Colorectal cancer

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More than 1·2 million patients are diagnosed with colorectal cancer every year, and more than 600 000 die from the disease. Incidence strongly varies globally and is closely linked to elements of a so-called western lifestyle. Incidence is higher in men than women and strongly increases with age; median age at diagnosis is about 70 years in developed countries. Despite strong hereditary components, most cases of colorectal cancer are sporadic and develop slowly over several years through the adenoma–carcinoma sequence. The cornerstones of therapy are surgery, neoadjuvant radiotherapy (for patients with rectal cancer), and adjuvant chemotherapy (for patients with stage III/IV and high-risk stage II colon cancer). 5-year relative survival ranges from greater than 90% in patients with stage I disease to slightly greater than 10% in patients with stage IV disease. Screening has been shown to reduce colorectal cancer incidence and mortality, but organised screening programmes are still to be implemented in most countries.

Epidemiology

Incidence and mortality

Colorectal cancer is the third most common cancer and the fourth most common cancer cause of death globally, accounting for roughly 1·2 million new cases and 600 000 deaths per year.[1] Incidence is low at ages younger than 50 years, but strongly increases with age. Median age at diagnosis is about 70 years in developed countries.[2] The highest incidence is reported in countries of Europe, North America, and Oceania, whereas incidence is lowest in some countries of south and central Asia and Africa.[3] In 2008, estimated age-standardised incidence by region ranged from 4·3 cases per 100 000 people in central Africa to 45·7 per 100 000 in Australia and New Zealand in men (figure 1), and from 3·3 per 100 000 to 33·0 per 100 000 in the same regions in women.[1,4] However, rapid increases in previously low-risk countries, such as Spain and several countries in eastern Europe and east Asia, have been noted, which have been ascribed to changes in dietary patterns and risk factors towards a so-called western lifestyle.[5] However, in the USA and several other high-income countries, incidence has stabilised or started to decrease, probably because of increased use of sigmoidoscopy and colonoscopy with polypectomy.[3,6]

In 2008, estimated age-standardised mortality ranged from 3·5 per 100 000 people in central Africa to 20·1 in central and eastern Europe in men, and from 2·7 to 12·2 in the same regions in women.[1] In several high-income countries and countries of east Asia and eastern Europe, mortality has been decreasing since the 1980s, probably because of improved early detection and treatment, but rates have continued to increase in countries or areas with poor health-care resources (figure 2), including countries in Central and South America and rural areas in China.[3,7,8]

Search strategy and selection criteria

Data for this Seminar were identified by searches of PubMed, Cochrane, and ISI Web of Knowledge databases, and references from relevant articles, with various combinations of the search terms "colon cancer", "colorectal cancer", "colorectal neoplasms", "colorectal tumor", "chromosomal instability", "diagnosis", "drug therapy", "epidemiology", "genomic instability", "microsatellite instability", "molecular pathogenesis", "mortality", "prevention", "prognosis", "radiotherapy", "risk factors", "screening", "surgery", "survival", and "therapy". Articles solely reported in the form of abstracts or meeting reports were excluded. Articles published only in English between January, 1980, and March, 2013, were included.

Prognosis

The prognosis of patients with colorectal cancer has slowly but steadily improved during the past decades in many countries. 5-year relative survival has reached almost 65% in high-income countries, such as Australia, Canada, the USA, and several European countries, but has remained less than 50% in low-income countries.[2,10,11] Relative survival decreases with age, and at young ages is slightly higher for women than for men. Stage at diagnosis is the most important prognostic factor. For example, in the USA in 2001–07, 5-year relative survival of patients diagnosed with colorectal cancer was 90·1% for patients with localised stage, 69·2% for patients with regional spread, and 11·7% for patients with distant tumour spread.[2]

Risk and preventive factors

Unlike other cancers, such as lung cancer, no single risk factor accounts for most cases of colorectal cancer. Apart from age and male sex, the following risk factors (which often co-occur and interact) have been identified and established in epidemiological studies: family history of colorectal cancer,[12] inflammatory bowel disease,[13] smoking,[14] excessive alcohol consumption,[15] high consumption of red and processed meat,[16] obesity,[17] and diabetes[18] (table 1). With relative risks greater than 2, the risk increase is strongest for people with first-degree relatives with colorectal cancer (especially for those with multiple affected relatives or relatives diagnosed at young ages) and people with inflammatory bowel disease. However, the other risk factors, which are more common and are in principle modifiable, account for a larger proportion of the disease burden at the population-level, despite lower relative risks (mostly between 1·2 and 2·0).

