumour localisations is generally agreed upon.

Liver surgery has evolved towards low-risk surgery for even extensive disease. Resection of liver metastases is increasingly considered within a multimodality approach with systemic treatment and other local ablative techniques.<sup>79</sup> Radiofrequency ablation is still the preferred local ablative therapy for the liver, which can also be applied percutaneously. For larger lesions and those close to vascular structures, microwave ablation or stereotactic radiotherapy might be good alternatives. Local treatment of lung metastases is more controversial, with resection, stereotactic radiotherapy and radiofrequency ablation as available. Peritoneal metastases have long been considered as an untreatable condition. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy have resulted in improved survival in a subset of patients with limited disease,<sup>80</sup> although the role of hyperthermic intraperitoneal chemotherapy in addition to cytoreductive surgery is unclear.

### Systemic treatment

As an adjuvant therapy fluoropyrimidine-based chemotherapy improves survival in resected stage III, and in a



subset of stage II colon cancers (eg, high-risk T4, poorly differentiated). Several landmark studies, including the MOSAIC study,<sup>81</sup> established the addition of oxaliplatin to a fluoropyrimidine (fluorouracil or capecitabine) as the new standard.<sup>82–84</sup> The main drawback of the addition of oxaliplatin chemotherapy is the development of cumulative sensory neuropathy. For stage II tumours, presence of dMMR is a good prognostic sign and these patients do not benefit from adjuvant therapy.<sup>85,86</sup> Rectal cancers are treated similarly, although the value of adjuvant chemotherapy in patients who have received preoperative chemoradiotherapy is controversial.<sup>87</sup> Additions of other agents that work well in metastatic settings (eg, irinotecan and biologics) have not worked in the adjuvant setting of rectal cancer treatment.<sup>88–92</sup>

For years, 6 months of adjuvant chemotherapy was the standard of care. However, the IDEA collaboration, drawing on six randomised, phase 3 clinical trials, showed that limiting adjuvant chemotherapy to 3 months might reduce toxicity (eg, less cumulative neuropathy) without impairing treatment efficacy for at least the low-risk stage III colon cancers (not T4 or N2).<sup>93</sup>

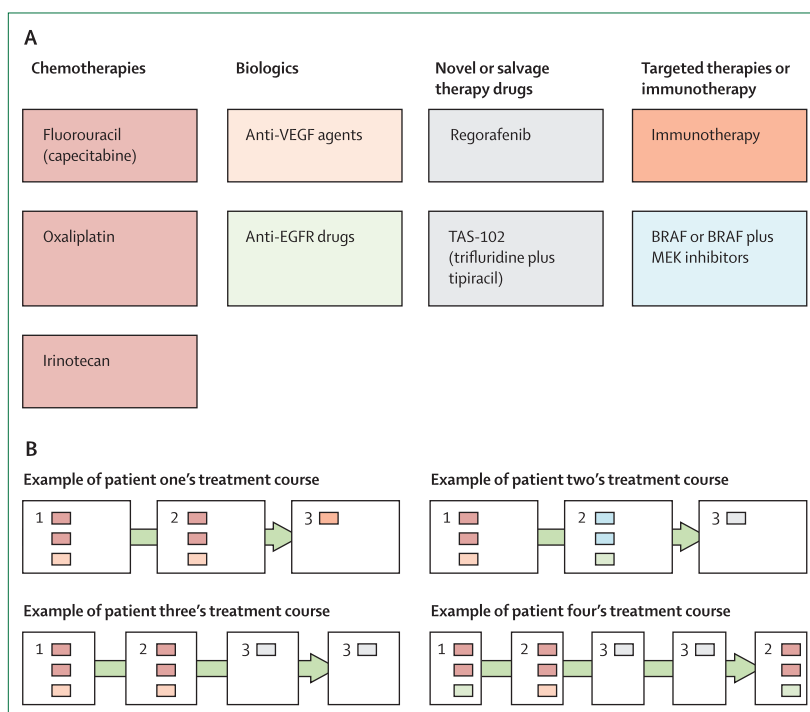
Systemic therapy for metastatic colorectal cancer is tailored with patient-specific and disease-specific predictive markers. Paralleled with the advances in surgical and allied specialties, the increasing number of effective drugs for colorectal cancer has led to substantial improvement of overall survival (figure 7).

