Colorectal Cancer 31

H.L. Kindler, R.L. Schilsky

31.1 Epidemiology and Risk Factors

Colorectal cancer is a major public health problem in Western countries with the highest incidence rates reported in North America, Australia, New Zealand, and western Europe. An estimated 135,000 cases will be diagnosed in the United States in 2001 and approximately 57,000 people will die of the disease [1]. Colorectal cancer is the third most common cancer in men and women and the third most common cause of cancer death in both sexes. The age-specific incidence rises sharply after age 40, with 90% of cancers occurring in individuals age 50 and older. Within the large intestine, 69% of cancers occur in the colon and 31% in the rectum. More than half of all colonic cancers occur either in the sigmoid colon (35%) or in the cecum (22%), although, in recent years, right-sided lesions are becoming more common [2].

Although the specific etiology of colorectal cancer remains unknown, it is likely that the disease results from the accumulation of genetic mutations in the colonic epithelium which ultimately result in the neoplastic phenotype. In some cases, genetic mutations may be inherited as germline mutations, often manifest as familial colon polyp or cancer syndromes. In other cases, somatic mutations in the colonic epithelium, perhaps related to environmental or nutritional exposures, ultimately result in the formation of colon cancer. In most cases, adenomatous polyps are precursors to the development of invasive cancer.

Familial syndromes associated with an increased risk of colorectal cancer are summarized in Table 31.1. Familial adenomatous polyposis (FAP) is inherited in an autosomal dominant pattern and is characterized by the development of hundreds or thousands of adenomatous polyps throughout the colon and rectum. The average age of onset of polyps is during the 20s and virtually 100% of affected individuals will develop colorectal cancer by age 35–40 if total colectomy is not performed [3]. Germline mutations of the FAP gene located at chromosome *5q22* are detectable in all affected individuals and provide a means of diagnosing the disease prior to the onset

Table 31.1. Familial colon cancer syndromes

Feature	Syndrome	
	FAP[a]	HNPCC
Age of onset	20s	40s
Number of adenomas	>100	<10
Adenoma distribution	Left or total	Right
Cancer distribution	Random	Right
Other cancers	Periampullary	Endometrial, ovarian, periampullary, ureteral
Germline mutation	APC gene at *5q22*	hMSH2, hMLH1, hPMS1, hPMS2

[a] Includes Gardner's syndrome of colon polyps, multiple osteomas, desmoid tumors, neoplasms of thyroid, adrenal, biliary tree, liver.

FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colon cancer.

of symptoms. Widespread genetic testing may be difficult, however, because each kindred is likely to have a unique FAP mutation.

The hereditary nonpolyposis colorectal cancer syndromes (Lynch syndromes I and II) are characterized by early age of onset of colorectal cancer, autosomal dominant pattern of inheritance, preponderance of right-sided colon tumors and an excess of synchronous and metachronous colonic and extracolonic tumors [4]. Endometrial and ovarian cancers have been noted to occur in excess in Lynch syndrome I families, while gastric, periampullary, and ureteral tumors are increased in frequency in families with Lynch syndrome II. Genetic linkage analysis has demonstrated a high frequency of microsatellite instability in the germline DNA of Lynch syndrome families. Further studies have revealed mutations in the human homologues of the bacterial DNA mismatch repair genes (*hMSH2*, *hMLH1*, *hPMS1*, *hPMS2*) in these families, which likely contribute to the development of epithelial tumors [5].

Adenomatous polyps are precursors to the development of most colorectal cancers. The genetic abnormalities that accumulate during the progression from adenoma to carcinoma have now been extensively characterized by Vogelstein and colleagues [6]. This progression typically involves mutations in oncogenes such as *FAP*, *ras* and *c-myc* as well as mutations in tumor suppressor genes such as *p53* and *DCC* [7–9]. There is approximately a 5% probability that carcinoma will be present in an adenoma. Adenomatous polyps less than 1 cm in diameter have about a 1% chance of being malignant; those larger than 2 cm contain invasive carcinoma in about 40% of cases.

Patients with inflammatory bowel disease have an increased risk of developing colorectal cancer. Carcinoma complicating ulcerative colitis is related to the duration of active disease, extent of colitis, duration of symptoms, and development of mucosal dysplasia [10]. The risk of developing carcinoma in those with total colitis is estimated at 10–25 times that of the general population. A similar increase in risk has been estimated for those with Crohn's disease; these patients also have an increased risk of small-bowel carcinomas.

Nutritional factors have been implicated in the development of colorectal cancer, including diets high in fat or low in fiber as well as deficiencies in vitamin D, vitamin E, calcium, and selenium [11–13]. While the specific pathobiology has not been elucidated, these observations have prompted study of various dietary interventions to attempt to protect against the development of colorectal cancer, though none have yet produced definitive results [14]. A high-fiber diet had no effect on the rate of recurrent adenoma formation in a randomized trial recently reported by Alberts and colleagues [15].