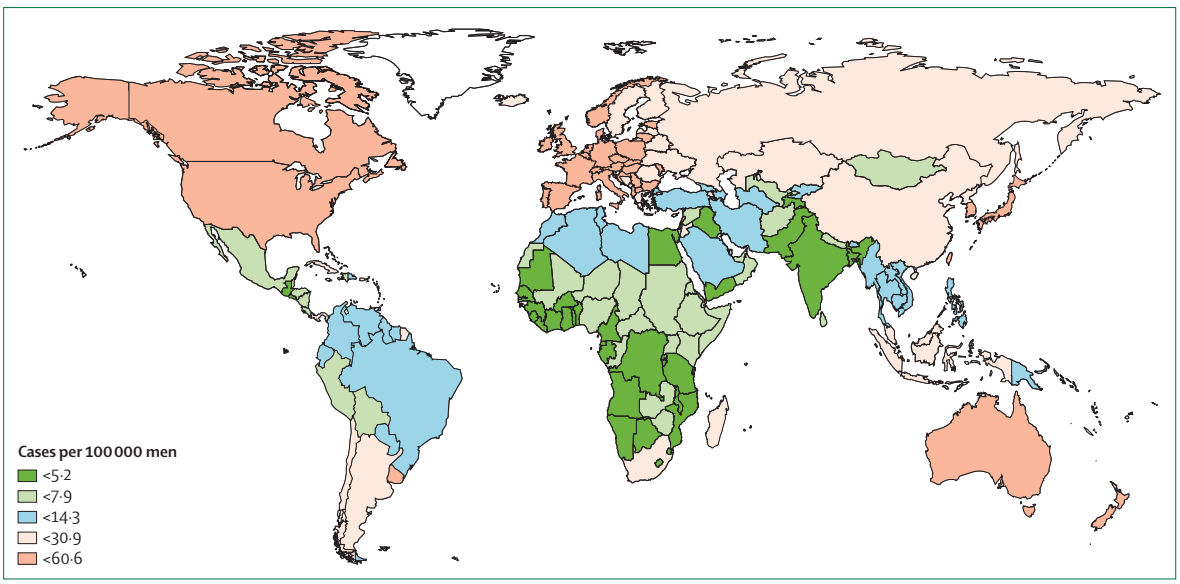

Figure 1: **Estimated age-standardised colorectal cancer incidence for men in 2008**
Data from Globocan 2008.[1]

Further emerging evidence suggests that infection with *Helicobacter pylori*, *Fusobacterium* spp, and other potential infectious agents might be associated with an increased risk of colorectal cancer.[19–21]

Established preventive factors include physical activity,[22] use of hormone replacement therapy,[23] and aspirin,[24,25] with risk reduction in the order of 20–30%, and endoscopy with removal of precancerous lesions,[26,27] for which the strongest risk reduction has been reported (table 1). Although not as consistent, some data suggest a weak protective effect of diets rich in fruit, vegetables, cereal fibre and whole grains,[28,29] dairy products,[30] or fish[31] and, possibly, statin therapy.[32] Epidemiological studies[33] have consistently shown an inverse association between serum vitamin D concentrations and risk of colorectal cancer, but whether and to what extent this association is causal needs to be established.

Colorectal cancer has a substantial heritable component. According to a large twin study,[34] 35% of colorectal cancer risk might be attributable to heritable factors. Apart from hereditary forms, such as familial adenomatous polyposis and hereditary non-polyposis colon cancer (Lynch syndrome), which are determined by well known genetic aberrations, but account for less than 5% of all colorectal cancer,[35] genetic factors that determine the risk of disease are still incompletely understood. Genome-wide association studies have identified an increasing number of single nucleotide polymorphisms (SNPs) showing statistically significant but typically very small associations with risk of colorectal cancers. Furthermore, meta-analyses suggest that few of these SNPs seem to show true associations,[36] that the SNPs identified so far together account for only a small proportion of colorectal cancer risk,[37] and that interactions with known environmental risk factors do not play a major part.[38]

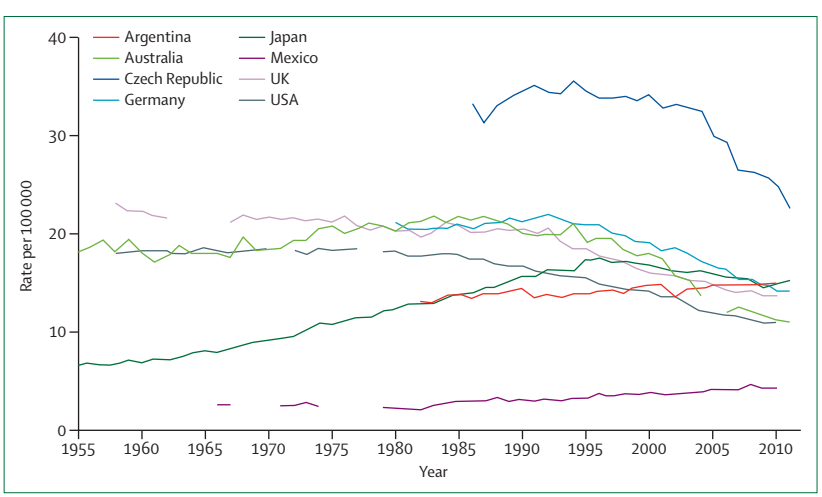

Figure 2: **Trends in age-standardised colorectal cancer mortality for men in selected countries, 1955–2010**
Data from WHO mortality database.[9]

Histopathological classification

Colorectal cancers are classified according to local invasion depth (T stage), lymph node involvement (N stage), and presence of distant metastases (M stage; table 2).[39] These stages are combined into an overall stage definition (table 3), which provides the basis for therapeutic decisions.[39]

Although classification according to TNM and Union Internationale Contre le Cancer (UICC) stage provides valuable prognostic information and guides therapy decisions, the response and outcome of individual patients' therapy is not predicted. This is a drawback for patients with UICC stage II and III colorectal cancer in particular. Adjuvant chemotherapy is recommended for UICC stage III patients and for stage II patients with

	Risk
Sociodemographic factors	
Older age	↑↑↑
Male sex	↑↑
Medical factors	
Family history	↑↑
Inflammatory bowel disease	↑↑
Diabetes	↑
Helicobacter pylori infection	(↑)
Other infections	(↑)
Large bowel endoscopy	↓↓
Hormone replacement therapy	↓
Aspirin	↓
Statins	(↓)
Lifestyle factors	
Smoking	↑
Excessive alcohol consumption	↑
Obesity	↑
Physical activity	↓
Diet factors	
High consumption of red and processed meat	↑
Fruit and vegetables	(↓)
Cereal fibre and whole grain	(↓)
Fish	(↓)
Dairy products	(↓)

↑↑↑=very strong risk increase. ↑↑=strong risk increase.↑=moderate risk increase. ↓↓=strong risk reduction. ↓=moderate risk reduction. Parentheses show probable but not fully established associations.

Table 1: **Overview of risk and preventive factors of colorectal cancer**

additional risk factors; however, a substantial proportion of these patients do not seem to benefit from chemotherapy. Improved informative markers could help to identify patients at high risk of relapse who might benefit from adjuvant therapy.

