Colorectal cancer in 2003: old principles, new strategies

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In the last two decades the prognosis of colorectal cancer has improved for two reasons: (i) the proportion of patients with localized disease has increased and treatment has been standardized, and (ii) new chemotherapeutic agents have led to a longer life expectancy for patients with advanced disease. In this review the current insights in disease etiology and treatment of localized and disseminated colorectal cancer are discussed. *Anti-Cancer Drugs* 14:97–102 © 2003 Lippincott Williams & Wilkins.

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Epidemiology

Colorectal cancer is the third most common malignant neoplasm worldwide [1]. The risk of colorectal cancer begins to increase at the age of 40, and rises sharply at the ages of 50 and 55; the risk doubles with each decade and continues to rise exponentially. Efforts to identify causes have led to the hypothesis that adenomatous polyps are precursors for the vast majority of colorectal cancers [2]. Genetics, experimental and epidemiologic studies suggest that the development of colorectal cancer results from complex interactions between inherited susceptibility and environmental factors [3–8]. Heritable factors include familial polyposis colorectal cancer and hereditary non-polyposis colorectal cancer. Inflammatory bowel disease is also related with a higher colorectal cancer risk. Dietary factors considered to increase colorectal cancer risk are high total fat intake, and the consumption of meat and alcohol [9–12]. Dietary factors considered to decrease colorectal cancer risk are fiber and calcium [13–15]. The use of non-steroidal anti-inflammatory drugs also appears to decrease colorectal cancer risk [16]. This is thought to be due to the inhibition of cyclooxygenase-2 (COX-2), an enzyme which indirectly induces resistance to apoptosis, systemic immunosuppression and tumor angiogenesis [17]. Ongoing clinical trials are currently testing the potential therapeutic role of COX-2 inhibitors in both prevention and treatment of different human cancers.

Because of the high incidence of colorectal cancer, an effective screening program would be more than welcome. Fecal occult blood testing is a useful procedure if performed properly and several randomized controlled trials have confirmed that a mortality reduction of 16% can be achieved [18]. However, the cost of the initial testing and the subsequent colonic assessment has not been subjected to a proper cost–benefit analysis and the performance of this test is not common practice in the Netherlands.

Staging and prognostic features

Up to now, only the Dukes classification (and later modifications)—based on tumor extension and nodal involvement—has been implicated in therapeutical decision making [19]. Since 1932, this classification has been modified several times [20,21]. The latest classification—based on tumor extension, nodal involvement and presence of distant metastases (TNM status)—has been formulated by the International Union against Cancer in cooperation with the American Joint Committee on Cancer. The Dukes classification is, however, still most often used in clinical practice. Its relation with more recent modifications and TNM status is depicted in Table 1. The reliability of tumor staging clearly depends on the number of lymph nodes recovered from the resection specimen. Several studies have shown that survival of Dukes B colorectal cancer patients increases with the number of negative lymph nodes examined [22–24]. There is no *communis opinio* regarding the clinical relevance of micrometastases and the results of the studies performed are conflicting [25–28].

The prognosis is strongly related with tumor stage and in the 1980s, 5-year survival percentages used to be about 82, 73 and 40% for Dukes A, B and C tumors, consecutively [29,30]. Early diagnosis, adherence to general guidelines and new treatment strategies have resulted in improvement of these figures over the last two decades [31–33]. Several histological factors, such as thymidine phosphorylase expression, mitotic index and vascular density, appear to have independent prognostic significance [34–41]. There are also certain genetic mutations, such as inactivation of the p53 suppressor

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Table 1 **Relation between TNM status and older staging systems for colorectal cancer**

Dukes (1932) [19]	Dukes modification according to Astler and Coller (1954) [20]	Dukes modification according to Turnbull (1967)	UICC (1987)
A: Tumor penetration into but not through bowel wall	A: Tumor penetration into but not through bowel wall	A	T1N0M0
B: Penetration through bowel wall	B1: penetration through muscularis propria	B1	T2N0M0
	B2: penetration through serosa	B2	T3N0M0, T4N0M0
C: Tumor-positive lymph nodes	C1: B1 and positive lymph nodes	C1	T2N1M0, T2N2M0
	C2: B2 and positive lymph nodes	C2	T3N1M0, T3N2M0 T4N1M0, T4N2M0
		D: beyond the limit of surgical resection	any T, any N, M1

gene, which have shown a negative impact on prognosis [42,43].