31.2 Pathology and Staging

Adenocarcinomas account for 90%–95% of all colorectal tumors; the remainder include squamous cell, neuroendocrine, and undifferentiated carcinomas. Adenocarcinoma variants that may be associated with a worse prognosis include mucinous and signet-ring tumors. In addition to depth of invasion through the bowel wall and extent of regional lymph node involvement, histopathologic features that may be of prognostic importance are perineural and/or lymphatic invasion, evidence of obstruction or perforation, and grade of differentiation [16, 17].

The current TNM staging system for colorectal cancer is shown in Table 31.2. The estimated 5-year survival for patients with node-negative tumors depends primarily on depth of invasion through the bowel wall but is generally about 70%–85% after surgery alone. The survival of patients with regional lymph node metastases following surgery alone depends on the number of involved nodes, ranging from 40% to 60% for patients with one to three positive nodes to as low as 25% for those with more than four positive nodes. Patients with rectal cancer are also at high risk of local recurrence in the pelvis. For early-stage, node-negative tumors, the risk of local recurrence is about 5%–10%; it increases to 50% or more if there is transmural penetration of the tumor and involvement of multiple regional nodes.

Recent studies have attempted to identify biologic characteristics of the tumor cells that may be of prognostic importance. Factors such as DNA ploidy and S-phase fraction, deletion of the *DCC* gene, overexpression of thymidylate synthase, and mutation of the *Ki-ras* and *p53* genes have been as-

Table 31.2. Staging of colorectal cancer

TNM staging criteria		
T1	Involves the submucosa but does not invade the muscularis propria	
T2	Invades, but does not penetrate, the muscularis propria	
T3	Penetrates through the muscularis propria into subserosa, or into nonperitonealized pericolonic or perirectal tissues	
T4	Invades other organs or involves the free peritoneal cavity	
N0	No nodal metastases	
N1	One to three pericolic or perirectal nodes involved	
N2	Four or more pericolic or perirectal nodes involved	
N3	Involvement of any regional node along a named vascular trunk	
M0	No distant metastases	
M1	Distant metastases present	
AJCC group staging criteria		*Modified Aster-Coller*
Stage I	T1 N0 M0	A
	T2 N0 M0	B1
Stage II	T3 N0 M0	B2
	T4 N0 M0	B3
Stage III	T1–2 N1–3 M0	C1
	T3 N1–3 M0	C2
	T4 N1–3 M0	C3
Stage IV	Tany Nany M1	D

sociated with a worse prognosis in small series, although none have yet been validated as prognostic markers in large prospective clinical trials [18–23]. The impact of such markers may vary based on the pathologic stage of the tumor and the therapy employed.

A high preoperative CEA level (>5 ng/ml) is the only clinical feature of colorectal cancer that has been consistently predictive of a poor prognosis.

31.3 Work-up and Staging

31.3.1 Evaluation of the Primary Tumor

The presenting symptoms of colorectal cancer, while highly variable and often nonspecific, usually include rectal bleeding, change in bowel habits, and/or abdominal pain and discomfort. Right-sided tumors frequently present with fatigue from the anemia that results from chronic occult blood loss. Left-sided tumors are more likely to present with bright red blood per rectum, constipation or diarrhea alternating with constipation, change in stool caliber, or left lower-quadrant abdominal pain. Tenesmus, rectal bleeding, and a sense of incomplete evacuation are symptoms characteristic of rectal cancer. Systemic symptoms such as anorexia and weight loss occur most commonly in the setting of metastatic disease, and jaundice or right upper-quadrant pain is a frequent harbinger of advanced liver metastases.

The initial evaluation of a patient suspected of having colorectal cancer should include a complete physical examination, including rectal exam with evaluation of the stool for occult blood. Laboratory testing should include a complete blood count and a chemistry panel that includes renal and liver function tests. A colonoscopy should be performed to examine the entire length of the colon and any detected lesions should be biopsied. Proctosigmoidoscopy alone is insufficient since even flexible instruments are able to examine only the distal 60 cm of the colon and may miss right-sided lesions. A carefully performed air contrast barium enema is a useful diagnostic tool but needs to be followed by colonoscopy if lesions are detected. Therefore, colonoscopy has become established as the preferred diagnostic test for patients suspected of having colorectal cancer.

Once a diagnosis of colorectal cancer has been confirmed by biopsy, additional preoperative evaluation should include measurement of serum carcinoembryonic antigen (CEA) level and chest X-ray. The use of preoperative abdominal CT scans to search for metastatic disease is controversial. Synchronous metastatic disease occurs in less than 5% of patients who have a normal physical exam, no weight loss, normal liver function results, and a normal preoperative CEA level. Thus, in the majority of patients, abdominal CT scans are likely to be unrevealing and not cost-effective. Even if metastatic disease is detected preoperatively, most patients still require surgical resection of the primary tumor to prevent complications of obstruction, perforation, or bleeding. However, detection of liver metastases might allow the surgeon to plan for metastasectomy

during the laparotomy. In addition, since cysts and hemangiomas of the liver are common, baseline CT scans can provide useful information that might be important in future clinical decision making.

There is currently no role for other diagnostic modalities prior to laparotomy. In particular, new scanning techniques that employ radiolabeled monoclonal antibodies are not cost-effective in the preoperative evaluation of patients with colorectal cancer.