Molecular pathogenesis

The molecular pathogenesis of colorectal cancer is heterogeneous. The molecular mechanisms underlying development of this cancer are clinically important because they are related to the prognosis and treatment response of the patient.[40,41] The interconnections between molecular pathogenesis, prognosis, and therapy response have become increasingly apparent during the past two decades, including the identification of the molecular mechanisms and genetic changes that cause the hereditary forms of colorectal cancer.[42]

Adenoma–carcinoma sequence

Colorectal cancer often develops over more than 10 years, and dysplastic adenomas are the most common form of premalignant precursor lesions.[43] *APC* gene mutations are an early event in the multistep process of colorectal cancer formation and occur in more than 70% of colorectal adenomas.[42] The adenoma–carcinoma sequence is further promoted by activating mutations of the *KRAS* oncogene and inactivating mutations of the *TP53* tumour suppressor gene.[44] These characteristic gene mutations are often accompanied by chromosomal instability—ie, changes in numbers of chromosomes and profound structural changes of the chromosomes.[45]

However, more than 15% of sporadic colorectal cancers develop through fundamentally different pathways of molecular events. These cancers include those originating from serrated precursor lesions, which are typical premalignant precursor lesions in the proximal colon,[46] and are often characterised by the CpG island methylator phenotype and activating *BRAF* oncogene mutations. Identification of these lesions during colonoscopy can be difficult because of their flat, inconspicuous nature.

Most cancers arising from sessile serrated adenomas display the high-level microsatellite instability (MSI-H) phenotype as a consequence of *MLH1* gene promoter methylation,[47] and occur in the proximal colon of elderly people, with a female predominance.[48]

Inherited forms

Hereditary forms contribute to about 3–5% of all colorectal cancers.[49,50] Hereditary colorectal cancer is a highly valuable model for the study of the molecular pathogenesis of colorectal cancer. In hereditary cancer, important tumour suppressor or DNA repair genes are inactivated by monoallelic gene expression in the germ line, and a somatic event (second hit) abrogating the functionality of the remaining wildtype allele can lead to tumour formation.[51]

The two most common forms of hereditary colorectal cancers are hereditary non-polyposis colon cancer (Lynch syndrome, estimated allele frequency 1:350 to 1:1700)[52] and familial adenomatous polyposis coli (estimated allele frequency 1:10 000). Both syndromes are autosomal dominant disorders and follow the molecular pathogenesis typical of colorectal cancer: Lynch syndrome-associated cancers show signs of mismatch repair deficiency and consequently MSI-H,[49,53] whereas familial adenomatous polyposis-associated cancers follow the classic adenoma–carcinoma sequence.[54] Figure 3 shows the contribution of inherited tumours to all colorectal cancer.

Mismatch repair deficiency and MSI-H

Mismatch repair-deficient colorectal cancers are characterised by the accumulation of many insertion or deletion mutations at microsatellites spread along the genome.[53] Clinically, MSI-H cancers show the following characteristics: localisation in the proximal colon, manifestation in people younger than 50 years (hereditary form) or in elderly people (sporadic form), synchronous occurrence with additional tumours,[55] and large local tumours, and are only rarely accompanied by organ metastases. Identification of MSI-H cancers by histopathology can be supported by: poor or mixed differentiation (high grade),

dense infiltration with tumour-infiltrating lymphocytes, and expansive and cohesive pattern of invasion.[56] Immunohistochemically, MSI-H cancers display loss of expression of at least one DNA mismatch repair protein in greater than 90% of lesions.[57] Figure 4 shows a representative colorectal cancer section.

Although inactivation of DNA mismatch repair genes seems to accelerate rather than initiate colorectal cancer formation,[44] the exact time of DNA mismatch repair inactivation during development of this cancer is still unclear. The discovery of non-dysplastic mismatch repair-deficient crypt foci in the intestinal mucosa from carriers of Lynch syndrome mutation suggests that colorectal carcinogenesis might be initiated by mismatch repair deficiency at least in a subset of MSI-H cancers.[58]

The clinical significance of the MSI-H phenotype relates to the identification of patients and families affected by Lynch syndrome. In these cases, *BRAF* mutation analysis can be useful to distinguish between sporadic and Lynch syndrome-associated MSI-H colorectal cancers because *BRAF* oncogene mutations are almost exclusively restricted to sporadic MSI-H type.[48]

Molecular markers of prognosis and therapy prediction

Microsatellite instability

In addition to the identification of families with hereditary colorectal cancer, microsatellite instability analysis can provide valuable information about the prognosis and therapy response of patients. Patients with MSI-H colorectal cancer have a better prognosis than do patients with microsatellite stability. A systematic review[59] of 32 eligible studies (7642 patients with colorectal cancer) estimated a hazard ratio (HR) of 0·65 (95% CI 0·59–0·71) for overall survival. Additionally, the MSI-H phenotype seems to be useful for prediction of the response to chemotherapy. Patients with MSI-H colorectal cancer did not show benefit from adjuvant therapy with fluorouracil (HR 1·24, 95% CI 0·72–2·14).[59] By contrast, patients with MSI-H colorectal cancer had an improved response to irinotecan-based chemotherapy,[60,61] but results are controversial. Such findings have nurtured the ongoing discussion of the need to undertake molecular tumour analysis in all patients with colorectal cancer given adjuvant chemotherapy.

