Colorectal cancer

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Every year, more than 945 000 people develop colorectal cancer worldwide, and around 492 000 patients die. This form of cancer develops sporadically, in the setting of hereditary cancer syndromes, or on the basis of inflammatory bowel diseases. Screening and prevention programmes are available for all these causes and should be more widely publicised. The adenoma-carcinoma sequence is the basis for development of colorectal cancer, and the underlying molecular changes have largely been identified. Prognosis depends on factors related to the patient, treatment, and tumour, and the expertise of the treatment team is one of the major determinants of outcome. New information on the molecular basis of this cancer have led to the development of targeted therapeutic options, which are being tested in clinical trials. Further clinical progress will largely depend on the broader implementation of multidisciplinary treatment strategies following the principles of evidence-based medicine.

Colorectal cancer is one of the most common cancers worldwide. In this review, we aim to summarise recent advances about this tumour.

Epidemiology

Colorectal cancer is the third most common cancer and the fourth most frequent cause of cancer deaths worldwide. The WHO estimates that 945 000 new cases occur yearly, with 492 000 deaths.[1] This cancer is more common in developed than developing countries. In developed countries, it is the second most common tumour, with a lifetime incidence of 5%, but its incidence and mortality are now decreasing.[1–3] The worldwide variability of outcome is proportional to access to specialists and availability of modern drug therapy; the overall 5-year survival rate in the USA exceeds 60%, but is less than 40% in less developed countries.[1]

Risk factors and causes

Sporadic

Most cases of colorectal cancer are sporadic, and genetic and environmental factors are important (panel 1).[1] About 20% of all patients with this cancer are estimated to have some component of familial risk without fulfilling the strict criteria for hereditary colorectal cancer.[4] Family history should therefore always be taken when assessing a patient; the Bethesda guidelines are valuable in this context. However, taking a family history by interview often underestimates family history of colorectal cancer.[5]

Hereditary

Roughly 5–10% of all colorectal cancers develop in the setting of defined hereditary cancer syndromes. The two main forms are hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP).[4] Various hamartomatous polyposis syndromes are also associated with an increased risk of such cancer, such as Peutz-Jeghers syndrome, juvenile polyposis syndrome, and Cowden syndrome.[4,6]

FAP is an autosomal-dominant disease. In about 80% of affected individuals, a germline mutation can be identified in the adenomatous polyposis coli (*APC*) gene.[4,6] A subset of people with FAP and attenuated FAP has biallelic mutations of the *MYH* gene.[7,8] FAP patients can develop more than 100 colorectal adenomas (50% of patients by age 15 years, 95% by age 35 years); if left untreated, colorectal cancer arises in almost all patients by age 40 years. Extracolonic manifestations, such as periampullary duodenal carcinoma (4–6% of patients) and desmoids (10–20% of patients), are a major cause of mortality and morbidity.[6,9,10] An important variant is attenuated FAP with ten to 100 colorectal adenomas. A clear genotype-phenotype exists: *APC* mutations between codons 1445 and 1578 are associated with increased risk of desmoid tumours—patients with attenuated FAP typically have mutations at the 5′ (proximal to codon 1517) or the 3′ end (distal to codon 1900) of the *APC* gene.[11] FAP patients without identifiable mutation are at higher risk for a severe phenotype.[12]

HNPCC is an autosomal-dominant disorder caused by germline mutations of mismatch repair genes. Tumours that arise in the setting of HNPCC typically have a molecular characteristic called microsatellite instability, which helps in making the diagnosis. This instability is defined as frequent mutations in microsatellites, which are short repeated DNA sequences.[11] The penetrance of colorectal cancer in HNPCC is 70–85%. Risk is also increased for tumours of the genitourinary system, stomach, biliary system, pancreas, small intestine, and CNS.[4,6,13] A genotype-phenotype correlation was

Search strategy and selection criteria

We searched the databases MEDLINE and PREMEDLINE from January, 1999, to July, 2004. The keywords "colorectal cancer", "rectal cancer", and "colon cancer" were combined with the Boolean operator "and" with the following keywords: "epidemiology", "risk factors", "prevention", "screening", "pathogenesis", "prognostic factors", "diagnosis", "treatment" ("surgery", "radiotherapy", "chemotherapy"), and "follow-up". We screened the bibliography of each relevant article for further relevant studies. More recent publications and randomised controlled trials were prioritised.

***Panel 1:* Risk factors and causes**

Sporadic colorectal cancer (88–94%)
Older age
Male sex
Cholecystectomy
Ureterocolic anastomosis
Hormonal factors: nulliparity, late age at first pregnancy, early menopause

Environmental factors
Diet rich in meat and fat, and poor in fibre, folate, and calcium
Sendentary lifestyle
Obesity
Diabetes mellitus
Smoking
Previous irradiation
Occupational hazards (eg, asbestos exposure)
High alcohol intake

Personal history of sporadic tumours
History of colorectal polyps
History of colorectal cancer (risk is 1·5–3% for second such cancer in first 5 years)
History of small bowel, endometrial, breast, or ovarian cancer

Familial colorectal cancer (20%)
First or second degree relatives with this cancer, criteria for hereditary colorectal cancer not fulfilled:
- One affected first-degree relative increases risk 2·3-fold
- Two or more affected first-degree relatives increase risk 4·25-fold
- Index case <45 years increases risk 3·9-fold
- Familial history of colorectal adenoma increases risk 2-fold

Colorectal cancer in inflammatory bowel disease (1–2%)
Ulcerative colitis
Crohn's colitis

Hereditary colorectal cancer (5–10%)
Polyposis-syndromes: familial adenomatous polyposis (FAP), Gardner's syndrome, Turcot's syndrome, attenuated adenomatous polyposis coli, flat adenoma syndrome
Hereditary non-polyposis colorectal cancer (HNPCC)
Hamartomatous polyposis syndromes (Peutz-Jeghers syndrome, juvenile polyposis syndrome, Cowden syndrome)

suggested for patients with HNPCC.[14] On average, affected patients develop colorectal cancer by age 44 years, tumours tend to be right-sided, and have classical histological features (panel 2).