31.3.2 Work-up for Metastatic Disease

The evaluation of patients suspected of having metastatic disease is based entirely on clinical signs and symptoms. The most common sites of metastases are liver, lung, and bone. Peritoneal metastases also occur. Local tumor recurrence in the pelvis is common in patients with rectal cancer. Most often, metastases are asymptomatic and are first detected by palpation of hepatomegaly or abdominal mass on physical exam or by the occurrence of abnormal liver function tests or a progressively rising CEA level. Symptoms that suggest the presence of metastatic disease include dyspnea with nonproductive cough, bone pain, anorexia and weight loss, abdominal pain, jaundice, pelvic pain, and urinary frequency. The initial diagnostic test of choice is usually a CT scan of the affected area. Radioimmunodiagnostic scans such as the Oncoscint scan or the CEAscan can provide useful complementary information, particularly for detection of metastatic deposits in the retroperitoneum, peritoneal cavity, and pelvis. Both imaging techniques have superior sensitivity to CT scanning in these areas of the body [24, 25].

31.4 Treatment of Colorectal Cancer

31.4.1 Early-Stage Disease

31.4.1.1 Colon Cancer

Surgery is the initial therapy of choice for localized, potentially curable colon cancer. Disease-free and overall survival following surgical resection depend primarily on the pathologic stage of the tumor. Adjuvant chemotherapy has clearly been shown to reduce the risk of recurrence and increase the likelihood of survival of patients with node-positive colon cancer. The combination of 5-FU and levamisole administered for 1 year postoperatively results in a 41% reduction in risk of recurrence and a 33% reduction in risk of death compared with no adjuvant therapy [26]. The results of several large randomized trials have led to the replacement of this regimen with the combination of 5-FU and leucovorin administered for 6 months [27–30]. INT-0089, a large multicenter randomized clinical trial, compared 5-FU plus levamisole to 5-FU with high-dose leucovorin, 5-FU with low-dose leucovorin, or the three drug combination of 5-FU, low-dose leucovorin, and levamisole. With a median follow-up of 5 years, there were no significant differences in relapse-free (DFS) or overall survival (OS) [31]. In each case, 5-year DFS and OS were approximately 60% and 66%, respectively. The three drug combination of 5-FU/low-dose leucovorin and levamisole produced superior survival compared with 5-FU/levamisole. The overall conclusion from the study was that 6 months of chemotherapy with 5-FU/leucovorin should be considered the standard adjuvant regimen for patients with resected high-risk colon cancer. A similar trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP CO-4) compared 5-FU/levamisole with 5-FU/high-dose leucovorin or 5-FU/high-dose leucovorin/levamisole. Preliminary results suggest that 5-FU/high-dose leucovorin is superior to 5-FU/levamisole and equivalent to the three-drug

Table 31.3. Commonly used adjuvant chemotherapy regimens for colon cancer

Roswell Park regimen
Leucovorin 500 mg/m^2 weekly × 6
5-Fluorouracil 500 mg/m^2 weekly × 6
Two week break, then repeat
Duration of therapy: 48 weeks
Mayo Clinic regimen
Leucovorin 20 mg/m^2 daily × 5
5-FU 425 mg/m^2 daily × 5
Repeat every 28 days
Duration of therapy: 6 months

regimen [32]. A trial conducted by the North Central Cancer Treatment Group demonstrated that leucovorin does not add to the benefits of 12 months of adjuvant therapy with 5-FU/levamisole but that 6 months of therapy with 5-FU/levamisole is inferior to 6 months of therapy with the three-drug combination [33]. Acceptable 5-FU/leucovorin (5-FU/LV) regimens for adjuvant therapy of colon cancer are summarized in Table 31.3.

Ongoing adjuvant chemotherapy trials compare standard 5-FU/LV alone to oral fluoropyrimidines, including capecitabine and UFT/LV. The three-drug regimen of irinotecan (CPT-11) in combination with 5-FU/lecovorin is being compared to 5-FU/leucovorin alone in patients with stage III colon cancer in an intergroup study. The three-drug combination of oxaliplatin with 5-FU/leucovorin is also being compared to 5-FU/leucovorin alone in patients with stage III colon cancer.

The use of adjuvant chemotherapy for patients with stage II (node-negative) colon cancer remains controversial. The NSABP performed a retrospective analysis of outcomes in 1565 stage II patients treated on a series of adjuvant chemotherapy protocols (C01–C04) [34]. The results suggested that stage II patients may benefit from adjuvant therapy to the same extent as stage III patients. In contrast, a similar retrospective analysis of 1016 patients with stage B2 colon cancer randomized in five clinical trials to 5-FU/LV or observation by the IMPACT B2 investigators concluded that there is insufficient data to support the use of adjuvant chemotherapy in these patients [35]. While it may be possible to identify stage II patients at particularly high risk of relapse based on biochemical or molecular features of their tumors, prospective trials have not yet shown that the prognosis of such patients can be improved with the use of adjuvant chemotherapy. At the present time, the use of adjuvant chemotherapy for node-negative patients should be an individualized decision based on the clinical, pathologic, and biologic characteristics of the tumor, the patient's general medical condition, and willingness to receive chemotherapy.