Infiltration with cells of the immune system

The MSI-H phenotype is closely associated with a high density of tumour-infiltrating lymphocytes.[56,62] This association is probably attributable to a pronounced antitumoural immune response, resulting from the generation of frameshift antigens induced by a deficiency in mismatch repair, which might be recognised by the host's immune system as tumour antigens.[63] This immune response could contribute to the improved prognosis of MSI-H colorectal cancer. Local immune cell infiltration has been shown to be a potent factor for prognostic classification. Patients with colorectal cancer lesions showing dense infiltration with CD45R0-positive and CD3-positive lymphocytes in the tumour centre and infiltration front showed excellent prognosis, irrespective of UICC stage. Conversely, low lymphocyte infiltration was independently associated with a poor outcome.[64] A

	Definition
T stage	
Tx	No information about local tumour infiltration available
Tis	Tumour restricted to mucosa, no infiltration of lamina muscularis mucosae
T1	Infiltration through lamina muscularis mucosae into submucosa, no infiltration of lamina muscularis propria
T2	Infiltration into, but not beyond, lamina muscularis propria
T3	Infiltration into subserosa or non-peritonealised pericolic or perirectal tissue, or both; no infiltration of serosa or neighbouring organs
T4a	Infiltration of the serosa
T4b	Infiltration of neighbouring tissues or organs
N stage	
Nx	No information about lymph node involvement available
N0	No lymph node involvement
N1a	Cancer cells detectable in 1 regional lymph node
N1b	Cancer cells detectable in 2–3 regional lymph nodes
N1c	Tumour satellites in subserosa or pericolicor perirectal fat tissue, regional lymph nodes not involved
N2a	Cancer cells detectable in 4–6 regional lymph nodes
N2b	Cancer cells detectable in 7 or greater regional lymph nodes
M stage	
Mx	No information about distant metastases available
M0	No distant metastases detectable
M1a	Metastasis to 1 distant organ or distant lymph nodes
M1b	Metastasis to more than 1 distant organ or set of distant lymph nodes or peritoneal metastasis

Table 2: **Classification of colorectal cancers according to local invasion depth (T stage), lymph node involvement (N stage), and presence of distant metastases (M stage)[39]**

	T	N	M
Stage 0	Tis	N0	M0
Stage I	T1/T2	N0	M0
Stage II	T3/T4	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
Stage III	Any	N+	M0
IIIA	T1–T2	N1	M0
	T1	N2a	M0
IIIB	T3–T4a	N1	M0
	T2–T3	N2a	M0
	T1–T2	N2b	M0
IIIC	T4a	N2a	M0
	T3–T4a	N2b	M0
	T4b	N1–N2	M0
Stage IV	Any	Any	M+
IVA	Any	Any	M1a
IVB	Any	Any	M1b

Table 3: **Overall Union Internationale Contre le Cancer stage classification of colorectal cancers[39]**

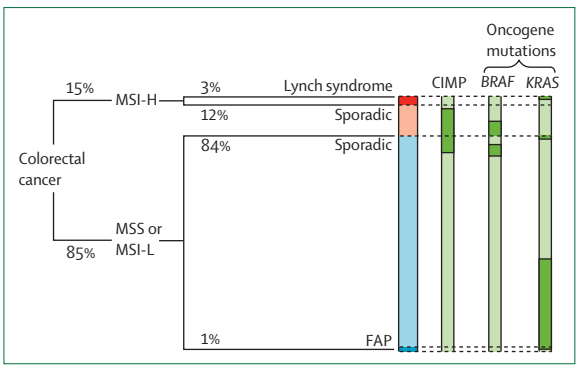

Figure 3: **Molecular subtypes of colorectal cancer**
Most colorectal cancers (85%, light blue and dark blue) show MSS or MSI-L phenotype, but are characterised by chromosomal changes. Most of these cancers develop through the classic adenoma–carcinoma pathway, but about 1% develop with inherited syndrome FAP (dark blue). About 15% of colorectal cancers (red and pink) have the MSI-H phenotype as a result of DNA mismatch repair deficiency. About 3% of colorectal cancers have MSI-H in context of the inherited Lynch syndrome (red), whereas 12% develop as sporadic tumours (pink), with sessile serrated adenomas as a typical precursor lesion. The distribution of typical molecular changes including the CIMP and mutations of the *BRAF* or *KRAS* oncogenes are sketched in green. Dark green is the proportion of positive or mutant changes and light green is the proportion of negative or wildtype changes. MSI-H=high-level microsatellite instability in relation to the phenotypes in the first bar. CIMP=CpG island methylator phenotype. MSS=microsatellite-stable. MSI-L=low-level microsatellite instability. FAP=familial adenomatous polyposis.

multinational effort is currently underway to develop an immunoscore as a novel instrument for classification of colorectal cancer.[65]

KRAS and other mutations as predictive markers

The most prominent example of molecular markers that have entered clinical routine is analysis of *KRAS* mutation in patients with metastatic colorectal cancer. Mutations of the *KRAS* oncogene render affected cells unresponsive to treatment with anti-EGFR antibodies, thus lowering response rates from monotherapy from about 20% to almost 0%.[66] Whether mutations of *BRAF* have a similar predictive potency is under investigation.[67,68]

Novel classification systems that are based on complex mutational profiles or gene expression patterns of colorectal cancer lesions are promising methods for the identification of patients that could respond to certain therapy regimens.[40] Molecular classification has led to the prognostically relevant identification of a subtype of colorectal cancer that is distinct from types of colorectal cancer that have classic unstable chromosomes or MSI-H. Tumours of this subtype, which cannot be characterised by typical tumour suppressor or oncogene mutations, have a dismal prognosis, are mostly microsatellite stable, and often show the CpG island methylator phenotype.[41]

Diagnosis and staging

Diagnosis of colorectal cancer is made histologically from biopsy samples taken during endoscopy. Complete colonoscopy or CT colonography is mandatory to detect synchronous cancers that are present in about 2–4% of patients.[69,70] If this is not possible preoperatively, complete visualisation of the colon should be done within 6 months after curative resection.