Diagnosis is difficult because no typical phenotypic features occur. Therefore, clinical criteria defining HNPCC were developed (Amsterdam I and II criteria, panel 2).[11,13] The Bethesda guidelines are less stringent, and only define individuals who should undergo further testing (panel 2).[15]

Colorectal cancer in inflammatory bowel disease

Colorectal cancer accounts for about a third of deaths related to ulcerative colitis, and risk depends on disease duration (2% of affected people by 10 years, 8% by 20 years, and 18% by 30 years), extent of inflammation, presence of primary sclerosing cholangitis, and backwash ileitis.[16,17] Crohn's colitis is also associated with increased risk of colorectal cancer; the relative risk is similar to that for ulcerative colitis.[16]

Screening and prevention

Screening is effective in reducing mortality from colorectal cancer. Screening procedures include faecal occult-blood tests, flexible sigmoidoscopy, double-contrast barium enema, and colonoscopy.[18] One of these options should be offered to asymptomatic people aged 50 years or older.[19] The ideal screening method is still controversial, with no test unequivocally better than another. Risk, costs, and effectiveness need to be taken into account when discussing the different options.[19] Total colonoscopy certainly has the advantage of allowing assessment of the entire colon with the possibility of simultaneous biopsy or polypectomy. These advantages have to be balanced against the higher costs, risks, and inconvenience to the patient. Sigmoidoscopy and faecal occult-blood tests might be less effective in terms of cancer prevention, but are less invasive. For patients with a personal or familial history of colorectal neoplasms, FAP, HNPCC or inflammatory bowel diseases, special surveillance guidelines exist taking into consideration the higher risk.[19] Educational efforts are important, since the rate of screening in many developed countries is less than 50%.[20]

New techniques such as magnification endoscopy and chromoendoscopy increase the sensitivity of colonoscopy.[21,22] They result in a better demarcation of the lesions, which facilitates more exact endoscopic resection of adenomas and selected cases of early cancer (figure 1).[23] Confocal laser endomicroscopy allows in-vivo histology during colonoscopy with a diagnostic yield similar to conventional histology after biopsy.[24] This and other new screening modalities such as virtual colonoscopy, molecular stool tests, and serum proteomics are promising, but are not yet ready for routine clinical use.[18,19,25]

Development of a blood test to assess the personal risk for colorectal cancer would be of enormous benefit. Detection of loss of imprinting of the insulin growth factor II gene (*IGF2*) is a promising candidate in this context. This loss is four times more common in patients with colorectal adenomas and eighteen times more common in those with colorectal cancer than in healthy individuals.[26] A second biomarker for this cancer could be insulin-like growth factor 1 (IGF1).[27] Further studies will have to prospectively assess the validity of these factors in individualised screening strategies.

The most important and cheapest form of prevention of colorectal cancer is a change in lifestyle. Observational studies indicate that tobacco avoidance, physical activity, and weight control can reduce risk.[28]

Even though clinical trials with dietary interventions (eg, increases in fibre, fruits, and vegetables, and reductions in fat and alcohol) have shown little effect, several observational studies support a role of dietary modifications.[29] Many drugs are being investigated for chemoprevention of this cancer.[29] Although a significant risk reduction for colorectal cancer or adenomas has already been recorded for several drugs (eg, aspirin, nonsteroidal anti-inflammatory drugs), the role of chemoprevention needs to be further defined.[30]

Surgical prevention is established for FAP and ulcerative colitis, and restorative proctocolectomy with ileoanal J-pouch is the recommended procedure for most patients.[6,16] For HNPCC, the role of prophylactic surgery is less well defined, but some suggest prophylactic colectomy.[6] Because prophylactic surgery is mostly on young, apparently healthy people, morbidity and mortality from surgery has to be kept to a minimum.[31]

Pathogenesis

The adenoma-carcinoma sequence is the basis for development of colorectal cancer with corresponding accumulation of genetic changes.[32,33] Traditionally, colorectal carcinogenesis is explained by two pathways, the gatekeeper and the caretaker pathway.[34] The gatekeeper pathway is responsible for about 85% of sporadic colorectal cancers, and is the mechanism of carcinogenesis in patients with FAP. Gatekeepers are genes that regulate growth. One of the key steps of this pathway is mutation of the tumour-suppressor gene *APC*. Many other tumour-suppressor genes (eg, *DCC*, *DPC4/Smad4*, *p53*, *nm32*) and oncogenes (eg, K-*ras*, *c-myc*, *c-neu*, *c-erb-2*, *c-src)* are also involved.[35]

The caretaker pathway is characterised by mutations or epigenetic changes of genes that maintain genetic stability (eg, mismatch repair genes).[4] HNPCC is the hereditary form of this pathway; about 15% of sporadic colorectal cancers are also thought to be caused by this mechanism.[36] Besides oncogenes and tumour-suppressor genes in the gatekeeper pathway, further tumour-suppressor genes such as *TGFβRII*, *IGF2R*, and *BAX* are mutated in this pathway.[4,32,37]

In fact, the two pathways might not be completely separated since the *APC* gene can act as a caretaker and mismatch repair genes can affect cell proliferation.[37] Additional pathways could exist—eg, the serrated pathway as well as distinct pathways for carcinogenesis of flat and depressed colorectal neoplasms and for carcinogenesis in inflammatory bowel disease.[17,37–39] Epigenetic mechanisms such as change in DNA methylation, loss of imprinting, and histone acetylation, as well as modifier genes, such as the cyclooxygenase-2 gene and the peroxisome proliferator-activating receptor gene also seem to be involved in the genesis of colorectal cancer.[32,33,40–42] Other genes, such as those for tyrosine phosphatases,[43] activin type 2 receptor,[44] phosphatidylinositol 3-kinases,[45] and hCDC4[46] might also contribute to colorectal carcinogenesis.