An alternative to chemotherapy is the use of immunotherapy in the adjuvant postoperative setting. A randomized clinical trial compared administration of the murine monoclonal antibody 17-1A to surgery alone for patients with potentially curable cancer of the colon and rectum. With a median follow-up of 7 years, treated patients had a significant reduction in risk of recurrence (27%) and improvement in survival (30%); the magnitude of the benefit was similar to that originally reported for 5-FU/levamisole [36]. A confirmatory phase III trial of 5-FU/leucovorin plus or minus antibody vs antibody alone in 2761 patients with stage III disease demonstrated that the addition of antibody to chemotherapy did not improve disease-free or overall survival. Antibody monotherapy was associated with a significantly shorter disease-free and overall survival [37]. A trial of antibody vs surgery alone in stage II patients is ongoing.

Perioperative infusion of chemotherapy directly into the portal vein has also been studied as a means of reducing the risk of developing hepatic metastases. NSABP CO-2 randomly assigned 1158 patients with Dukes' A, B, and C disease to curative resection alone or resection followed by perioperative portal vein infusion of 5-FU at a dose of 600 mg/m^2 per day for 7 days. With 7 years of follow-up, there was a significant improvement in disease-free (68% vs 60%) and overall survival (76% vs 71%) for the treated group; however, there was no reduction in the incidence of hepatic metastases [38]. These results suggested that, while perioperative administration of chemotherapy might be beneficial, the route of administration directly into the portal vein might not be critically important. A meta-analysis of ten randomized trials of adjuvant portal vein infusion of chemotherapy suggests a 10%–15% reduction in risk of death compared with surgery alone for patients treated with portal vein infusion of 5-FU [39].

31.4.1.2 Rectal Cancer

Local/regional recurrence in the pelvis occurs in 25%–50% of patients with rectal cancer; the magnitude of the risk is related to the depth of penetration of the primary tumor and the number of involved regional nodes. Both preoperative and postoperative pelvic radiation (RT) reduce the risk of local failure, although most randomized trials have failed to demonstrate a survival benefit [40]. A

Swedish multicenter randomized trial demonstrated that preoperative RT given as 25 Gy delivered in five fractions in 1 week followed by surgery within 1 week later resulted in a significant reduction in the risk of local recurrence and significant improvement in overall survival (58% vs 48% at 5 years) compared with surgery alone [41].

In the United States, combined modality postoperative adjuvant therapy has been considered the standard based on the results of a series of randomized clinical trials. Most studies have employed sequential administration of chemotherapy followed by pelvic RT with concurrent chemotherapy followed by additional cycles of chemotherapy. Treatment typically begins within 6 weeks of surgery and is completed over approximately 6 months. These studies have clearly demonstrated that combined-modality therapy results in superior local control and overall survival compared to surgery alone or surgery followed by pelvic RT [42–44], that continuous infusion of 5-FU during pelvic RT reduces both loco-regional and distant failure compared to intermittent bolus administration of 5-FU during RT [45], and that the addition of levamisole, leucovorin or their combination to 5-FU results in increased systemic toxicity without a clear improvement in local tumor control or overall survival [46]. Thus, at the present time, standard postoperative adjuvant therapy for patients with stages II and III rectal cancer consists of two cycles of systemic administration of 5-FU alone followed by pelvic RT with concomitant administration of continuous intravenous infusion of 5-FU, followed by two additional cycles of 5-FU chemotherapy.

Selected patients with early-stage rectal cancer and distal rectal lesions can be managed successfully with local excision of the tumor, thereby preserving normal sphincter function. Tumors amenable to this approach are often small, exophytic, mobile tumors without adverse pathologic features (i.e., high grade, blood or lymphatic vessel invasion, perineural invasion, penetration into or through the muscularis propria). T1 tumors generally require no further therapy following excision; however, more deeply invasive tumors or those with adverse pathologic features may have risks of local recurrence or positive regional nodes in the range of 15% to 20% and therefore require additional postoperative therapy. A multi-institutional phase II trial for patients with distal rectal T1/T2 lesions evaluated transanal excision followed by postoperative combined modality therapy for patients with T_2 tumors [47]. After a median follow-up of 48 months, 8 of 113 patients died of cancer. Two T1 and seven T2 patients developed isolated local recurrences; all underwent salvage abdominoperineal resection, and five of these patients remain disease-free.

31.4.2 Metastatic Colorectal Cancer

31.4.2.1 Surgical Therapy

Metastases to the liver and lungs account for the majority of non-nodal metastases from colorectal cancer. Resection of metastases has been associated with long-term disease-free survival in as many as 25%–40% of selected patients. Patients most likely to benefit from resection of hepatic metastases include those with an early-stage primary tumor and a long disease-free interval (> 1 year) from initial diagnosis to the appearance of the metastatic lesions; patients with asymptomatic metastases; patients with no more than four liver lesions; and patients in whom a negative 1-cm surgical margin can be obtained at resection [48, 49]. The size and location of metastases in the liver do not by themselves impact on prognosis as long as adequate surgical margins can be obtained. Resection of hepatic metastases is contraindicated in patients with extrahepatic disease. Therefore, all operative candidates should be carefully evaluated with a preoperative CT scan of the chest, abdomen and pelvis, colonoscopy, serum chemistries, and CEA determination. Intraoperative biopsy of all suspicious lesions should occur prior to proceeding with definitive hepatic resection and intraoperative ultrasound of the liver should be performed to attempt to identify small lesions that might have been missed by other radiographic procedures.

