Chapter 12
Colon Cancer

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12.1 Introduction

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States [1]. Worldwide, bowel cancer is the third most commonly diagnosed cancer, with approximately 1.4 million cases per year, and the fourth leading cause of cancer death [2]. The global incidence of CRC varies by more than tenfold. The highest incidence rates are in Australia, New Zealand, Europe and North America, and the lowest rates are in Africa and South Central Asia. This geographic variation appears to be due to differences in the dietary and environmental exposures that are imposed on a background of genetically determined susceptibility [3]. In the United States the incidence and mortality for colorectal cancer decreased in the last 20 years as a result of cancer prevention and earlier diagnosis [4]. However, this is not true worldwide, because access to diagnosis and treatment is heterogeneous, resulting in late diagnosis, advanced stage disease and poor treatment in some countries [2].

In this chapter, we summarize the recommendations for the management of colon cancer (CC). These recommendations are focused on the risk assessment, clinical presentation, diagnosis, clinical and pathologic staging, surgical management, perioperative treatment, patient surveillance, management of recurrence and metastatic disease.

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12.2 Risk Assessment

Environmental and genetic factors can increase the likelihood of developing CRC [5]. Although inherited susceptibility results in the most striking increase in risk, the majority of CRCs are sporadic instead of familial. The risk factors can be separated into those that confer a sufficiently high risk to alter the recommendations for CRC cancer screening, and those that do not alter the screening recommendations because they are thought to confer a small or uncertain magnitude of risk. Approximately 20 % of colon cancer cases are associated with familial clustering, and first-degree relatives of patients with newly diagnosed CRC adenomas or invasive cancer are at an increased risk of CRC [6]. Therefore, it is recommended that all patients with colon cancer be asked about their family history and considered for risk assessment.

The following are the risk factors that currently influence screening recommendations: familial adenomatous polyposis (FAP); Lynch syndrome (HNPCC); MUTYH-associated polyposis (MAP); personal or familial history of sporadic CRC or adenomatous polyps; inflammatory bowel disease; and abdominal irradiation.

The following are the risk factors that do not alter screening recommendations: diabetes mellitus and insulin resistance; the use of androgen deprivation therapy; cholecystectomy; alcohol; and obesity.

FAP and HNPCC are the most common of the familial colon cancer syndromes, but these two conditions, combined, account for only 5 % of CRC [7, 8]. However, many institutions recommend the use of immunohistochemistry (IHC) and microsatellite instability (MSI) testing in all newly diagnosed CRC cases, regardless of the family history, to identify the patients who should undergo genetic testing for Lynch syndrome [9, 10]. The cost effectiveness of this approach has been confirmed for CRC, and this approach has been endorsed by the Evaluation of Genomic Application in Practice and Prevention (EGAPP) working group [11]. The NCCN Colon/Rectal Cancer Panel endorses a selective approach as follows: test all patients with CRC diagnosed at <70 years, as well as patients diagnosed at older ages, who meet the Bethesda Guidelines [12].

CRC screening recommendations:

1. Average risk: age >50 years, no history of adenoma or sessile serrated polyps (SSPs) or CRC, no history of inflammatory bowel disease, and a negative family history for CRC.
    1.1. Colonoscopy: if there are no polyps, rescreen with any modality in 10 years; if polyps are detectable, perform polypectomy; if polyps are hyperplastic, non-SSP, and <1.0 cm, rescreen in 10 years; and for polyps with adenoma/SSP, follow up with patients post-polypectomy [13, 14].
    1.2. Stool-based (high-sensitivity guaiac-based or immunochemical-based) testing: if negative, rescreen with any modality in 1 year and if positive, perform colonoscopy [15, 16].

2. Increased risk: inflammatory bowel disease (IBD); HNPCC; and FAP.
    2.1. IBD: initiation 8–10 years after the onset of symptoms of pancolitis with colonoscopy every 1–2 years; [17]
    2.2. HNPCC: initiation of colonoscopy at age 20–25 years, or 10 years prior to the earliest age of colon cancer diagnosis in the family (whichever comes first); colonoscopy should be repeated annually [18, 19].
    2.3. FAP: initiation of colonoscopy at age 10–15 years; colonoscopy should be repeated annually until age 35–40 if negative [20].

A large number of factors have been associated with a decreased risk of CRC. These include physical activity, dietary factors, and the regular use of aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs).