Deciding whether the therapy is going to be curative or palliative is crucial and depends primarily on the tumour burden. Patients might have few (or oligo) metastases that can be resected and rendered cured. Moreover, patients with widely metastatic disease might become suitable candidates for local treatment pending a great response to systemic therapy. Downsizing these tumours with conversion therapies is increasingly being used.<sup>94</sup> Given the complexity and multidisciplinary nature of care needed, all patients with metastatic colorectal cancer, should receive input from a specialist, tertiary care centre.

Systemic therapy for metastatic colorectal cancer typically includes a chemotherapy backbone paired with a biologic. Fluoropyrimidines, oxaliplatin, and irinotecan chemotherapies form the chemotherapy backbone in various iterations of two-drug or three-drug regimens (figure 7). A biologic (anti-VEGF or anti-EGFR antibody) is added to the chemotherapy regimen depending on tumour-specific and patient-specific factors. Patients with metastatic colorectal cancer typically receive several lines of therapy depending on the situation (figure 7A, B).

#### Biologics, salvage therapy, immunotherapy, and future directions

Bevacizumab, an anti-VEGF monoclonal antibody targeting angiogenesis, was the first biologic agent approved for metastatic colorectal cancer and was shown to benefit all patients with this type of cancer.<sup>95</sup> Subsequently, the addition of bevacizumab to other chemotherapy backbones has been shown to better progression-free



**Figure 7: Classes of drugs used in patients with metastatic colorectal cancer**

Different classes of drugs available for patients with metastatic colorectal cancer (A), often used in combination (eg, two or three chemotherapy drugs paired with a biologic). Patients with metastatic colorectal cancer are often treated with multiple treatment regimens one after another (B) depending on patient-related and tumour-related factors (eg, sidedness, mutations, or mismatch repair status—such as immunotherapy for microsatellite instability-high tumours).

survival but not necessarily overall survival.<sup>96,97</sup> Other anti-VEGF agents approved for use in patients with metastatic colorectal cancer include aflibercept and ramucirumab.<sup>98,99</sup>

Right-sided colorectal cancers do not benefit from anti-EGFR therapies in the first-line metastatic setting, possibly because of different embryological origins to left-sided tumours (figure 4).<sup>34</sup> The difference is striking (eg, 16·4 months for right-sided vs 37·5 months for left-sided metastatic colorectal cancer in patients treated with cetuximab, hazard ratio 1·97; 95% CI 1·56–2·48 months).<sup>34</sup> Pooled analysis of multiple randomised studies has further corroborated this difference.<sup>100</sup> Beyond sidedness, colorectal cancer should be tested for extended RAS and RAF (KRAS, NRAS, and BRAF) mutations before considering anti-EGFR therapies.<sup>101–106</sup>

At present, for left-sided RAS and RAF-wild-type metastatic colorectal cancer in first-line settings, either anti-EGFR agents (cetuximab or panitumumab) or anti-VEGF agents (bevacizumab) can be used.<sup>107,108</sup> The sequence of biologics is controversial. In practice, for patients, in whom response might be a key variable (conversion therapy), anti-EGFR agents might be chosen for left-sided RAS and RAF-wild-type tumours.<sup>107</sup>

Identification of BRAF-V600E mutant colorectal cancer is important since outcomes are 2–3 times worse.<sup>85</sup> These

tumours are aggressive and do not respond well to systemic therapy. Upfront triplet chemotherapy with bevacizumab is recommended. Combinatorial strategies (BRAF-inhibitors and anti-EGFR antibodies paired with chemotherapy or MEK inhibitors) have shown improvement in outcomes in several randomised clinical trials and are now included in consensus guidelines.<sup>109–111</sup>