Resection of pulmonary metastases can be considered for patients with disease confined to the lungs who have sufficient pulmonary function to tolerate resection. Thus, candidates for resection re-

quire extensive preoperative evaluation. Operative mortality averages 1% in contemporary surgical series and 5-year survival ranges from 15% to 40% [50].

Patients with metastatic disease confined to the liver who are not surgical candidates due to poor hepatic function, previous resection, or bilobar tumors may be appropriate for tumor ablation with cryosurgery or radiofrequency ablation (RFA). Cryosurgery uses a liquid nitrogen probe to freeze tumor tissue; it can be performed on larger tumors and requires a laparotomy. Radiofrequency ablation employs radiofrequency current to generate heat within the tumor. It can be performed laparoscopically, at celiotomy, or percutaneously. RFA can only be used on tumors smaller than 3 cm in diameter [48].

31.4.2.2 Systemic Chemotherapy

The drug 5-fluorouracil has been the cornerstone of chemotherapeutic treatment of colorectal cancer for over 40 years. The relatively modest response rates achieved with this drug has prompted numerous evaluations of modulating agents and alternate schedules of administration. The modulation of 5-FU by leucovorin is perhaps the most successful biochemical modulation strategy to be brought from laboratory to clinic. By repleting intracellular stores of reduced folates, the addition of leucovorin results in more sustained inhibition of thymidylate synthase by fluorodeoxyuridylate and increased 5-FU cytotoxicity [51]. A meta-analysis of nine randomized trials comparing 5-FU/LV to 5-FU alone concluded that the addition of leucovorin to 5-FU improves response (11% vs 23%) but not survival [52]. Therapy with 5-FU/LV achieves objective tumor regression in 15%–20% of patients with measurable disease and yields a median time to disease progression of 6 months and a median survival of 10–12 months. Other attempts at improving the efficacy of 5-FU chemotherapy by the addition of cisplatin, ∝-interferon or N-(phosphonacetyl)-L-aspartate (PALA) have not been effective in randomized clinical trials [53]. Increased response rates have been achieved when a lipid soluble antifolate, trimetrexate, is administered 24 h prior to a 5-FU/LV combination. Phase II studies of this regimen have demonstrated response rates of 35%–50% with acceptable toxicity [54, 55]. This combination is presently being compared to 5-FU/LV in a multicenter, randomized placebo-controlled clinical trial.

Numerous schedules of 5-FU have been assessed (Table 31.4). Toxicity varies with schedule of 5-FU administration: the weekly regimen causes more diarrhea, the monthly regimen more stomatitis and neutropenia, and continuous infusion, primarily hand-foot syndrome. A meta-analysis of randomized trials that compared IV bolus to continuous IV infusion of 5-FU demonstrated a modest survival advantage for infusional therapy (median survival 11.3 vs 12.1 months) [56].

The oral fluoropyrimidines were designed to facilitate protracted drug exposure without the need

Table 31.4. Commonly used schedules of 5-FU for patients with metastatic colorectal cancer

Mayo Clinic	5-FU 425 mg/m^2 i.v. bolus q day × 5 days, leucovorin 20 mg/m^2 i.v. bolus q day × 5 days; repeat q 28–35 days
Roswell Park	5-FU 600 mg/m^2 i.v. bolus midway through LV; leucovorin 500 mg/m^2 i.v. over 2 h; q week × 6 every 8 weeks
Protracted continuous infusion	300 mg/m^2/day continuous infusion × 6 weeks every 8 weeks
AIO	Leucovorin 500 mg/m^2 i.v. over 2 h then 5-FU 2600 mg/m^2 by continuous infusion over 24 h q week × 6 every 8 weeks
DeGramont [69]	Leucovorin 200 mg/m^2 i.v. over 2 h days 1 and 2, followed by 5-FU 400 mg/m^2 i.v. bolus days 1 and 2, followed by 5-FU 600 mg/m^2 over 22 h by continuous infusion days 1 and 2 q 2 weeks
Saltz [64]	Irinotecan 125 mg/m^2 i.v. over 90 min; leucovorin 20 mg/m^2 i.v. bolus; 5-FU 500 mg/m^2 i.v. bolus q week × 4 every 6 weeks

for indwelling catheters and infusion pumps. The drug 5-fluorouracil cannot be orally administered due to rapid metabolism to inactive metabolites by dihydropyrimidine dehydrogenase (DPD) located in the gut wall and liver. To circumvent this, 5-FU prodrugs that are not substrates for DPD have been designed or 5-FU has been administered in combination with specific DPD inhibitors. Both strategies have been effective in permitting delivery of pharmacologically active concentrations of 5-FU into the systemic circulation. Capecitabine and UFT are both metabolized to 5-FU following oral administration and have shown activity in colorectal cancer.