Treatment of a primary colorectal carcinoma

Current therapy for Dukes A and B colon cancer consists of resection only. For Dukes C colon cancer 6 months of adjuvant chemotherapy is common practice as this reduces recurrence risk and improves survival. As the risk of local recurrence is much higher in rectal cancer, the efficacy of both adjuvant chemotherapy and adjuvant radiotherapy has been tested. Such studies used to be biased by the diversity of operation procedures. In the late 1990s, due to its low rate of local recurrences, total mesorectal excision (TME) became the standard procedure [44–46]. In a recent randomized controlled trial it has been shown that local recurrence risk can be lowered from 8.2 to 2.4% by the addition of a short cycle of preoperative radiotherapy to the TME procedure [47]. Adjuvant chemotherapy may eliminate distant micrometastases, enhance the local radiotherapy effect and improve overall survival. There are, however, no reports of prospective phase III trials which have tested the efficacy of both preoperative radiotherapy and adjuvant chemotherapy in patients who have undergone total mesorectal excision.

A separate group is formed by patients with locally advanced rectal cancer. New promising approaches aimed at improving operability are intraoperative radiotherapy and radiotherapy in combination with hyperthermia. These procedures are, however, complicated and require the setting of a specialized center. Randomized prospective studies are lacking and only the former procedure has thus far shown a positive impact on clinical outcome [48,49].

Surgical palliation for advanced colorectal carcinoma

Metastasectomy

Surgical intervention is applied in selected patients with hepatic and/or pulmonary metastases.

In case of isolated liver metastases the number, location and size of the metastases, the possibility to excise the metastases with a tumor-free margin of at least 1 cm, and the volume of the remaining liver tissue play a deciding role in the choice whether or not to operate. The results of metastasectomy have never been compared with the results of chemotherapy in a randomized prospective fashion. The former procedure results in a 5-year survival percentage of 25, which is much better than the outcome after chemotherapy [50–54]. However, one should realize that the extension of metastasis is usually smaller and the performance status better in patients who undergo metastasectomy than in patients who undergo systemic chemotherapy, which could partly explain the apparent superiority of metastasectomy. The extension of hepatic metastasis is a strong independent prognostic indicator of survival [55]. In the last decade the indication field for hepatic metastasectomy has widened for two reasons.

Firstly, local ablation techniques, such as cryotherapy and radiofrequency ablation, have enabled the surgical treatment of patients with resectable and irresectable liver metastases [56–71]. The studies on cryotherapy have the longest follow-up and a median survival of 26–32 months has been reported [56–58,60,70]. Both procedures differ in field of indication and complication rate; the maximum treatable diameter of liver metastases is considerably smaller for radiofrequency ablation than for cryotherapy. Radiofrequency ablation is, however, far less invasive and its complication rate lower.

Secondly, a favorable chemotherapy response can render metastatic disease which was previously considered irresectable resectable [72,73].

In case of isolated pulmonary metastases, surgical resection can also be very rewarding [74–83]. After previous pulmonary or hepatic metastasectomy the recurrent disease may again appear resectable and a second metastasectomy may result in a durable disease-free interval for a selected group of patients [84].

Regional chemotherapy

For cases of localized irresectable disease the concept of regional chemotherapy seems attractive, as systemic toxicity is no longer a dose-limiting factor. Regional

chemotherapy can be applied in case of hepatic or peritoneal metastases. Several investigators have tested the potential of cytoreductive surgery and i.p. hyperthermic chemotherapy in patients with peritoneal metastases. The results appeared too poor to justify this therapy outside clinical trials [85–87]. Recently, Zoetmulder *et al.* have published very hopeful results: in a prospective phase III study patients with colorectal cancer metastases confined to the peritoneal cavity were randomized to either palliative chemotherapy or a combination of operative cytoreduction, i.p. hyperthermic chemotherapy and subsequent i.v. chemotherapy. The 2-year survival in the former group was 16% and in the latter group 43%, a significant difference [88].