***Panel 2:* Revised Bethesda guidelines for detection of patients at risk for HNPCC who should undergo microsatellite instability testing of tumour (only one criterion need be fulfilled),[15] and Amsterdam I and II criteria for clinical definition of HNPCC patients (all criteria must be met)[13]**

Bethesda guidelines

- Colorectal cancer diagnosed in patient who is younger than 50 years
- Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumours, irrespective of age*
- Colorectal cancer with the MSI-H† histology‡ diagnosed in a patient who is younger than 60 years§
- Colorectal cancer diagnosed in one or more first degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under the age 50 years.
- CRC diagnosed in two or more first or second degree relatives with HNPCC-related tumours, irrespective of age

Amsterdam I and II criteria

- One individual diagnosed with colorectal cancer (or extracolonic HNPCC-associated tumours)¶ before age 50 years
- Two affected generations
- Three affected relatives, one a first-degree relative of the other two
- FAP should be excluded
- Tumours should be verified by pathological examination

*HNPCC-related tumours include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot's syndrome) tumours, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel. †HSI-H=microsatellite instability-high in tumours refer to changes in two or more of the five US National Cancer Institute-recommended panels of microsatellite markers. ‡Presence of tumour infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern. §No consensus was reached among the workshop participants on whether to include the age criteria in guideline 3 above; participants voted to keep younger than 60 years in the guidelines. ¶Amsterdam II criteria: extracolonic HNPCC-associated tumours also considered.

Prognostic factors

Prognostic factors can be divided into three main groups: patient, treatment, and tumour related factors. We mainly discuss the last two.

Treatment related prognostic factors

Outcome of patients with colorectal cancer depends on treatment. The so-called volume/outcome relation postulates that a higher caseload and specialisation results in improved outcome. Besides long-term prognosis, other outcome measurements are being investigated in this context (table 1). Most studies show that higher caseloads and specialisation are associated with better outcome.[57] It has been estimated that 43 318 life-years could be saved in the USA if all patients with colon cancer (n=93 045) were treated at very high volume hospitals.[56]

Quality of surgery and pathological work-up can be assessed by the number of removed lymph nodes. Patients with more such nodes have better prognosis in most studies, which relates to a more precise staging of

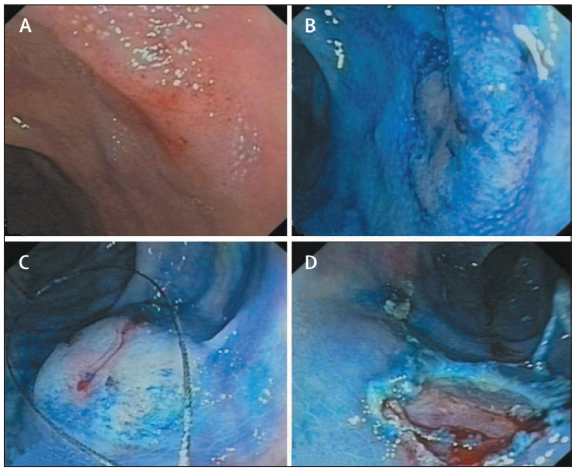

Figure 1: **Flat adenoma with high-grade intraepithelial neoplasia: chromoendoscopy and mucosal resection**
A: reddish mucosa in sigmoid. B: chromoendoscopy with methylene blue shows flat adenoma. Borders of lesion become clearly visible after staining. C: mucosal resection with snare after injection of saline in submucosal layer to lift lesion. D: Red muscularis propria becomes visible after complete resection of lesion.

the patients as well as to potential therapeutic benefits of more thorough lymphadenectomy.[58]

The status of the resection margin after surgery is one of the most important prognostic factors.[59,60] It is one of the links between treatment and tumour related prognostic factors, because it depends on surgical competence as well as on tumour biology. In rectal cancer surgery, assessment of completeness of the specimen is a valuable method of surgical quality control with proven prognostic effect.[61]

Tumour related prognostic factors

The basis for therapeutic decisions is the TNM-system of the International Union Against Cancer (UICC, table 2).[59] This staging system does not allow precise prediction of prognosis for an individual patient. To overcome this limitation, molecular characterisation of the tumour has been advocated; many potential molecular prognostic markers have been described (panel 3).[60,67–76] None of these factors, however, is yet of any value in routine clinical practice. Since colorectal carcinogenesis is a complex mechanism, one genetic marker seems unlikely to predict individual prognosis. DNA arrays and tissue arrays could be more suitable in this respect. Using DNA microarrays, Bertucci and others[77] were able to divide a group of 22 patients with colon cancer into two subgroups of patients with a 5-year overall survival of 100% *vs* 30% (p=0·001). Wang and colleagues[78] examined tumours from 74 patients with Dukes' B colon cancer with DNA microarray techniques, and defined a 23-gene signature profile that accurately predicted the clinical course in 78% of patients.