For rectal cancer, exact local staging at the time of diagnosis is essential and is the basis for requirement of neoadjuvant treatment. Apart from the exact distance from the anal verge, definition of the local tumour extent is important. Endoscopic ultrasononography is accurate for determination of the T-stage of rectal cancer,[71] and is the method of choice for regional tumours because of high accuracy to differentiate between non-invasive and invasive neoplasia.[72] The most accurate method to define advanced T-stages is MRI (figure 5).[73,74] Local staging of rectal cancer after neoadjuvant therapy is less reliable for all methods because of changes induced by radiation.[75]

For both rectal and colon cancer, distant metastases should be ruled out. About 20% of patients with newly diagnosed colorectal cancer present with distant metastases.[76] The most common location is the liver, and thus liver imaging should be done for all patients with colorectal cancer. In a meta-analysis[77] of prospective studies with 3391 patients who had not undergone treatment, the sensitivity of CT on a per-patient basis was slightly lower than that of MRI (83·6% *vs* 88·2%). MRI had a significantly higher sensitivity than did CT for lesions less than 10 mm. The sensitivity of abdominal ultrasononography for the detection of liver metastases was lower than the sensitivity of other staging methods.[78] The sensitivity can be improved with contrast enhanced ultrasononography, with similar results to multislice CT in some studies.[79,80]

Investigators identified lung metastases in 2·1% of patients newly diagnosed with colorectal cancer in a large cancer registry in France.[81] Frequency was nearly three times higher for patients with rectal cancer than for patients with colon cancer. Smaller studies[82–84] using chest CT have shown isolated lung metastases in 9–18% of patients with rectal cancer. The clinical effect of detection of lung metastases is unknown. Staging of colorectal cancer is generally advised to include a chest radiograph. With respect to the prevalence of lung metastases, a chest CT in patients with locally advanced rectal cancer seems justified. Although distant metastases can be identified in other organs including the bone and brain, no evidence supports routine investigation of these locations. Furthermore, data do not support routine use of PET-CT in patients without suspected metastatic disease. Investigators of a trial[85] comparing PET-CT with CT in patients with liver metastases eligible for hepatic resection reported reduced futile laparoscopies, but no benefit in survival.

Management

Role of multidisciplinary teams

Like other patients with cancer, those with colorectal cancer should be assessed by a multidisciplinary team. The multidisciplinary team should include a colorectal

surgeon, a medical oncologist, a gastroenterologist, a radiotherapist, a radiologist, and a pathologist. Depending on the tumour extent, the addition of a hepatic or thoracic surgeon is necessary. Patients with rectal cancer for whom a decision has to be made about need for neoadjuvant therapy and all patients with distant metastases should be assessed before treatment is started. For patients with colon cancer without signs of distant metastases, assessment of the need for adjuvant therapy after surgery is probably sufficient. The assessment by a multidisciplinary team has been associated with a reduced rate of positive circumferential resection margins for rectal cancer[86] and increased rates of adjuvant therapy for patients with colon cancer[87] and of metastasis surgery for patients with stage IV disease.[88] In a study[89] in Denmark where multidisciplinary teams were introduced in all hospitals, investigators identified an increased use of MRI and reduced perioperative mortality for patients with rectal cancer, but no effect on survival.

Surgery

The standard surgical procedure for the treatment of rectal cancer is total mesorectal excision—ie, removal of the rectum together with the mesorectum around it and the surrounding envelope, the mesorectal fascia.[90] Complete removal of the mesorectum is important because it contains most of the involved lymph nodes and tumour deposits. Several studies[91] have shown the importance of achievement of clear lateral margins (the so-called circumferential margin). A clear circumferential margin is generally defined as a distance of greater than 1 mm between the tumour border and the resection margin. Patients with involved circumferential margin have increased risk of local recurrence and development of distant metastases.[91,92] The plane of the mesorectal fascia is used for resection, but resection has to be extended laterally if the tumour spreads beyond the fascia.

In colon cancer surgery, the tumour and the corresponding lymph vessels are removed. The extent of surgery is predetermined by the tumour localisation and the supplying blood vessels. In analogy with total mesorectal excision for surgery of rectal cancers, some experts have proposed complete mesocolic excision for colon cancer surgery, with separation of the mesocolic plane from the parietal plane and central ligation of the supplying arteries and draining veins. Complete mesocolic excision results in resection of increased mesocolon and lymph nodes.[93] Further data for the risks and benefits of complete mesocolic excision are needed.

Open surgery used to be the only option available; however, laparoscopic resection has developed as an alternative. Several meta-analyses[94–96] have shown that laparoscopic resection of colorectal cancer achieves the same long-term results as open surgery, and is associated with a reduced number of patients requiring blood transfusions (3·4% *vs* 12·2%), faster return of bowel function (first bowel movement after 3·3 days *vs* 4·6 days), and a shorter duration of hospital stay (9·1 days *vs* 11·7 days); however, operating times are longer (208 min *vs* 167 min) and operative costs are higher. Some evidence supports the use of robotic surgery for rectal cancer,[97] but further data are needed.