Physical Activity In a meta-analysis of 21 studies, there was a significantly reduced risk of 27 % and 26 % for proximal and distal colon cancer, respectively, when comparing the most and least active individuals [21].

Dietary Factors Many studies have reported an association between the intake of a diet high in fruits and vegetables and protection from colorectal cancer. However, discordant data have also been published. A meta-analysis of 19 cohort studies concluded that there was a weak protective effect of the highest versus lowest intake of fruits and vegetables [22]. Studies have identified a role for dietary fiber in the pathogenesis of CRC. The American Gastroenterology Association guidelines recommend a total fiber intake of at least 30–35 g/day to reduce the risk of colon cancer [23]. Omega 3 fatty acids (mainly as fish oil) have been associated with a reduced incidence of CRC. A meta-analysis of 22 prospective cohorts and 19 case-control studies found an overall lower incidence of CRC among individuals with the highest consumption [24].

Aspirin or Nonsteroidal Anti-inflammatory Drugs (NSAIDs) A meta-analysis was published showing the benefit of aspirin in preventing CRC in individuals who have a history of colorectal adenomas [25]. However, the majority of medical societies believe that the harms of such a strategy outweigh the benefits for patients who have average risk. For patients with Lynch syndrome, aspirin is recommended at a dose 600 mg/day to reduce the risk of CRC [26]. Sulindac was analyzed for chemoprevention in patients with FAP. Although the study demonstrated regression of colonic and rectal cancer adenomas with sulindac, which reduced the number and size of adenomas, the effect is incomplete. As a result, this treatment approach is unlikely to replace colectomy as the primary prevention therapy [27]. However, there are no FDA-approved drugs for chemoprevention in FAP.

12.3 Clinical Presentation

Colon cancer can produce signs and symptoms that depend on the location, size and extension of the tumor. They vary from asymptomatic to very symptomatic patients. The most common include hematochezia or melena, abdominal pain, otherwise

unexplained iron deficiency anemia, and/or a change in the bowel habits, constipation, diarrhea, nausea or vomiting, anorexia, weight loss, obstruction, and perforation [28].

12.4 Diagnosis

Colon cancer can be diagnosed in asymptomatic (screening) or symptomatic patients (through investigation of the symptoms/signs above).

Colonoscopy is the most accurate and versatile diagnostic test. It can be used to locate and biopsy lesions as well as detect obstructions, synchronous neoplasms, polyposis and remove polyps. The correct description of these alterations is very import for planning the treatment and follow-up for the patients [29].

Flexible sigmoidoscopy is generally not considered an adequate diagnostic study for a patient who is suspected of having colon cancer. It can access only the left colon and rectum. In such cases, a full colonoscopy is needed to evaluate the remainder of the colon for synchronous polyps and cancer, which should be preferentially performed before the surgery.

Virtual colonoscopy provides a computer-simulated endoluminal perspective of the air-filled distended colon. It can be used in a patient who has refused traditional colonoscopy to investigate suspected colon cancer or for a patient with incomplete colonoscopy in an initial diagnostic test [30].

The diagnosis will sometimes be suspected in the presence of metastasis identified by clinical examination or radiologic testing. In this case, a sample of metastatic tissue can be obtained, allowing for conclusive diagnosis without the use of an endoluminal examination test.

12.5 Clinical Staging

After reaching a diagnosis, staging is mandatory to planning the best treatment. A physical examination that pays particular attention to hepatomegaly, ascites and lymphadenopathy is recommended. Radiologic evaluation will include CT scan (chest, abdominal and pelvis) and a complete colonoscopy. Laboratory tests include evaluation of carcinoembryonic antigen (CEA), liver enzymes and the complete blood count. Other exams are ordered according to the symptoms, signs or clinical comorbidities [31–34].

Liver Magnetic Resonance Imaging (MRI): MRI is generally reserved for patients who have suspicious, but not definitive, findings on CT scan, particularly if a better definition of the hepatic disease burden is needed to make decisions about potential hepatic resection. Liver-specific contrast agents have improved the capacity for identifying liver metastases and making a differential diagnosis [35–37].

Positron Emission Tomography (PET/CT) Scans: There is consensus that a PET/CT scan is not routinely indicated at baseline for the preoperative workup. PET/CT is recommended in patients with an increasing CEA level and nondiagnostic conventional imaging evaluation following primary treatment. In this case, it can localize occult disease, allowing for the development of individualized treatment. PET/CT is also recommended for evaluating patients who are thought to be present or future candidates for resection of metastasis to reduce the use of futile surgery [38–42].