Since disseminated tumour cells are thought to be the basis for distant tumour recurrence after curative resection, detection of these cells is a logical approach to identify patients at higher oncological risk. The prognostic significance of these cells, however, is still under critical debate.[79,80] Detection of disseminated tumour cells in bone marrow samples could be a surrogate marker for assessing the effectiveness of neoadjuvant radiochemotherapy of rectal cancer.[81] Detection of tumour cells in blood samples obtained intraoperatively seems to be a valid technique for identification of intraoperative tumour cell shedding,

	Number of patients	Cases per year		Perioperative mortality		p
		Low volume	High volume	Low volume	High volume	
Perioperative mortality						
Urbach et al, 2004[47]	18 898	<53*	⩾53*	3·7%	3·8%	ns
Callahan et al, 2003[48]	48 582	⩽27†	>79†	6·3%	2·8%	<0·001
		<192*	>551*	5·8%	3·0%	<0·001
Dimick et al, 2003[49]	20 862	<55*	>150*	3·7%	2·5%	0·006
Hodgson et al 2003[50]	7257	<7*	>20*	4·8%	1·6%	<0·001
Birkmeyer et al, 2002[51]	304 285	<33*	>124*	5·6%	4·5%	<0·001
Hannan et al, 2002[52]	22 128	<3†	⩾9†	4·8%	2·2%	<0·001
		<21*	⩾63*	4·6%	2·1%	<0·001
Schrag et al, 2000[53]	27 986	<58*	⩾166*	5·5%	3·5%	<0·001
Harmon et al, 1999[54]	9739	⩽5†	>10†	4·5%	2·6%	<0·01
Economic outcome		**Cases per year**		**Economic outcome**		
Harmon et al, 1999[54]	9739	⩽5†	>10†	LOS: 10·1	LOS: 9	<0·01
				$13 025‡	$11 642‡	<0·01
Sphincter preservation		**Cases per year**		**Odds ratio of APR**		
Hodgson et al, 2003[50]	7257	⩽7*	>20*	1·37	1	<0·05
Long-term outcome		**Cases per year**		**Median survival/5-year survival**		
Rabeneck et al, 2004[55]	34 888	<25*	⩾25*	1·0§	0·92§	<0·001
Finlayson et al, 2003[56]	86 671	<17*	>65*	6·8 years	7·4 years	ng
Hodgson et al, 2003[50]	7257	<7*	>20*	2·64§	1·0§	<0·05

ns=not significant. LOS=length of stay (days). APR=abdominoperineal resection. ng=not given. *Cases per hospital. †Cases per surgeon. ‡Hospital charges. §Relative risk of dying from cancer. Only studies including more than 5000 patients presented.

Table 1: **Published studies about volume/outcome relation**

T—primary tumour				
TX	Primary tumour cannot be assessed			
T0	No evidence of primary tumour			
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria			
T1	Tumour invades submucosa			
T2	Tumour invades muscularis propria			
T3	Tumour invades through the muscularis propria into subserosa or into non-peritonealised pericolic or perirectal tissues			
T4	Tumour directly invades other organs or structures and/or perforates visceral peritoneum			
N—regional lymph nodes				
NX	Regional lymph nodes cannot be assessed			
N0	No regional lymph node metastasis			
N1	Metastasis in 1 to 3 regional lymph nodes			
N2	Metastasis in 4 or more regional lymph nodes			
M—distant metastasis				
MX	Distant metastasis cannot be assessed			
M0	No distant metastasis			
M1	Distant metastasis			
Stage	**T**	**N**	**M**	**5-year overall survival[62–66]**
Stage I	T1, T2	N0	M0	80–95%
Stage IIA	T3	N0	M0	72–75%
Stage IIB	T4	N0	M0	65–66%
Stage IIIA	T1, T2	N1	M0	55–60%
Stage IIIB	T3, T4	N1	M0	35–42%
Stage IIIC	Any T	N2	M0	25–27%
Stage IV	Any T	Any N	M1	0–7%

Table 2: **TNM staging system for colorectal cancer and published survival rates for different stages[59]**

which probably is of prognostic relevance in some patient groups.[82]

Diagnosis

Colonoscopy is the gold standard for diagnosis of colorectal cancer; in addition to physical examination, abdominal ultrasound and chest radiography are routinely done. The necessity of routine preoperative CT scans is still debated because this method alters the surgical approach in only a few cases.[83]

Better imaging of rectal cancer is important for planning of treatment. Local staging can be done by endorectal ultrasound (figure 2), CT (figure 3), or MRI (figure 4).[84] High-resolution MRI is a promising tool for depiction of important anatomical structures such as the mesorectal fascia.[85] Comparison of cost and clinical effectiveness of preoperative staging procedures in rectal cancer indicated a significant advantage for MRI.[86]

Positron emission tomography (PET) is valuable for detection of recurrent colorectal cancer, but has little effect on staging of primary cancer.[84] New developments such as combining PET and CT cameras

Panel 3: Molecular markers with potential prognostic importance

Tumour suppressor genes and oncogenes (*K-ras, c-myc, p53, DCC, smad4, nm23*)
Apoptosis and cell suicide-related genes (*bcl-2, BAX*)
DNA synthesis-related genes (*thymidylate synthase, thymidine phosphatase*)
Growth factors and growth factor receptor genes (*TGFα, TGFβ, HER-2/neu, EGFR*)
Mismatch repair genes (*MSH2, MLH1*)
Angiogenesis-related genes (*VEGF*)
Cyclins and cyclin dependent kinase inhibitors (p27, p21, p16)
Adhesion molecules and glycoprotein genes (cd44, E-cadherin, ICAM-1)
Markers of invasion (MMPs, urokinase-type plasminogen activator)
Proliferation indices (Ki-67, Mib-1, proliferation cell nuclear antigen)
Antioxidants (Superoxide dismutase, GST-pi)
Telomere length

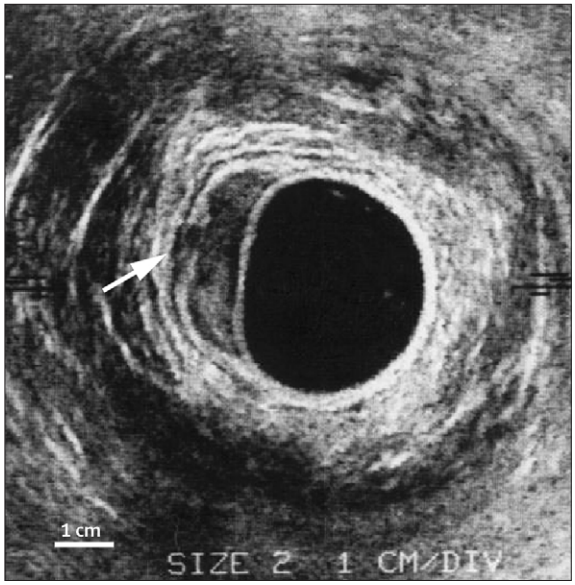

Figure 2: **Endorectal ultrasound of rectal cancer**
Arrow indicates tumour infiltration of muscularis propria leading to classification uT2, N0.