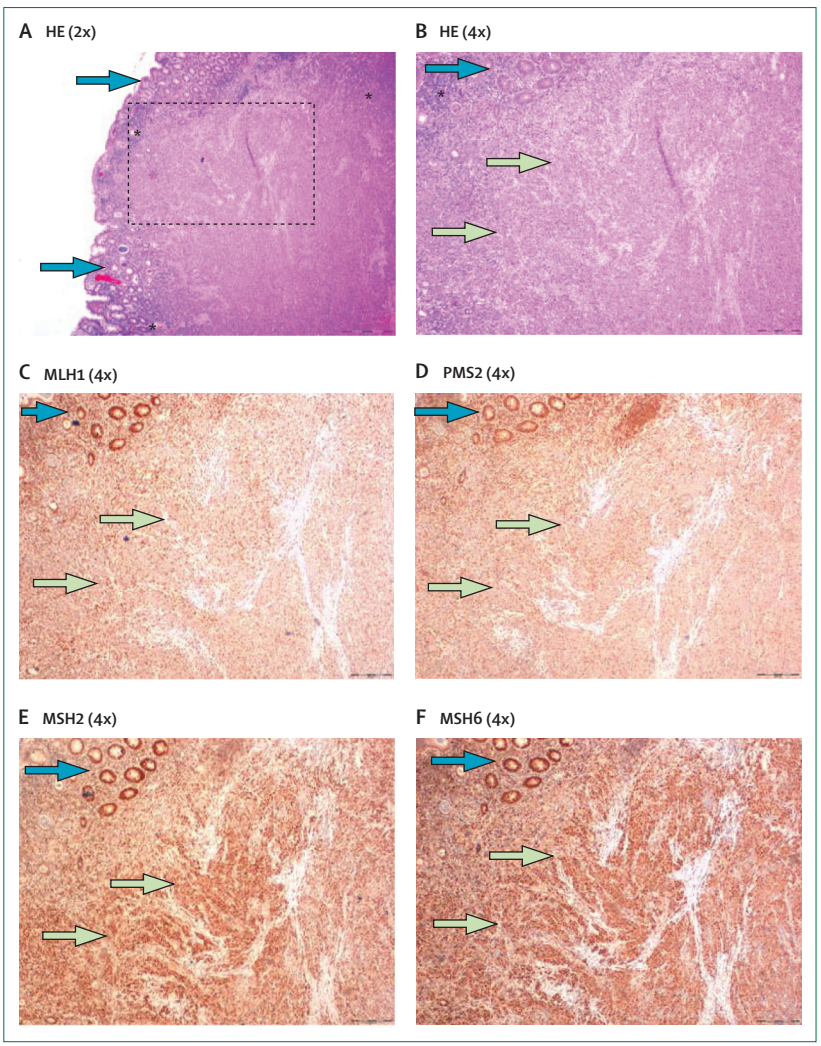

Figure 4: **Histology sections of a colorectal carcinoma**
(A) Overview and (B) detailed HE staining of a poorly differentiated colorectal carcinoma. Dense lymphocyte infiltration that is characteristic of DNA mismatch repair-deficient cancers is shown by asterisks. Immunohistochemical staining of DNA mismatch repair proteins shows retained expression of all four proteins: MLH1, PMS2, MSH2, and MSH6 in non-malignant colon crypts (blue arrows). Tumour cells show lack of MLH1 expression (C, green arrow) and PMS2 expression (D, green arrow), but retained expression of MSH2 expression (E, green arrow) and MSH6 expression (F, green arrow). Objective magnifications are given in brackets. HE=haematoxylin-eosin.

Neoadjuvant therapy

Since the introduction of total mesorectal excision, the rate of local recurrences after surgery of rectal cancer has fallen substantially. van Gijn and colleagues[98] have shown that the rate of local recurrence for total mesorectal excision with neoadjuvant therapy was reduced after neoadjuvant radiotherapy (5% *vs* 11% overall, 9% *vs* 19%

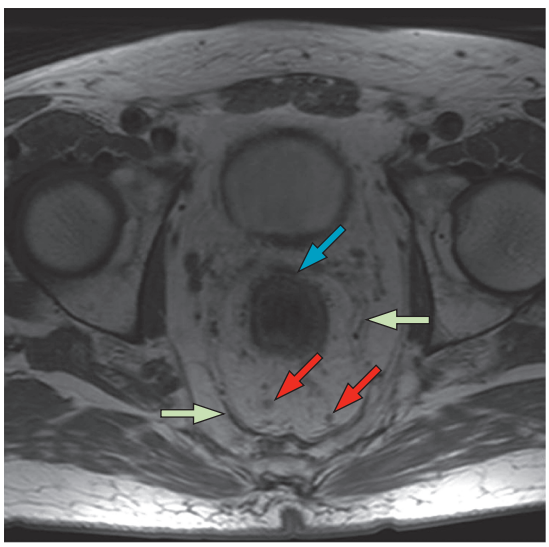

Figure 5: **MRI of a patient with T3 rectal cancer**
T3 rectal cancer extends beyond the muscularis propria (blue arrow) with positive lymph nodes (red arrows). The mesorectal fascia (green arrows) is not involved by the tumour, and although small the lymph nodes contains tumour cells.

stage III), which shows a remaining role for neoadjuvant therapy. The question is whom to treat and how. Patients with stage I disease should not be given any treatment in addition to surgery because the local recurrence rate is low (about 3%) and the benefit from neoadjuvant treatment very small (number needed to treat to prevent one local recurrence=38).[98] Patients with stage III disease benefit from additional treatment, whereas the benefit for patients with stage II disease is less clear.[98–100] Benefit is generally accepted for patients with T4 and advanced T3 tumours infiltrating the mesorectal fascia. The use of neoadjuvant treatment for T3 tumours with greater than 1 mm distance from the mesorectal fascia (irrespective of N status) has been questioned by some investigators,[101] and is under investigation in the OCUM-trial (NCT01325649).

With respect to the timing of radiotherapy, neoadjuvant therapy is better than adjuvant therapy, with reduced rates of local recurrences and toxic effects.[102] However, questions remain about the use of short-course radiotherapy (5×5 Gy) versus long-course radiotherapy (50·4 Gy) combined with chemotherapy. In the USA and some European countries, long-course radiotherapy is preferred, whereas other countries (eg, Sweden, Norway, and Netherlands) mainly use short-course radiotherapy.

Short-course radiotherapy is generally followed, without delay, by surgery, and thus does not achieve pronounced downsizing of the tumour. In cases in which downsizing or staging of the tumour is desired (patients with T4 or T3 tumours infiltrating the mesorectal fascia), long-course radiotherapy combined with chemotherapy is the preferred option. In a randomised trial,[103] long-course radiotherapy achieved lower rates of involved circumferential margins than did short-course radiotherapy (4% *vs* 13%). The ideal treatment of patients with T3 tumours is less clear. The first randomised trial[104] comparing short-course radiotherapy with long-course radiotherapy in combination with chemotherapy of T3 rectal cancers showed that the local recurrence rate was lower for long-course radiotherapy than short-course, particularly in patients with distal rectal cancer, but the difference was not statistically significant. Nevertheless, these and other data suggest that for patients with T3 distal rectal cancer, long-course radiotherapy with chemotherapy might be preferred, whereas for proximal rectal cancer short-course radiotherapy is a valid alternative if the mesorectal fascia does not seem involved. Most studies[100] have used fluorouracil for combined radiochemotherapy but capecitabine seems to be a valid alternative.