12.6 Pathological Staging

Pathological staging is decisive for determining the prognosis and adjuvant treatment of colon cancer. A complete description, including of the gross appearance (macroscopy), histologic type, margins, vascular and lymphatic invasion, perforation, invasion (adjacent structures), and lymph nodes (at least 12), is required at a minimum [43–45] (Table 12.1).

TNM 7th – Definitions **[43]**

Primary Tumor (T)

TX – Primary tumor cannot be assessed

Table 12.1 TNM 7th – anatomic stage/prognostic groups [43]

Stage					
	T	N	M	Dukes[a]	MAC[b]
0	Tis	N0	M0	–	–
I	T1	N0	M0	A	A
	T2	N0	M0	A	B1
IIA	T3	N0	M0	B	B2
IIB	T4a	N0	M0	B	B2
IIC	T4b	N0	M0	B	B3
IIIA	T1–T2	N1/N1c	M0	C	C1
	T1	N2a	M0	C	C1
IIIB	T3–T4a	N1/N1c	M0	C	C2
	T2–T3	N2a	M0	C	C1/C2
	T1–T2	N2b	M0	C	C1
IIIC	T4a	N2a	M0	C	C2
	T3–T4a	N2b	M0	C	C2
	T4b	N1–N2	M0	C	C3
IVA	Any T	Any N	M1a	–	–
IVB	Any T	Any N	M1b	–	–

[a]Dukes classification
[b]Modified Astler-Coller classification

T0 – No evidence of primary tumor
Tis – Carcinoma in situ: intraepithelial or invasion of the lamina propria
T1 – Tumor invades the submucosa
T2 – Tumor invades the muscularis propria
T3 – Tumor invades through the muscularis propria into the pericolorectal tissues
T4a – Tumor penetrates into the surface of the visceral peritoneum
T4b – Tumor directly invades or is adherent to other organs or structures

Regional Lymph Nodes (N)

NX – Regional lymph nodes cannot be assessed
N0 – No regional lymph node metastasis
N1 – Metastasis in 1–3 regional lymph nodes
N1a – Metastasis in one regional lymph node
N1b – Metastasis in 2–3 regional lymph nodes
N1c – Tumor deposit(s) in the subserosa mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2 – Metastasis in four or more regional lymph nodes
N2a – Metastasis in 4–6 regional lymph nodes
N2b – Metastasis in seven or more regional lymph nodes

Distant Metastasis (M)

M0 – No distant metastasis
M1 – Distant metastasis
M1a – Metastasis confined to one organ or site (e.g. liver, lung, ovary, or nonregional node)
M1b – Metastasis in more than one organ/site or the peritoneum

12.7 Surgical Management

Surgery is the cornerstone treatment for colon cancer. Only surgery can cure colon cancer. Therefore, efforts are necessary to train skilled surgeons to perform the operations. The choice of the approach (open versus laparoscopic) and extent of resection (partial or total colectomy) are planned based on the clinical staging and risk assessment (i.e., FAP, etc.). The goal of surgical resection of primary cancer is the complete removal of the tumor, major vascular pedicles, and lymphatic drainage of the affected colonic segment. When possible, the laparoscopic approach is preferred. Laparoscopic colectomy demonstrates faster recovery with no detrimental impact on the recurrence or survival compared to open colectomy [45–51].

12.8 Adjuvant Treatment

The decisions for adjuvant treatment are mainly based on the pathological staging. Therefore, we describe the recommendations according to the stage.

12.8.1 Stage I

Surgery resection alone confers >95 % overall survival in 5 years, and adjuvant treatment is unnecessary [52]. Endoscopic resection of a malignant polyp containing invasive carcinoma (pT1) must be individualized. Endoscopic resection is only sufficient for tumors involving the submucosa superficially (Sm1), polyp without fragmentation, clear margins (1 mm), grade 1 or 2 and no lymphovascular invasion [53–55].

12.8.2 Stage II

En bloc tumor resection (colectomy and lymphadenectomy) is sufficient in the majority of cases. Adjuvant chemotherapy is reserved for selected patients with the following poor prognostic factors: perforation or intestinal obstruction, T4 tumors, poorly differentiated histology and MSI-high, lymphovascular invasion, perineural invasion, and inadequately sampled nodes (<12 lymph nodes). For those cases, chemotherapy can be offered after balancing the risks and benefits, including patient discussion.