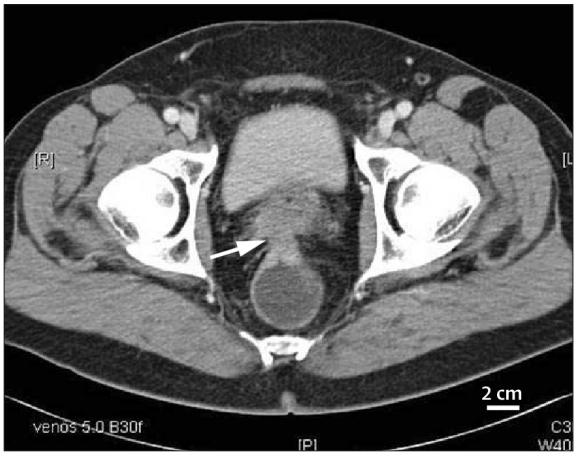

Figure 3: **CT-scan of rectal cancer**
Arrow indicates tumour infiltration of prostate leading to classification uT4, N0.

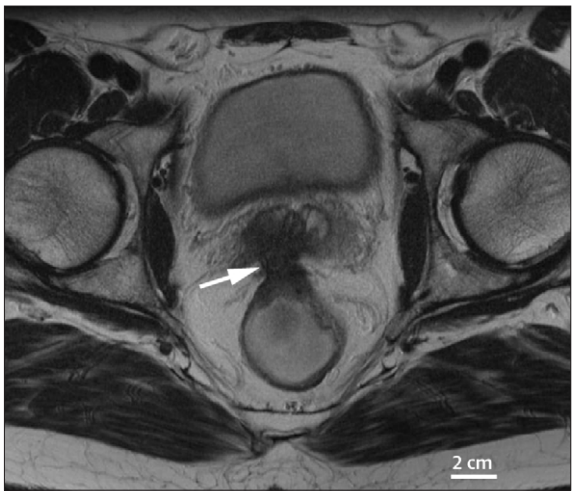

Figure 4: **MRI of rectal cancer**
Arrow indicates tumour infiltration of prostate leading to classification uT4, N0 (as in figure 3).

might help further improve accuracy of PET imaging in primary cancer.[87]

No consensus has been reached about the most sensitive method for detection of liver metastases of colorectal cancer. A meta-analysis[88] showed that PET is the most sensitive modality, and is also especially valuable for detection of extrahepatic disease. However, no randomised study has yet proved the value of PET in this setting; therefore, CT and MRI remain the diagnostic standards.

Treatment

Surgery is the basis of therapy for colorectal cancer, and important developments have occurred.

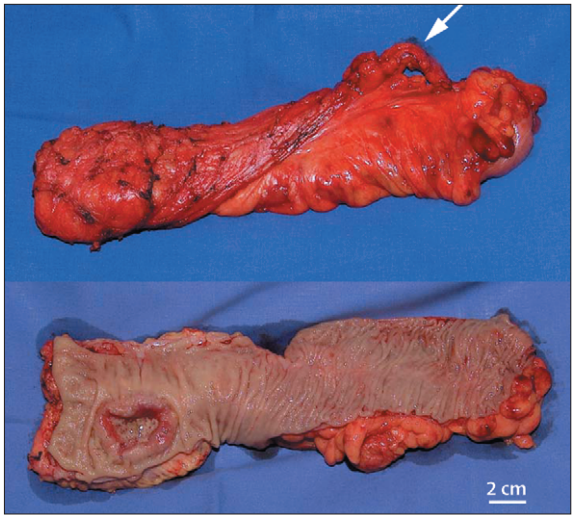

Figure 5: **Specimen of low anterior resection (total mesorectal excision) of rectal cancer**
Arrow indicates inferior mesenteric artery. Note adequate distal margin of about 2 cm.

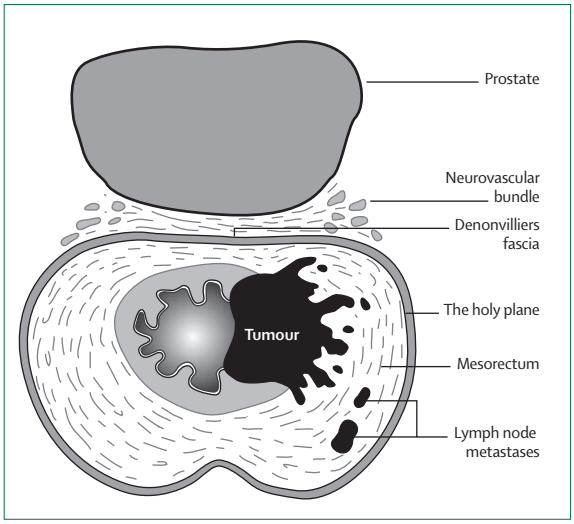

Figure 6: **Anatomical relations of the mesorectum**
The holy plane (according to Heald) is plane of dissection for total mesorectal excision, allowing complete removal of regional lymph nodes while sparing neurovascular bundles.[89,90]