Several studies are examining the exact role and timing of chemotherapy in patients undergoing short-course radiotherapy and the effect of delayed surgery.[105] Most studies have not shown differences in rates of distant metastases and overall survival for the use of radiotherapy.[102]

Data for the role of neoadjuvant treatment in locally advanced colon cancer are scarce. A pilot trial[106] including 150 patients with radiologically staged locally advanced tumours showed that preoperative chemotherapy was feasible, with acceptable toxicity and perioperative morbidity, and statistically significantly (p=0·002) increased the rate of R0 resections. However, further data from randomised trials are needed for definitive conclusions.

Adjuvant therapy

Patients with stage III colon cancer have a risk of recurrence ranging between 15% and 50%. Adjuvant chemotherapy is recommended for all patients with stage III colon cancer without contraindications after curative resection. Regimens containing fluorouracil reduce recurrence rate by 17% units and increase overall survival by 13–15% units.[107] Alternatively, capecitabine, an oral prodrug of fluorouracil, can be used with comparable efficacy.[108] To improve disease-free survival and overall survival, several large prospective trials have investigated the addition of oxaliplatin to fluorouracil and capecitabine (table 4). The addition of oxaliplatin increased the absolute 5-year disease-free survival by 6·2 to 7·5% units and the overall survival by 2·7 to 4·2% units in patients with stage III colon cancer.[109–111] However, secondary subset analyses of two studies suggest that the benefit of oxaliplatin might be limited to patients younger than 65 years[112] or younger than 70 years.[111] In large randomised trials,[112,113] the addition of bevacizumab or cetuximab to an oxaliplatin containing regimen did not show any benefit on disease-free survival. Additionally, the use of irinotecan combined

	Regimen	Patients (n)	Stage (n)	DFS rate	OS rate
MOSAIC[109]	FU/LV *vs* FOLFOX4	2246	II (899), III (1347)	After 5 years: Overall 67·4% *vs* 73·3% (HR 0·80; 95% CI 0·68–0·93); p<0·003 Stage II 79·9% *vs* 83·7% (HR 0·84, 95% CI 0·62–1·14); p=0·258 Stage III 58·9% *vs* 66·4% (HR 0·78, 95% CI 0·65–0·93); p=0·005	After 6 years: Overall 76·0% *vs* 78·5% (HR 0·84, 95% CI 0·71–1·00); p=0·046 Stage II 86·8% *vs* 86·9% (HR 1·00, 95% CI 0·70–1·41); p=0·986 Stage III: 68·7% *vs* 72·9% (HR 0·80, 95% CI 0·65–0·97); p=0·023
XELOXA[110]	FU/LV *vs* XELOX	1886	III	After 55 months: 62·5% *vs* 68·7% (HR 0·80, 95% CI 0·69–0·93); p<0·005	After 57 months: 74·2% *vs* 77·6% (HR 0·87, 95% CI 0·72–2·05); p=0·15
NSABP C-07[111]	FU/LV *vs* FLOX	2409	II (695) III (1714)	After 5 years: Overall 64·2% *vs*. 69·4% Stage II 80·1% *vs* 82·1% Stage III 57·8% *vs* 64·4%	After 5 years: Overall 78·4% *vs* 80·2% Stage II 89·6% *vs* 89·7% Stage III 73·8% *vs* 76·5%

DFS=disease-free survival. OS=overall survival. MOSAIC=Multicenter International Study of Oxaliplatin/5FU-LV in the Adjuvant Treatment of Colon Cancer. FU=fluorouracil. LV=leucovorin. FOLFOX4=folinic acid+fluorouracil+oxaliplatin. HR=hazard ratio. XELOXA=XELOX in Adjuvant Colon Cancer Treatment (XELOXA) trial. XELOX=capecitabine+oxaliplatin. NSABP C-07=National Surgical Adjuvant Breast and Bowel Project C-07 trial. FLOX=fluorouracil+leucovorin+oxaliplatin.

Table 4: **Randomised trials of the effect of oxaliplatin for adjuvant therapy for colorectal cancer**

with fluorouracil did not show any benefit and was associated with increased toxic effects.[114,115]

Stage II colon cancer is associated with statistically significantly better disease-free survival and overall survival than stage III colon cancer. Accordingly, the survival benefit from adjuvant chemotherapy seems to be reduced, and thus is generally recommended only for patients at high risk of relapse (T4 tumours, perforated tumours, bowel obstruction at the time of surgery, and <12 lymph nodes removed). In the Quasar trial,[116] a fluorouracil containing chemotherapy regimen after curative resection was associated with a relative risk of 0·82 (95% CI 0·70–0·95) of death from any cause. If 5-year mortality without chemotherapy is 20%, these data translate to an absolute improvement in survival of 3·6% units (95% CI 1·0–6·0).

Patients with distant metastases

A detailed review of treatment of patients with colorectal cancer with distant metastases is outside the scope of this Seminar. Generally, patients with resectable liver or lung metastases should be offered surgical resection of the metastases. Patients with irresectable distant metastases should be offered palliative chemotherapy. Major advances have been achieved in the chemotherapeutic treatment of colorectal cancer, including the development of substances that inhibit the effect of vascular endothelial growth factor (bevacizumab and aflibercept) and monoclonal antibodies that inhibit epidermal growth factor receptor (cetuximab and panitumumab) and kinase inhibition (regorafenib). Cetuximab and panitumumab should be used only for patients without mutations in the *RAS* gene (wildtype) in the tumour and are generally used as part of a combination therapy. Because of the use of intensified combination chemotherapies, the median overall survival of this group has increased to more than 20 months in some studies.[117] Some patients with liver metastases that were judged to be unresectable at the time of diagnosis can be resected after chemotherapy with a 5-year disease-free survival of about 30%.[118] The choice and intensity of chemotherapy depend on several factors, including age of the patient, comorbidities, and extent of the disease.

Prevention

Primary prevention

With increased knowledge about risk and preventive factors, measures to reduce those risk factors and promote preventive lifestyles have potential for primary prevention. Several risk factors, including smoking, alcohol consumption, and obesity, are shared with other common chronic diseases, and primary prevention can and should be included in comprehensive primary prevention strategies.