The most important trials that specifically address the benefit of fluoropyrimidine-based chemotherapy are the following: QUASAR, IMPACT B2, and INTERGROUP ANALYSIS [56–58]. The Ontario Group Analysis included a systematic review of 37 trials and 11 meta-analyses that were published after 1987 on adjuvant therapy for stage II colon cancer performed in Cancer Care Ontario. An analysis of a subset of 12 trials (4,187 patients) with surgery exclusive in the control arm and fluoropyrimidine-based chemotherapy in the experimental arm showed a significant improvement in the disease free survival (DFS) without significant improvement in the overall survival (OS). These results do not support the routine use of adjuvant chemotherapy for stage II colon cancer [59].

Two important trial analyses, MOSAIC and NSABP C-07, describe the benefit of adding oxaliplatin to fluoropyrimidine (5-FU) in the adjuvant setting [60, 61]. Again, a subgroup analysis of the stage II patients showed a trend of improving the DFS without improving the OS.

One strategy to facilitate the decision about whether to offer adjuvant chemotherapy is MSI evaluation. Patients with poor differentiated histology and MSI-H may have a good prognosis and do not benefit from adjuvant fluoropyrimidine-based chemotherapy [60].

12.8.3 Stage III

After surgery, adjuvant chemotherapy is recommended in the majority of cases.

The benefit for adjuvant 5-FU plus levamisole was initially reported in a North Central Cancer Treatment Group (NCCTG). In that study, patients with stages II and III colon cancer were randomly assigned to observation for 1 year of levamisole with or without 5-FU [62]. After the demonstration of the inferiority of 5-FU/levamisole compared to 5-FU plus leucovorin (LV), the use of levamisole for adjuvant therapy was abandoned [63, 64]. 5-FU plus LV became the standard treatment until 2004, which is when the MOSAIC trial was published, showing the benefit of adding oxaliplatin to 5-FU/Leucovorin (FOLFOX4) in the adjuvant setting for stage III colon cancer [60]. After 6-year follow-up, patients who receive FOLFOX achieved a 20 % reduction in risk of death [65]. Better outcomes with oxaliplatin were also reported with the FLOX and XELOX protocols [66]. In summary, the chemotherapy recommendations are as follows:

- FOLFOX or XELOX or FLOX are the approved regimens in the adjuvant setting.
- The duration of the treatment is 6 months.
- Chemotherapy with fluoropyrimidines without oxaliplatin remains an option for elderly patients (>70 years) and patients with contraindications for oxaliplatin. 5-FU/Leucovorin or capecitabine have similar efficacy based on the European/Canadian X-ACT study that randomly assigned 1987 patients with resected stage III colon cancer to 6 months of capecitabine alone (1,250 mg/m^2 twice daily for 14 of every 21 days) or monthly bolus 5-FU/LV (the Mayo regimen). The trial was statistically powered to demonstrate therapeutic equivalence, and the DFS was the primary endpoint [67].
- There is no consensus about the optimal time for initiating adjuvant chemotherapy. The majority of the medical societies recommended the initiation of chemotherapy within 6–8 weeks of resection, which has become an accepted approach [68, 69].
- The benefit of the addition of oxaliplatin to 5-FU/leucovorin in patients aged 70 and older has not been proven [70].

12.8.4 Stage IV (Metastatic Disease)

In the stage IV, patients are divided into the following three categories:

- Metastatic with resectable disease.
- Metastatic with potentially resectable disease.
- Metastatic with unresectable disease.

Metastatic with Resectable Disease The patients can be treated with upfront surgery (primary tumor and metastatic tumor) followed by adjuvant chemotherapy for

6 months (see adjuvant stage III chemotherapy), or patients can be treated with upfront chemotherapy neoadjuvant (2 or 3 months) followed by surgery [71, 72]. In the upfront chemotherapy strategy, it is possible to identify the patients with a tumor response. FOLFOX4 and XELOX are the preferential regimens of this strategy [73].