Surgery for rectal cancer

One of the most important advances for surgery of rectal cancer has been the concept of total mesorectal excision, which reduces local recurrences and perioperative morbidity (figures 5 and 6).[89] With good surgical technique and selection of patients, excellent results can be obtained by surgery alone without radiotherapy, even in lymph-node-positive patients.[90]

Management of cancers close to the dentate line has always been controversial. For some patients, sphincter-preserving surgery with a distal margin of 1 cm seems possible.[91] Whether quality of life after sphincter preservation for very low tumours is better than abdominoperineal resection is still debated. Improved quality of life after sphincter preservation has been shown after long-term follow-up.[92] Options for reconstruction after low anterior resection are straight anastomosis, side-to-end anastomosis, colonic J-pouch, and transverse coloplasty pouch.[93–95] The last three options seem to have better functional outcome than straight anastomosis, but further trials will have to clarify the best method.

Fast-track surgery

Most of the traditional methods in colorectal surgery, such as urinary catheters, drains,[96] nasogastric tubes,[97] preoperative bowel preparation,[98] postoperative fasting, and intraoperative fluid excess[99] can be safely omitted. Fast-track surgery reduces hospital stay, perioperative morbidity, and costs.[100–102]

Laparoscopic surgery

Colorectal cancer can be safely treated laparoscopically. Long-term oncological results are similar to the

conventional approach (table 3). The postulated advantages to short-term outcome are most probably less substantial than previously thought. A randomised masked study[107] showed no difference in length of hospital stay, duration of ileus, or gastrointestinal transit rates between both approaches with the fast-track approach.

Sentinel lymph-node mapping

Stage II patients are judged to have a good prognosis, but many develop recurrences. In fact, such patients might not have been lymph-node negative but understaged instead. The sentinel lymph-node concept aims to enable the pathologist to analyse more meticulously one or a few lymph nodes harbouring the highest risk of metastatic disease.[112] One or more sentinel nodes can be detected in 90–100% of patients. An overall accuracy rate of around 96% has been reported for prediction of lymph-node status with staging of sentinel lymph nodes.[112] A false-negative rate of 56% was reported for rectal cancer.[113] Additionally, the prognostic significance of micrometastases in such lymph nodes has first to be proven before this approach can be introduced into standard clinical practice.

Treatment of peritoneal carcinomatosis

Patients with peritoneal carcinomatosis are commonly judged to be incurable. However, aggressive cyto-reduction combined with hyperthermic intraperitoneal chemotherapy can improve median survival from 12·6 to 22·3 months.[114] This strategy seems to be most effective in patients with minimum carcinomatosis after surgery and offers new hope for patients with advanced colorectal cancer.[115–117]

Radiotherapy and radiochemotherapy

Radiotherapy aims to reduce local recurrence and improve survival for patients with rectal cancer. Traditionally, adjuvant radiochemotherapy was considered standard care for patients with stage II and III rectal cancer. Neoadjuvant radiochemotherapy was reserved for advanced rectal cancers (uT4). Recently, neoadjuvant methods have been advocated for stage II and III patients too on the basis of two theoretical advantages—better local tumour control and lower morbidity.[118]

The Dutch CKVO 95-04 trial[119] compared surgery alone (standard total mesorectal excision) with surgery combined with short-term preoperative radiation (5×5 Gy). After a median follow-up of 2 years, the local recurrence rate was 2·4% in the radiation group compared with 8·2% in the control group (p<0·001); however, overall survival was not improved. Several important conclusions can be drawn from this trial: radiotherapy reduced the risk of local recurrence in low (inferior margin <10 cm from the anal verge) but not in high rectal cancers and was only beneficial in stage II and III tumours.[119] Neoadjuvant short-term radiation did not lead to tumour downstaging and did not reduce the local recurrence rate in patients with positive margins.[120,121] A cost-utility analysis showed that preoperative short-term radiation is cost-effective.[122] The question has been raised as to whether surgical quality of excision was high enough in this trial to support the conclusion that radiation improves local control in patients undergoing optimised surgery, since detailed analysis identified tumour-free margins without spillage of tumour in only 77% of patients. Furthermore, the local recurrence rates for the control group were reported to be higher than 10% after longer follow-up.[123]

The German CAO/ARO/AIO-94 trial[124] compared preoperative with postoperative long-term radiochemotherapy (50·4 Gy/fluorouracil) in 823 patients with resectable rectal cancer (uT3/4, uN+); 5-year local recurrence rates were 6% versus 13%, respectively (p=0·006). Distant-recurrence rates and survival were similar in both groups. Preoperative treatment was less toxic than was postoperative treatment. Stage distribution after surgery suggested a downstaging effect of preoperative radiochemotherapy. Of the patients whom the surgeon judged to need abdominoperineal resection before randomisation, 19% underwent a sphincter preserving procedure in the postoperative group compared with 39% in the preoperative group (p=0·004).

	Number of patients	Included patients	Outcome with laparoscopic surgery
COST, 2004[103]	872*	Colon cancer	Overall survival: no difference Disease free survival: no difference Morbidity: no difference Short-term outcome†: better‡
Janson et al, 2004[104]	210*	Colon cancer	Total costs to society: no difference Cost of operation: higher Health-care costs: higher
Kiran et al, 2004[105]	147§	Colorectal diseases	Blood loss: less Transfusions: fewer
Leung et al, 2004[106]	403*	Rectosigmoid carcinomas	Overall survival: no difference Disease-free survival: no difference Operation time: longer Treatment costs: higher
Basse et al, 2003[107]	32*	Colorectal diseases	Short-term outcome: better Short-term outcome: no difference
Delaney et al, 2003[108]	300§	Colorectal diseases	Short-term outcome: better Total costs: less
Lacy et al, 2002[109]	219*	Colon cancer	Overall survival: better Disease-free survival: better (locoreg. relapse of 14% for open colectomy) Operation time: longer Morbidity: lower Blood loss: less Short-term outcome: better
Quah et al, 2002[110]	170*	Rectal cancer	Male sexual function: worse
Weeks et al, 2002[111]	449*	Colon cancer	Short-term outcome: slightly better

*Randomised controlled trial. †Short-term outcome—eg, postoperative pain, postoperative bowel function, length of stay, quality of life. ‡Laparoscopic colectomy. §Matched pair analysis.