Regorafenib (a so-called dirty tyrosine-kinase inhibitor)<sup>112,113</sup> and TAS-102 (combination of trifluridine and tipiracil, an oral anti-metabolite)<sup>114</sup> are newer drugs, approved for all patients with refractory metastatic colorectal cancer who have not responded to upfront systemic therapies.<sup>115</sup>

For the 4–5% of tumours with dMMR or high MSI (MSI-H), PD-1 blockade with immunotherapies such as nivolumab or pembrolizumab is now approved.<sup>48,116,117</sup> Combination immunotherapy (nivolumab and ipilimumab) has also received US Food and Drug Administration's approval.<sup>118</sup> The responses with these immune checkpoint inhibitors have been unprecedented, durable, and possibly curative. These therapies, however, do not work for the mismatch–repair-proficient colorectal cancers, which constitute the fair majority. Clinical trials are looking at addition of novel agents to help augment immunotherapy.<sup>119</sup> A trial with a MEK inhibitor alongside PD-L1 blockade, however, did not show any survival benefit over regorafenib.<sup>120</sup>

For dMMR colorectal cancers, immunotherapy is being explored in front-line, adjuvant, and neoadjuvant settings for non-metastatic tumours.<sup>121–123</sup> For rectal cancers, trials are looking at moving therapy from the adjuvant setting to doing all of it in the neoadjuvant setting (total neoadjuvant therapy).<sup>124</sup> Selective omission of radiation is also being considered for those who have a great initial response to systemic therapy.<sup>125</sup>

Understanding of mutations is increasing. For example, the non-V600E *BRAF*-mutant colorectal cancers might have a better prognosis than previously reported.<sup>126</sup> A new emerging target of interest with prognostic and predictive potential is *HER2/Neu*,<sup>127</sup> which has been a focus of many trials and shows promise.<sup>128,129</sup> Newer markers are emerging (eg, CDX2, circulating tumour DNA or Immunoscore; HalioDx, Richmond, VA, USA) for early disease.<sup>130–132</sup> Circulating tumour DNA so-called liquid biopsies, are also showing value in metastatic setting.

Finally, for the two cytotoxic chemotherapies (fluorouracil and irinotecan), genes that determine how they are metabolised have been identified (*DPD* for fluorouracil and *UTG1A1* for irinotecan).<sup>133</sup> Although multiple studies and analyses have shown its feasibility and value, pharmacogenomics testing has not been widely adopted at present.

### Quality of life during and after treatment

Colorectal cancer can impair quality of life through direct and indirect consequences of the disease. Direct consequences are, for instance, abdominal pain, fatigue

because of anaemia, and change in bowel habits. Furthermore, treatment by means of surgery, radiotherapy, and chemotherapy can reduce quality of life. Each treatment method is associated with specific adverse effects and complications.

Perioperative care has been optimised, trying to keep physiology and daily functioning to healthy conditions as much as possible. Diet restrictions, drains, and fluid administration are minimised, and patients are motivated and facilitated to mobilise as early as possible with optimised pain control. These multi-interventional enhanced recovery programmes are widely implemented on the basis of high-quality evidence.<sup>134</sup> The increasing older population ( $\geq 70$  years) with colorectal cancer requires specific attention, and geriatric assessments have been developed to identify the high-risk groups for tailored preoperative interventions.<sup>135</sup>

Restoration of bowel continuity can be mostly accomplished in colon cancer but might need a tailored approach in rectal cancer. The closer the anastomosis is to the anus, the higher the risks are and poorer the functional outcome is. Bowel dysfunction after restorative rectal cancer resection is called low anterior resection syndrome.<sup>136</sup> Patients often want to avoid a stoma, not overseeing the effect of bowel dysfunction on social life. Informing the patient with shared decision making is important,<sup>137</sup> but might be complicated by the wide ranges in reported quality of life after definitive colostomy or certain degree of low anterior resection syndrome. The syndrome can be managed by dietary changes, medication (eg, loperamide), and anal irrigation, but good evidence is lacking. Rectal cancer treatment, particularly combined radiation and surgery, can also affect bladder and sexual function.<sup>138</sup>

With respect to chemotherapy, important side-effects to be aware of are cumulative neuropathy (paraesthesia, numbness or tingling affecting activities of daily living from platinum chemotherapy), and liver toxicity.<sup>139</sup> The cumulative neuropathy is predictable as patients cross a threshold of cumulative oxaliplatin exposure and needs to be recognised early because it is often irreversible.<sup>140</sup> Targeted therapies also have important adverse effects that must be considered.