Metastatic with Potentially Resectable Disease Approximately 80–90 % of patients with metastatic colorectal cancer (mCRC) who are referred to specialist centers have unresectable metastatic liver disease [74]. The role of chemotherapy in these patient populations is to downstage the liver lesions in an attempt to convert their disease from unresectable to resectable. In 2008, a major systematic review on irinotecan and oxaliplatin for treating advanced colorectal cancer, published by the United Kingdom Health Technology Assessment Agency, evaluated all studies in which irinotecan or oxaliplatin were combined with 5-FU to downstage patients with unresectable colon liver metastases (CLM). The reported resection rates ranged from 9 % to 35 % for patients receiving irinotecan and 5-FU, while the rates for those receiving oxaliplatin and 5-FU ranged from 7 % to 51 %. There is no conclusive evidence that one is superior to the other as first-line therapy for downstaging CLM in terms of the progression free survival (PFS) and OS [75]. The current practice for patients whose metastases may be rendered resectable by conversion chemotherapy is to treat them with the most effective regimen that offers a high response rate (RR), according to the resection rate and PFS, coupled with the recommendation that surgery should be conducted as early as possible to minimize chemical damage to the liver. A phase III randomized trial that compared FOLFOXIRI with a standard infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) regimen demonstrated an improvement in the RR in the FOLFOXIRI arm of patients with unresectable mCRC (60 % vs 34 %, $P<0.0001$). The PFS and OS were both significantly improved in the FOLFOXIRI arm (median PFS, 9.8 vs 6.9 mo, $P=0.0006$; median OS, 22.6 mo vs 16.7 mo, $P=0.032$) [76].

The roles of adding cetuximab, an EGFR inhibitor, to chemotherapy to increase the RR, PFS and OS were studied in several mCRC trials. Optimistic results from two first-line therapy randomized trials, CRYSTAL (cetuximab combined with irinotecan) and OPUS (oxaliplatin and cetuximab) reinforced the role of cetuximab on the improvement of the RRs and resection rates when combined with standard first-line chemotherapy in patients with advanced CRC [77, 78]. However, the latest results from two randomized phase III studies unexpectedly challenged the benefit of adding cetuximab to oxaliplatin-based combination chemotherapy. In the MRC COIN study, 1,394 patients received the oxaliplatin combination (CAPOX/FOLFOX) as standard chemotherapy with or without cetuximab. An analysis according to the *KRAS* status did not result in any difference in either the OS or PFS between the patients treated with CAPOX/FOLFOX and those treated with CAPOX/FOLFOX plus cetuximab, even in the *KRAS* wild-type group [79]. Cetuximab combined with triple cytotoxic drug therapy is also being evaluated. The results from the preoperative chemotherapy for the hepatic resection (POCHER) study revealed an RR of 79 % and complete resection rate of 63 % for FOLFOXIRI plus cetuximab [80]. Another phase II trial that evaluated cetuximab in combination with

FOLFIRINOX demonstrated an ORR as high as 82 % and raised the question of this new therapeutic combination in first-line mCRC patients [81]. Cetuximab is only approved for patients with N-RAS wild type.

The addition of bevacizumab, a VEGF inhibitor, to chemotherapy in the perioperative setting for initially unresectable metastasis was evaluated in two large multicenter prospective trials (First BEAT and NO16966). The First BEAT trial reported a 6 % R0 hepatic resection in an unselected population and 12.1 % among patients with isolated liver metastasis alone. The resection rates were highest in patients who received oxaliplatin-based combination chemotherapy ($P = 0.002$). However, bevacizumab did not improve the RRs when added to XELOX or FOLFOX in the NO16966 study [82]. When added to FOLFIRI, bevacizumab showed an increase in the RR [83]. Recent data from a small phase II trial by the GONO group revealed that FOLFOXIRI plus bevacizumab yielded an ORR of 76 % [84]. However, these small benefits have come at the cost of significant treatment-related toxicity and will be used cautiously.

Metastatic with Unresectable Disease The majority of patients with unresectable mCRC cannot be cured. For these patients, the treatment is palliative and generally consists of systemic chemotherapy. For decades, 5-FU was the unique active agent. This changed with the approval of irinotecan, oxaliplatin and three humanized monoclonal antibodies that target the vascular endothelial growth factor (bevacizumab) and epidermal growth factor receptors (cetuximab and panitumumab) in 2000. These new combinations shifted the median OS from 6 to 30 months.