Capecitabine (Xeloda) is an oral fluoropyrimidine carbamate that is converted to 5-FU by a three-step process in liver and tumor tissues. A 109-patient randomized phase II trial demonstrated that the optimal schedule is 2500 mg/m^2 in two divided doses for 14 days every 21 days [57]. A randomized phase III trial in 605 previously untreated patients compared capecitabine to 5-FU/LV given on a daily × 5 schedule. Although the response rate for capecitabine was higher (24.8% vs 15.5%; $P = 0.005$), median survival and time to progression were not different [58]. Capecitabine is currently indicated for first-line treatment of colorectal cancer when fluoropyrimidine monotherapy is preferred.

UFT consists of uracil plus tegafur in a 4:1 molar ratio. UFT given with leucovorin is known as Orzel. Tegafur is a 5-FU prodrug, uracil competitively inhibits DPD, and LV modulates thymidylate synthase (TS). This results in prolonged therapeutic drug levels similar to continuous infusion 5-FU. An 816-patient randomized phase III trial compared Orzel to 5-FU/LV using a daily × 5 schedule. The two regimens achieved similar response rates (12 vs 15%) and there was no difference in survival or time to progression. There was a significantly lower rate of grade III–IV neutropenia (1% vs 56%) with the oral regimen [59].

Irinotecan (CPT-11), a topoisomerase-1 inhibitor, was initially approved for patients whose tumors progress following treatment with 5-FU. Response rates range from 15% to 20%; response duration is about 4 months [60, 61]. The dosage schedule most commonly used in the United States is 125 mg/m^2 weekly for 4 weeks followed by a 2-week rest period, while that most often used in Europe is 350 mg/m^2 every 3 weeks. The regimens seem to be equivalent in both efficacy and toxicity. A randomized trial has demonstrated that CPT-11, administered on the every 3 week schedule, results in improved survival compared with best supportive care in patients with 5-FU-refractory colorectal cancer [62]. CPT-11 was also superior to continuous infusion 5-FU in patients who failed previous treatment with 5-FU [63] Toxicities of CPT-11 include diarrhea and neutropenia. Intensive loperamide therapy is necessary to minimize the severity and duration of diarrhea in patients receiving CPT-11.

The standard of care for the front-line treatment of metastatic colorectal cancer changed in March 2000 from 5-FU/LV to the three-drug combination of 5-FU/LV/CPT-11, based on the results of two large randomized phase III trials. Saltz and colleagues compared 5-FU/LV, single-agent CPT-11, and 5-FU/LV/CPT-11 in 683 previously untreated patients. The three-drug combination resulted in a significantly higher response rate (39% vs 21%; $P < 0.001$), a longer progression-free survival (7.0 vs 4.3 months; $P = 0.004$), and a longer overall survival (14.8 vs 12.6 months; $P = 0.04$) than 5-FU/LV given on a daily × 5 schedule [64]. Similarly, Douillard and colleagues compared continuous infusion 5-FU/LV on the DeGramont or German AIO schedule (see Table 31.4 for details on these regimens) with or without CPT-11 in 387 patients. Treatment with the three-drug combination of 5-FU/LV/CPT-11 yielded higher responses rates, a longer time to progression, and superior survival compared with 5-FU/LV alone [65]. Not all patients can tolerate this regimen, however. Two cooperative group phase III clinical trials were suspended in the spring of 2001 when higher than expected toxic death rates were observed within the first 60 days of treatment with 5-FU/LV/CPT-11. Deaths were principally due to dehydration, diarrhea, neutropenia, and sepsis. This led to the institution of stricter dose-adjustment guidelines for patients receiving this regimen [66].

Patients whose tumors progress following 5-FU and CPT-11 are unlikely to respond to treatment with conventional chemotherapy and should be considered for participation in clinical trials of novel therapies if they have adequate performance status and organ function. Among the most active

drugs currently being investigated for treatment of colorectal cancer is oxaliplatin, a novel diaminocyclohexane (DACH) platinum that has produced objective tumor regression in 10% of patients with 5-FU refractory disease and in 24% of previously untreated patients [67, 68]. De Gramont and colleagues compared oxaliplatin with infusional 5-FU/LV to infusional 5-FU/LV alone in 420 previously untreated patients. The three-drug regimen resulted in a higher response rate (51% vs 22%) and a longer median survival (16.2 vs 14.7 months, $P = 0.12$) than 5-FU/LV alone [69]. Oxaliplatin is approved for the treatment of colorectal cancer in Europe. Phase III trials in the second- and third-line setting are ongoing in the United States.

31.4.2.3 Regional Therapy of Metastatic Disease

The delivery of chemotherapy into the hepatic artery has been facilitated by the development of implantable infusion pumps. The rationale for this approach is that the liver is the most common site of metastases from colorectal cancer and liver metastases derive most of their blood supply from the hepatic artery. Fluorodeoxyuridine (FUDR) is most commonly used because of its exceptionally high hepatic extraction. Seven prospective randomized trials comparing systemic fluoropyrimidine therapy with HAI FUDR have now been completed (Table 31.5) [70–75]. In each study, the response rate to hepatic artery infusion (HAI) therapy was significantly higher than to systemic treatment, yet no study demonstrated a clear survival advantage for HAI, in part because many patients receiving systemic therapy crossed over to HAI treatment at the time of disease progression. A meta-analysis of these studies has confirmed the significantly higher response rates for HAI therapy and also revealed a survival advantage [76]. HAI has also been evaluated for adjuvant treatment following resection of hepatic metastases. HAI with FUDR plus systemic 5-FU/LV was compared to systemic 5-FU/LV alone in a 156-patient phase III study. The rate of survival free of hepatic recurrence was higher in the combined treatment group, but overall survival was not significantly improved [77].