Metastatic disease can give rise to a range of additional symptoms that negatively affect quality of life. Maintaining optimal nutrient intake and physical condition, with exercise, adequate pain relief, and psychosocial support, can improve quality of life and should be assessed continually and repeatedly by all treating physicians.

### Prevention

#### Primary prevention

From a public health perspective, prevention of colorectal cancer is important. Accumulating evidence suggests that smoking cessation, a healthy diet, and regular exercise can prevent the development of colorectal cancer. This recommendation includes daily physical



activity of at least 30 min, consumption of milk, whole grains, fresh fruits, tree nuts, and vegetables, and intake of calcium and fibre.<sup>141</sup> Moreover, some chemopreventive agents can also reduce the risk of colorectal cancer development. Regular use of vitamin supplements<sup>141</sup> and hormone replacement therapy<sup>142</sup> have been associated with reduced risk for colorectal cancer. However, for several chemopreventive agents, observational studies and subsequent randomised trials had different results. For instance, epidemiological and preclinical data have suggested that higher intake and serum concentrations of vitamin D<sup>143</sup> and higher intake of calcium<sup>141</sup> reduce the risk of colorectal neoplasia. However, in a randomised trial in patients that underwent adenoma removal, daily intake of vitamin D and calcium supplements did not significantly reduce the risk for developing colorectal adenomas over a period of 3–5 years.<sup>144</sup>

Regular aspirin and non-steroidal anti-inflammatory drugs intake (NSAIDs) have also been associated with reduced colorectal cancer risk.<sup>145</sup> In 2016, the US Preventive Task Force<sup>146</sup> recommended the use of low-dose aspirin for the primary prevention of cardiovascular disease and colorectal cancer in adults aged 50–69 years. However, this recommendation was not followed by other countries and should be viewed on an individual basis, balancing its beneficial effects on both cardiovascular disease and colorectal cancer incidence against the potential harms, especially gastrointestinal bleeding. Possibly, there is a role for aspirin or NSAIDs as primary prevention in those patients with a defined hereditary predisposition (eg, Lynch syndrome and polyposis).<sup>147</sup>

The difficulty of primary prevention of colorectal cancer development lies in matching interventions that work to those individuals that would benefit most. Possibly, individual risk calculation models that include genetic and environmental factors along with family history for colorectal cancer could be useful to establish the risk of developing colorectal cancer and starting ages for screening.<sup>148</sup> These scoring systems might serve as a first step towards developing individualised colorectal cancer prevention strategies.

### Secondary prevention

The best method to prevent colorectal cancer is colonoscopy. Although invasive, it has a high sensitivity and specificity and offers the potential for direct removal of precursor lesions and early cancer. People at elevated risk (eg, those with a hereditary or familial risk), those with long-standing ulcerative colitis, and those with previous adenomas or colorectal cancer, are recommended to undergo regular surveillance by colonoscopy. For colorectal cancer screening, which is meant for the general population of a certain age range, several other methods are available.<sup>149</sup> The ideal alternative for colonoscopy should have a high sensitivity and specificity for colorectal cancer and precursor lesions. In the screening setting, the effectiveness of screening

programmes also relies heavily on participation. Among other factors, participation in screening is affected by the expected and perceived burden of the test, the risk of complications, the costs, the socioeconomic class and cultural beliefs of the screened individual, and the logistics of the programme.<sup>150</sup>