What we learned in the last 40 years:

- Fluoropyrimidine (5-FU or capecitabine)-based chemotherapy is the most active agent and used alone to increase the PFS and OS [85, 86].
- Infusional 5-FU is more active and safe than bolus 5-FU [87].
- Bolus 5-FU 5 days a week, every 4 weeks, in the classic Mayo Clinic protocol, has high risk toxicity and is not recommended. A weekly schedule, as presented in the QUASAR study, is preferred for patients selected to receive a 5-FU bolus [88].
- Adding oxaliplatin to 5-FU or capecitabine (FOLFOX, XELOX) increases the PFS and OS; [89].
- Adding irinotecan to 5-FU (FOLFIRI) increases the PFS and OS [90].
- Adding cetuximab to FOLFIRI in select RAS wild type patients increases the PFS and OS [77].
- Adding cetuximab or bevacizumab to FOLFIRI in selected RAS wild type patients results in a similar RR and PFS. The OS favored the cetuximab group with a median OS 28.7 months versus 25 months ($p = 0.017$). The primary end point of the FIRE-3 study was an objective response [91].
- Adding panitumumab to FOLFOX in selected RAS wild type patients was FDA approved as a first-line therapy. This combination increased the PFS and OS in the PRIME trial [92].
- Adding cetuximab to the oxaliplatin-based regimen increases the RR without benefiting the OS [78, 93].

- Adding bevacizumab to chemotherapy increases the PFS and OS, mainly in association with "weaker" regimen (IFL, 5FU/LV, and Capecitabine) [94]. The benefit of adding bevacizumab to a very active regimen (FOLFIRI, FOLFOX, and XELOX) will be the balancing of side effects, mainly in patients RAS WT, where cetuximab appears to perform better [91].
- FOLFOXIRI is a very active regimen and, compared with FOLFIRI, increased the PFS and OS, but the toxicity was high, and this regimen should be reserved to selected patients [95].
- Regorafenib was approved by the FDA to treat patients with mCRC who have been previously treated with fluoropyrimidine, oxaliplatin, and irinotecan-based chemotherapy, an anti-VEGF agent; if the patient is KRAS wild type, an anti-EGFR therapy may be used [96].

12.9 Patient Surveillance

There available data for recommending surveillance and secondary prevention measures for the survivors of CRC stages II and III. For patients with stage I and resectable metastatic disease, data are minimal for providing guidance. In December 10th, 2013, the American Society of Clinical Oncology published some ***Key Recommendations***. Our summary recommendations after treatment are as follows: [12, 97]

- Surveillance is especially important in the first 2–5 years, which is when the risk of recurrence is the greatest and should be guided by the presumed risk of recurrence. The functional status of the patient should be considered because early detection would lead to aggressive treatment, including surgery and/or systemic therapy. Patients who are not candidates for aggressive therapy should not be included in active surveillance;
- For stage I patients:
  - There are no recommendations for testing CEA or routinely performing a CT scan. Colonoscopy is recommended in the first year after surgery as well as in the third year and then every 5 years if no alteration (polyp) is detected.
- For stage II and III patients:
  - In the first 2.5 years, a medical history, physical examination, and CEA testing should be performed every 3 months and then every 6 months for 5 years. The data showing the risk of recurrence are 80 % in the first 2–2.5 years from the date of surgery and 95 % occur by 5 years.
  - Routine abdominal and chest imaging using a CT scan is recommended annually for 5 years. It is reasonable to consider imaging every 6 months for the first 3 years in patients who have a high risk of recurrence.
  - PET scans are not recommended for surveillance.

  - Colonoscopy should be performed approximately 1 year after the initial surgery as well as in the third year and then every 5 years if the findings of the previous one are normal. A complete colonoscopy should be performed reasonably soon after the completion of adjuvant therapy in patients who have not undergone a colonoscopy before diagnosis.

- For stage IV patients (after curative surgery of metastasis):
  - There are few evidence-based data for guidance. Based on the published data, we recommend surveillance similar to stage III.

- We recommend a characteristic lifestyle to improve the outcome in CRC survivors. It is reasonable to counsel patients on maintaining a healthy BMI, engaging in regular physical activity and eating a healthy diet (more fruits, vegetables, poultry, and fish; less red meat; more whole grains; and fewer refined grains and concentrated sweets).
- We recommend that a written treatment plan from the specialist should be sent to the primary care physician, who will be assuming cancer surveillance responsibilities.
- Finally, is very important to identify a patient who is not a surgical candidate or a candidate for systemic therapy (due to severe comorbid conditions) because surveillance tests should not be performed. This recommendation is based on cost-benefit analysis.

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