The toxicity of HAI, once considerable, has been ameliorated with the introduction of new drug combinations and new schedules of drug administration. The most significant toxicity is jaundice secondary to sclerosing cholangitis induced by chemotherapy. Ulceration of the gastric and/or duodenal mucosa has also been reported due primarily to inadvertent perfusion of the mucosa of the stomach or duodenum via collateral branches of the hepatic artery. Approaches that appear to reduce the toxicity of HAI therapy include addition of dexamethasone to the infusate, decreasing the duration of the infusion and alternating intraarterial (IA) administration of FUDR with IA 5-FU. Final assessment of the role of HAI chemotherapy in treatment of metastatic colorectal cancer awaits completion of a definitive randomized trial with

Table 31.5. Randomized trials of hepatic artery infusion chemotherapy for unresectable metastatic disease

		HAI			Systemic therapy		
Group	*N* patients	Drug	Response rate (%)	Survival (months)	Drug	Response rate (%)	Survival (months)
MSKCC	162	FUDR	53	17	FUDR	21	12
NCOG	143	FUDR	42	16.8	FUDR	10	16.1
NCI	64	FUDR	62	17	FUDR	17	12
Consortium	43	FUDR	58	NR	5-FU	38	NR
City of Hope	41	FUDR	56	NR	5-FU	0	NR
Mayo Clinic	69	FUDR	48	12.6	5-FU	21	10.5
France	163	FUDR	43	15	5-FU	9	11

NR, not reported; MSKCC, Memorial Sloan Kettering Cancer Center; NCOG, Northern California Oncology Group; NCI, National Cancer Institute.