Although some evidence from randomised trials[23,25] shows effective chemoprevention of colorectal cancer by specific drugs, such as aspirin or hormone replacement therapy, adverse effects of these drugs on other health outcomes restrict or preclude their use in primary prevention outside specific risk groups. Observational studies[33] have suggested vitamin D as a potentially promising candidate for chemoprevention if its preventive effects for colorectal cancer and other common chronic diseases can be confirmed by randomised trials.

Secondary prevention

Because most cases of colorectal cancer develop slowly over many years and the disease is mostly curable if detected at early stages, perspectives for secondary prevention by early detection and screening are much better for this cancer than for most other cancers. A meta-analysis[119] of randomised trials yielded a 16% reduction in colorectal cancer mortality with yearly offers of screening with faecal occult blood tests (25% reduction in those who attended). Results of randomised trials from Norway, the UK, Italy, and the USA on the effects of

screening by flexible sigmoidoscopy have been published recently. For example, a meta-analyses of intention-to-screen and per-protocol estimates yielded reductions in colorectal cancer incidence by 18% and 28% and in colorectal cancer mortality by 32% and 50%, respectively.[27] Even stronger reductions were estimated for the distal colon and rectum. Reported reductions most probably underestimate true protection because of contamination of the control groups by gastrointestinal endoscopy.[120] For example, in the US trial, almost half of the controls (46·5%) had a lower gastrointestinal endoscopy during the screening phase.[121]

Observational studies suggest even larger reductions in incidence and mortality by screening colonoscopy,[26,122] but randomised trials have only been recently started,[123] and results will not be available before the mid-2020s.

Mortality reduction in the faecal occult blood test trials have been achieved with guaiac-based faecal occult blood tests,[119] which have excellent specificity, but poor sensitivity, especially for detection of colorectal adenomas. In the past 30 years, faecal immunochemical tests for human haemoglobin in stool have been developed and increasingly used. These tests offer several advantages over guaiac faecal occult blood tests. Faecal immunochemical tests showed increased sensitivity for detection of both colorectal cancers and colorectal adenomas,[124,125] and higher acceptance and higher yield of colorectal neoplasms in population-based screening than did guaiac faecal occult blood tests.[126] Further advantages include the possibility of automated and standardised quantitative measurements and the specificity for detection of human haemoglobin, which make faecal immunochemical tests less prone to false-positive results from food ingredients and enable application without dietary restrictions.

Several model-based studies have investigated the effectiveness and cost effectiveness of colorectal cancer screening.[127] The most often studied screening schemes were annual or biannual screening with guaiac faecal occult blood or faecal immunochemical tests, sigmoidoscopy every 5 years, or colonoscopy every 10 years, typically starting at people aged 50 years. Studies have consistently shown each of these screening options to be effective and cost effective (if not cost saving), but results vary with respect to the most cost-effective screening method, because of factors such as incidence of colorectal cancer, costs of screening procedures and treatment which vary between countries and with time.

Major research efforts are ongoing towards the development of alternative non-invasive blood or stool-based screening tests, such as blood-based DNA methylation or protein markers or stool DNA tests.[128–130] Although their development is likely to thrive in the era of rapid advances in high-dimensional and high-throughput molecular diagnostics, so far these methods are not competitive in terms of diagnostic performance or cost effectiveness.

Extensive research is also ongoing to explore the potential of alternative imaging technologies, such as CT colonography (virtual colonoscopy) or capsule endoscopy for colorectal cancer screening. However, so far, their cost effectiveness is not competitive.[127,131] Use of CT colonography for primary screening is furthermore restricted because of exposure to radiation. Nevertheless, CT colonography might be the method of choice when complete endoscopic inspection of the large bowel is not possible—eg, in case of a stenosis.

On the basis of existing evidence, national and international screening guidelines mostly recommend colorectal cancer screening starting at 50 years of age for individuals at average risk, with use of either annual or biannual guaiac faecal occult blood or faecal immunochemical tests, flexible sigmoidoscopy every 5 years, or colonoscopy every 10 years.[132,133] A positive guaiac faecal occult blood or faecal immunochemical test has to be followed up by colonoscopy. If adenomas, serrated adenomas, large hyperplastic polyps (>1 cm), hyperplastic polyps located in the proximal colon, and mixed polyps are detected at sigmoidoscopy or colonoscopy, complete removal of these lesions is mandatory. Depending on the characteristics of the polyp, surveillance endoscopy might be warranted, but data for the exact timing are scarce. For individuals at increased risk, such as first-degree relatives of individuals diagnosed with colorectal cancer at young ages, beginning of screening at younger ages is recommended (eg, starting at age 40 years or 10 years before the youngest case in the immediate family). For high-risk groups (familial adenomatous polyposis, hereditary non-polyposis colon cancer, or inflammatory bowel disease) specialised and much more rigorous prevention programmes starting in early life are recommended. There is consensus that screening programmes should be offered in an organised manner, including personal invitations, monitoring, and quality assurance.[134] Such programmes are yet to be developed and offered for most countries.

Tertiary prevention

Research into the effect of tertiary prevention, especially through randomised trials, is scarce. Nevertheless, some evidence shows that exercise interventions might enhance health-related quality of life in survivors of colorectal cancer.[135] Emerging evidence for adverse effects of smoking on disease-specific and overall survival[136] suggests the potential for promotion and support of smoking cessation. Data suggests that for specific subgroups of patients with colorectal cancer prognosis might be enhanced by use of aspirin.[137,138] Further epidemiological and intervention studies are needed to more fully explore the potential of general and targeted tertiary prevention.

Contributors

Each author did the literature search for and drafted specific sections of the Seminar: HB for sections on epidemiology and prevention; MK for sections on histopathological classification, molecular pathogenesis, and molecular markers of prognosis and therapy prediction; and CPP for sections on diagnosis and staging and management. HB wrote the first full draft of the Seminar. All authors reviewed, edited, and agreed to submission of the final report.

Conflicts of interest

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