In case of isolated irresectable liver metastases there are two ways to increase the chemotherapy dose beyond the threshold of serious systemic toxicity; (i) the liver can be connected to a perfusion system (isolated liver perfusion) or (ii) one can deliver the chemotherapy through the hepatic artery (hepatic artery infusion). For this procedure floxuridine is currently used as cytostatic agent. Whereas isolated liver perfusion is still considered to be in an experimental stage, hepatic artery infusion has become a standard procedure in quite a few surgical departments. The response rate after hepatic artery infusion has been shown to be significantly higher than the response rate after systemic chemotherapy [89–94]. A survival advantage has, however, only been found in two studies with a heterogeneous control group of patients who received either supportive care or supportive care and systemic chemotherapy [93,94]. Relative disadvantages of hepatic artery infusion are procedure-specific complications, such as sclerosing cholangitis and chemical hepatitis, and the high cost of intra-arterial pump implantation.

Chemotherapeutical palliation for advanced colorectal carcinoma

5-Fluorouracil (5-FU)

For a long time 5-FU has been the most active single agent against advanced colorectal cancer and in the past decades research has focused on finding the most effective dosing regimen and on developing potent 5-FU-modulators, such as leucovorin and methotrexate.

Bolus 5-FU in combination with the biomodulator leucovorin used to be standard first-line treatment in both the adjuvant and palliative setting. The Mayo Clinics regimen (i.e. 5-FU 425 mg/m^2 and leucovorin 20 mg/m^2, administered on 5 consecutive days every 4 weeks) is the most often used treatment schedule. Several studies have shown that treatment with the Mayo Clinics regimen prolongs median survival with about 3–6 months in patients with advanced colorectal cancer in comparison with supportive care only (median survival 12 versus 6 months) [95–97]. Infusional 5-FU appears more effective in terms of response rate, but there is no difference between infusional and bolus 5-FU in terms of overall survival [98,99]. Some patients considered resistant to 5-FU bolus therapy have shown responses to infusional 5-FU in second-line [100–102].

Recently, oral fluoropyrimidines, such as capecitabine and UFT, have become available. Both drugs can be administered on an almost daytime basis and appear as effective as the Mayo Clinics regimen [103–106]. The convenience of staying at home during treatment in combination with a low toxicity profile (comparable to infusional 5-FU) and equal efficacy has lead to the recognition of oral fluoropyrimidines as standard first-line treatment [107].

Novel drugs

In the last few years two effective new drugs with a working mechanism which completely differs from the fluoropyrimidines have been introduced. They were initially introduced as second-line alternatives. CPT-11 (irinotecan), a topoisomerase I inhibitor, has been shown to prolong survival in 5-FU-resistant patients in comparison with supportive care only and in comparison with infusional 5-FU [108,109]. Another promising new drug is oxaliplatin, a cisplatin analog without renal toxicity. In combination with infusional 5-FU, it has shown a 25% response rate in 5-FU-pretreated patients, whereas the response rate after oxaliplatin only appeared much poorer [110–113]. This suggests a synergistic effect between 5-FU and oxaliplatin.

Meanwhile, CPT-11 and oxaliplatin have both emerged towards the frontline of palliative chemotherapy. In two randomized prospective trials the addition of CPT-11 to either bolus 5-FU or infusional 5-FU and leucovorin led to a higher response rate and about 3 months median survival benefit [114,115]. Three studies have shown that oxaliplatin in combination with infusional 5-FU and leucovorin also leads to a considerable increase in response rate in comparison with bolus 5-FU and leucovorin, but a survival gain has not been found [116–118]. Goldberg *et al.* have recently reported a survival benefit of 4 months (18.6 versus 14.1 months) in comparison with irinotecan, bolus 5-FU and leucovorin (also know as the Saltz regimen), but this difference might well be due to the fact that oxaliplatin was not available as second-line medication for the great majority of patients who had come to the Saltz regimen [119]. All these first-line therapy studies have undoubtedly been biased by the fact that second- and third-line alternatives were administered in an unstandardized and unrandomized fashion. There is no doubt about the efficacy of the fluoropyrimidines, irinotecan and oxaliplatin, and the studies mentioned above have shown that these agents

can add about 12 months to the median survival of patients with advanced colorectal cancer. The main issue is, however, in which order and in which combination these drugs should be administered. This question will be evaluated in a new Dutch Colorectal Cancer Group trial [120].

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