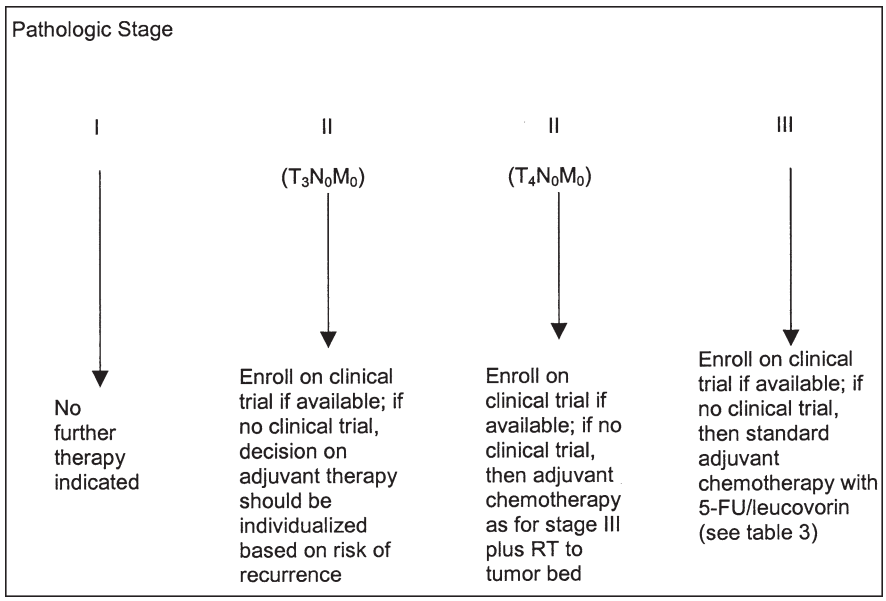

Fig. 31.1. Guidelines for adjuvant therapy of colon cancer

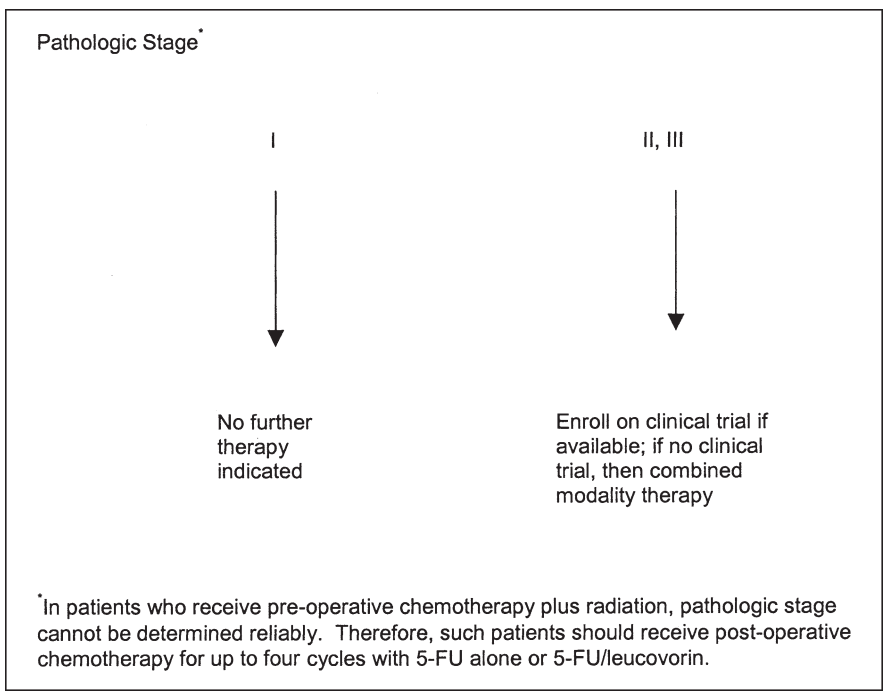

Fig. 31.2. Guidelines for adjuvant therapy of rectal cancer

Physical Exam:	Every 3 months for 2 years then every 6 months to 5 years
CBC and serum chemistries:	Same as for physical exam
CEA:	If elevated at diagnosis or post-colectomy then repeat every 6 months for 2 years, then annually for 5 years
Abdominal/pelvic CT:	Obtain 4-6 weeks after surgery as baseline. Repeat if clinically indicated
Chest X-ray:	Annually
Colonoscopy:	Repeat annually for 2 years; if negative x 2 then repeat every 3 years. If polyps detected, repeat annually

Fig. 31.3. Guidelines for follow-up of patients after completion of primary therapy

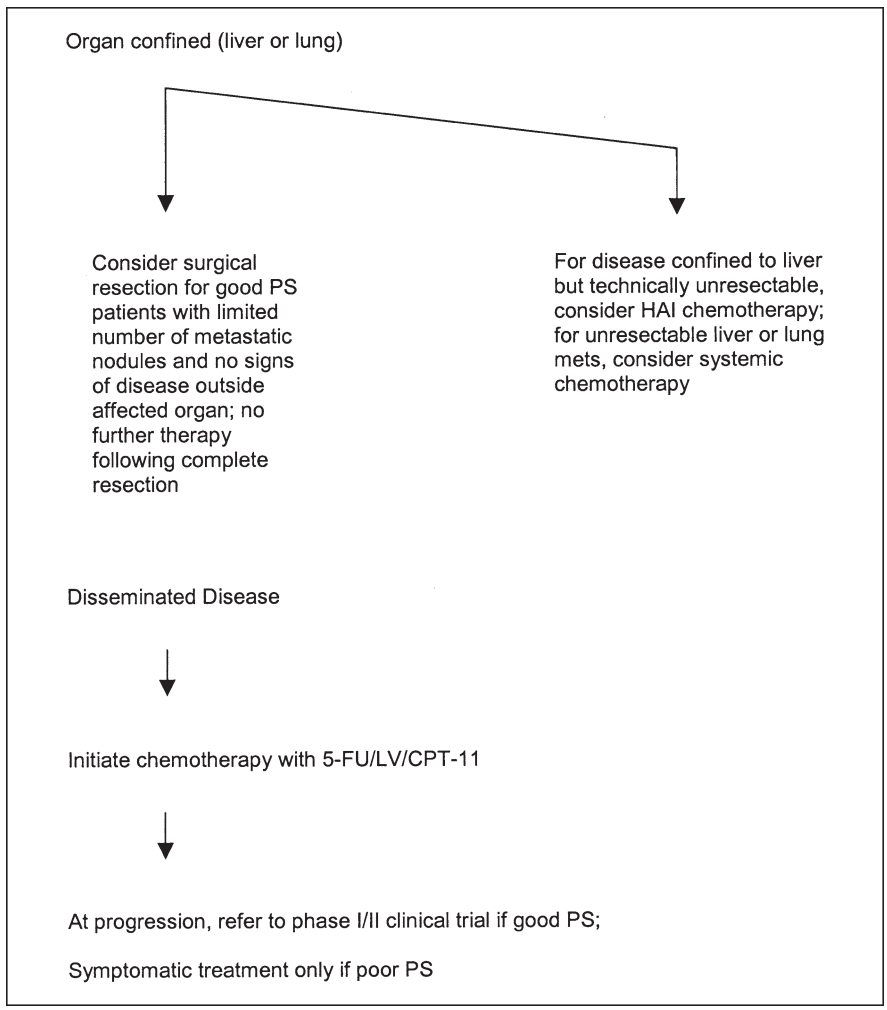

Fig. 31.4. Guidelines for therapy of metastatic colorectal cancer

adequate numbers of patients, prohibition of crossover, and inclusion of quality-of-life and economic endpoints in addition to response rate and survival.

31.5 Conclusion

As our understanding of the biology of colorectal cancer improves, it will inevitably lead to more effective strategies for prevention, early detection, and treatment. The biologic characteristics of tumors can already be used to assess prognosis and the likelihood of response to fluoropyrimidine therapy. Current therapeutic strategies, summarized in Figs. 31.1–31.4, will no doubt soon be modified to incorporate biologic markers into the current staging systems and to include new chemotherapeutic and cytostatic agents in the management of all stages of colorectal cancer.

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