Stool tests aim to detect potential markers that might be indicative for colorectal cancer (eg, blood or molecular markers in the stool). Those with a positive test should undergo a colonoscopy in a two-step screening programme. Screening for microscopic amounts of blood with the guaiac test (or guaiac-based faecal occult blood tests) reduced colorectal cancer mortality by approximately 16% more than a decade ago.<sup>151</sup> The quantitative and automated faecal immunochemical test (FIT) seems to outperform the guaiac test. Three cohort studies showed relative risks for colorectal cancer mortality that were 10–40% lower among those patients that underwent FIT screening.<sup>152–154</sup> An observational study showed a 22% reduction in colorectal cancer mortality by FIT screening compared with a prescreening time period.<sup>155</sup> FIT is the preferred and most used method for organised screening programmes in Europe with relatively high participation of up to 73% in the Netherlands.<sup>156</sup> In an effort to launch a more sensitive and specific test, multitarget stool DNA tests have been developed. Cologuard (Exact Sciences, Madison, WI, USA) has combined both DNA and FIT in a multicentre trial, and this test had a slightly higher sensitivity for colorectal cancer and advanced adenomas than FIT alone.<sup>157</sup> However, for now the cost of the test is relatively high and logistics complicated (whole stool is needed), limiting its use in organised screening programmes.

Non-invasive alternatives for colorectal cancer screening comprise blood-based tests. Although such tests are available, their use for population screening programmes will require improved sensitivity from the current 48·2% for the detection of cancers and advanced adenomas.<sup>158</sup>

Endoscopic methods include sigmoidoscopy and colonoscopy. Four large randomised controlled trials on sigmoidoscopy screening have been done: one in the USA and three in Europe.<sup>159–162</sup> All studies showed a reduced incidence in colorectal cancer (18–26%) in those that participated compared with those who did not. Moreover, three of four studies also showed a lowered relative risk of death from colorectal cancer (22–31%) among participants. However, in this two-step programme, participation was relatively low and logistics demanding, clearly reducing its cost-efficiency. Although colonoscopy has been available for decades, and is seen as the reference standard for the detection of colorectal cancer and its precursors, its preventive effect as a primary screening method, although possible, has not yet been shown. Several randomised controlled trials (NCT01239082, NCT00883792, NCT02078804) are underway and eagerly awaited.

CT colonography is another two-step screening strategy. A randomised controlled trial comparing CT colonography and colonoscopy showed similar detection rates for colorectal cancer, but lower rates for advanced adenomas.<sup>163</sup> When correcting for participation (relatively low, but higher than colonoscopy: 33% vs 22%), these differences disappeared.<sup>163</sup>

### Tertiary prevention

After treatment of colorectal cancer, several factors have been associated with improved outcomes and decreased risk of colorectal cancer-related death. These factors are largely the same as the factors for primary prevention. In a large multicentre study, patients who followed a healthy lifestyle were more likely to survive stage III colorectal cancer.<sup>164</sup> Moreover, patients who adapted to a healthier lifestyle after colorectal cancer diagnosis had a 33% lower risk of death during follow-up than those who did not change their lifestyle. The benefits of regular use of aspirin and other NSAIDs, although associated with improved survival, should be weighed against the increased risk of gastrointestinal bleeding and other potential harms.<sup>165</sup> Given that most of these data are derived from observational studies, randomised trials (eg, NCT01349881) are needed before their routine use can be recommended.

### Contributors

All authors searched the literature and drafted specific sections of the Seminar: ED drafted the risk factors, pathophysiology, and secondary prevention sections. PT drafted the imaging, surgical therapy, radiotherapy for rectal cancer, and local treatment options for metastatic disease sections. JLA drafted the sections on incidence and mortality, pathophysiology, quality of life during and after treatment, and primary and tertiary prevention sections. PMK drafted the sections on pathophysiology, diagnosis, and systemic treatment. MBW drafted the section on diagnosis and endoscopic management sections. ED and JLA wrote the first full draft of the Seminar. All authors reviewed, edited, and agreed the submission of the final report.

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