Table 3: **Trials comparing open versus laparoscopic surgery of colorectal cancer**

The randomised Lyon R98-02 trial[125] assessed addition of an endocavitary contact x-ray boost of 85 Gy to preoperative radiotherapy (13×3 Gy). Sphincter preservation was 76% in the boost group compared with 44% in the control group (p=0·004), with no detrimental effects on treatment toxicity.[125]

Further studies are needed to compare short-term with long-term neoadjuvant radiation in patients with resectable rectal cancer. The role of postoperative chemotherapy in patients who undergo neoadjuvant radiation also needs to be clarified; the EORTC-study 22921 addresses this issue.[126] Further investigation is needed into alternative ways of giving chemotherapeutic drugs, such as continuous and chronomodulated infusion of fluorouracil, as well as new drugs such as capecitabine, oxaliplatin, or irinotecan. For example, the combination of radiation with oxaliplatin and capecitabine seems to be very effective in terms of tumour downstaging.[127] The effect of more intensified radiochemotherapy on survival is under investigation.

The value of radiotherapy in colon cancer patients with high risk for local recurrence was assessed by the intergroup protocol 0130.[128] A total of 222 of 700 planned patients had been enrolled when the study was terminated prematurely because of slow accrual. After a median follow-up of 6·6 years overall and disease-free survival did not differ. Even though this study has several limitations, adjuvant radiotherapy cannot be recommended for colon cancer at this time.

Chemotherapy and immunotherapy

Adjuvant treatment

The use of adjuvant fluorouracil-based chemotherapy in patients with stage III colon cancer is thought to be standard care, but is not routinely recommended in stage II colon cancer.[129,130] For specific high-risk stage II patients (eg, T4-tumours, inadequate number of removed lymph nodes, perforation, bowel obstruction, poor differentiation), however, chemotherapy should be considered. Gill and colleagues[62] developed a model to estimate survival benefit by adjuvant chemotherapy stratified by T-stage, nodal status, grading, and patient age, which might help decision-making with regard to adjuvant therapy.

The value of new agents has been investigated in the adjuvant setting. The MOSAIC study compared FOLFOX (oxaliplatin, fluorouracil, and leucovorin) with infusional fluorouracil-leucovorin in 2246 patients with curatively resected colon cancer stage II or III.[131] With a median follow-up of 37·9 months, 3-year disease-free survival was 78·2% in the FOLFOX group versus 72·9% in the control group (p=0·002). No difference was noted for overall survival (87·7% *vs* 86·6%). 12% of patients in the FOLFOX arm suffered grade III neuropathy. A European trial (PETACC3/V-307) is comparing FOLFIRI (irinotecan, fluorouracil, and leucovorin) with infusional fluorouracil-leucovorin. A trial comparing irinotecan plus bolus fluorouracil and leucovorin (IFL) with fluorouracil-leucovorin[132] had to be stopped early because of increased toxicity and a high early death rate in the IFL group. Cassidy and co-workers[133] compared the oral fluoropyrimidine capecitabine with bolus fluorouracil-leucovorin. Capecitabine had an improved safety profile and recurrence-free survival in stage III patients, although no difference was noted for disease-free and overall survival.[133]

Adjuvant therapy with a monoclonal antibody against the glycoprotein 17-1A (edrecolomab) was investigated in a randomised trial including 2761 patients.[134] Compared with fluorouracil and leucovorin, patients treated with edrecolomab had significantly reduced 3-year disease-free survival (53% versus 65·5%, p<0·0001).

The best delivery route for adjuvant chemotherapy has been controversial. In a comparison of systemic versus intraportal fluorouracil-based chemotherapy, no survival difference could be established.[135] Hepatic-artery chemotherapy has been advocated after resection of liver metastases of colorectal cancer. A recent meta-analysis reported a reduced recurrence rate in the remaining liver by hepatic artery chemotherapy; however, overall survival was not improved.[136]

Palliative chemotherapy

Palliative chemotherapy for patients with metastatic colorectal cancer aims to improve survival and quality of life. It is crucial that resectability of the metastases is assessed by experienced surgeons before and during chemotherapy to avoid missing the opportunity for potentially curative resection, since resection of metastatic disease (hepatic or pulmonary metastases) can lead to 5-year survival rates of 35–58%.[137] In this context, it is important to realise that about 15% of patients with liver metastases initially judged to be unresectable will become resectable after systemic chemotherapy, with excellent long-term survival. By applying new concepts such as preoperative portal vein embolisation, two-stage hepatectomy, or combinations of resection with tumour ablation, even more patients with liver metastases might eventually be cured.[138]

Major progress has been made by the introduction of regimens containing new cytotoxic drugs such as irinotecan or oxaliplatin (FOLFIRI, FOLFOX). Response rates between 39% and 55% and progression-free survival between 7 and 9 months are now possible. The new therapeutic regimens led to almost a doubling of survival compared with single-agent fluorouracil (median survival >20 months compared with about 11–12 months). Trials are assessing the ideal combination and sequence of these regimens. Tournigand and others[139] randomly assigned patients to FOLFIRI then FOLFOX versus the reverse sequence.

Median survival and response rates were similar in both groups; however, the toxicity profile was different in both groups, which is important when counselling patients. Goldberg and co-workers[140] compared IFL, FOLFOX, and IROX (irinotecan plus oxaliplatin). Patients receiving FOLFOX had significant longer median survival time of 19·5 months compared with 15 months for IFL and 17·4 months for IROX. Because IFL contains bolus fluorouracil compared with FOLFIRI (infusional fluorouracil), these data can be interpreted as an argument for use of infusional fluorouracil in the palliative setting.[141] The toxicity profile is also better for regimens with infusional fluorouracil. The sequence of different available regimens seems to be less important. However, survival is improved if patients receive all active substances during the course of their disease.[142] When considering the role of palliative (and adjuvant) chemotherapy with patients, the physician should be aware that risk reduction might differ from perceived benefit for the patient. As mentioned, not only extension of life, but also toxicity profile and questions about quality of life are important. Other factors, such as the patient's comorbidities, also need to be considered.

Oral administration of prodrugs of fluorouracil could be an alternative to infusional fluorouracil. Capecitabine improved response rates and equivalent overall survival compared with bolus fluorouracil-leucovorin.[143] Tegafur-uracil plus leucovorin also results in similar response rates and overall survival to fluorouracil-leucovorin. Capecitabine and tegafur-uracil have a favourable toxicity profile, but hand-foot syndrome develops in 25% of patients receiving capecitabine. Randomised trials are investigating these agents in combination with oxaliplatin or irinotecan.

Several new drugs are under development that target growth factors, their receptors, or the intracellular signalling cascade, some with proven efficacy in phase II and III trials. Bevacizumab, an antibody that targets vascular endothelial growth factor was tested in combination with IFL in first-line treatment in the palliative setting.[144] Median survival was 20·3 months in the IFL plus bevacizumab group compared with 15·6 months in the IFL plus placebo group, with response rates of 44·8% and 34·8%, respectively (p=0·004). The combination regimen was well tolerated; main toxicities were mild proteinuria and grade III hypertension. In patients with metastatic colorectal cancer that is refractory to irinotecan, the combination of cetuximab (antibody-targeting epidermal growth-factor receptor) with irinotecan led to a response rate of 22·9% compared with 10·8% for cetuximab alone (p=0·007).[145] Only patients with evidence of epidermal growth factor receptor expression in their tumours were included in this trial. Interestingly, degree of expression of this receptor did not correlate with clinical response. Therefore, it remains unclear whether the amount of such expression should be used to select patients for treatment with cetuximab. Antibody therapy seems to enlarge the therapeutic arsenal, but the escalating costs need to be weighed up against the clinical benefit.[146] More trials with carefully defined treatment indications and long-term data are certainly needed before these treatment options can be accepted as standard therapy.[147,148]

For patients with unresectable metastases confined to the liver, intrahepatic arterial chemotherapy is a rational approach because liver metastases are mainly vascularised via the hepatic artery. In a randomised trial[149] no benefit was noted for intra-arterial therapy with fluorouracil compared with systemic therapy; however, compliance to the protocol was poor in the intra-arterial chemotherapy arm. Even though other studies reported encouraging response rates to such chemotherapy, this approach cannot be recommended outside of clinical trials.[150]

Recent advances in the understanding of tumour biology have led to the development of novel drugs targeting different important pathways for the malignant phenotype such as cell proliferation, invasion, and angiogenesis. Other approaches focus on cyclo-oxygenase 2 or aim to modulate immune response. Many of these drugs are currently in phase I and II clinical trials and promise to further expand the therapeutic options.[151–153]

Response prediction

Prediction of the response to chemotherapy would allow its selective use. For fluorouracil-based chemotherapy, intratumoral thymidylate synthase, dihydropyrimidine dehydrogenase, and thymidine phosphorylase as well as microsatellite-instability status could be such markers.[154–156] For oxaliplatin, intratumoral concentrations of ERCC1 (excision repair cross-complementing), and for irinotecan, intratumoral concentrations of topoisomerase 1 seem to allow response prediction.[157] However, there are no randomised trials that prove that survival is improved when management is guided by these markers.

Follow-up

The objectives of follow-up after curative resection of colorectal cancers are improvement of survival, psychological support, quality control of medical care, and facilitation of research.[158] Meta-analyses showed a significant improvement in survival after intense compared with routine follow-up (relative risk ratio 0·67–0·81).[159–161] The cost for one saved year of life by follow-up is estimated at about US$6000–14000, which is judged to be acceptable.[162]

Because of the heterogeneity of published studies, defining how follow-up should be done is difficult, explaining the diversity of published guidelines.[158] Colonoscopy is recommended every 3–5 years to detect metachronous colorectal cancer. For patients who are

healthy and willing to undergo surgery for recurrence, the most useful test seems to be carcinoembryonic-antigen testing every 3–6 months for up to 5 years. Other recommendations also include regular liver and chest imaging, but the benefit of these tests is less well documented.[158] It has been suggested that regular surveillance CT scans in combination with carcinoembryonic-antigen measurements might be of value in the follow-up.[163] Further trials are necessary to specify the best follow-up for patients with colorectal cancer.[164]

Future developments

The molecular genesis of colorectal cancer and therapies focusing on specific molecular targets attract the most attention and promise major advances. Individualised treatment according to genetic tumour profiles might become possible. However, we should not forget that better screening and prevention programmes could save many lives; public education should therefore be a top priority. In the future, prediction of the individual risk of colorectal cancer with individualised screening and prevention could become reality. Surgical quality control is very important, and should either result in better education of the surgical community or in centralisation of high-risk procedures. A multidisciplinary approach based on evidence-based medicine will allow further advances in the management of this common disease.

Conflict of interest statement

We declare that we have no conflict of interest.

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