Colon Cancer

25

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25.1 Introduction

Colon cancer is common and usually presents with a history of altered bowel habit, rectal bleeding, or anemia. The onset and severity of symptoms depends on tumor location. Advanced disease at first presentation is not uncommon because diagnosis of proximal tumors is difficult and often delayed. Outcome is most closely related to the extent of disease at presentation. Surgical resection is the primary treatment for any colon cancer, even in advanced stages; adjuvant chemotherapy improves outcome but the prerequesite of adjuvant treatment is complete removal of the primary tumor. Neoadjuvant chemotherapy should be discussed in selected cases.

25.2 Anatomy

The colon is topographically divided into cecum, ascending colon, transverse colon, descending colon, and sigmoid colon. Colonic tumors occur between the ileocecal junction and the rectosigmoid junction (15 cm from the anal verge, as measured with rigid sigmoidoscopy).

The great majority of colon cancers are adenocarcinomas. Rare tumors, such as neuroendocrine tumors (including carcinoid tumors), leiomyosarcoma, hematopoietic neoplasms, and lymphoid neoplasm, are not described in this chapter.

25.3 Incidence

Bowel cancer is the second most common cancer in Europe, with around 447,000 new cases diagnosed in 2012. In Europe in 2012, the highest age-standardized incidence rates for bowel cancer worldwide were in Slovakia for men and Norway for women. The incidence of colorectal cancer increases significantly starting at age 50 years, with the highest rates in the ≥85-year-old age group. Among adults, incidence rates are significantly higher for males than females (17:10). The risk for colorectal cancer is increased in certain groups (see below).

25.4 Etiology/Epidemiology

The great majority (approximately 90 %) of colon cancers are sporadic, and only 5 % are associated with a recognized familial pattern of inheritance. Several extrinsic factors are connected with an increased risk of developing colon cancer.

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25.4.1 Extrinsic Factors/Risk

There is some evidence that a diet rich in vegetables is protective because of the presence of substances with anticarcinogenic properties, such as carotenoids, folate, phenols, and flavonoids. Consumption of nondigestible fructo-oligosaccharides may selectively promote the growth and activity of potentially beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* species. Diets high in starch, nonstarch fiber, and carotenoids possibly decrease risk of developing colon cancer. Daily fiber uptake should achieve 30 g to decrease risk. Usage of dietary supplements (e.g., vitamins, calcium, or β-carotenoid) are not recommended. There is no evidence of risk reduction.

High physical activity is known to decrease risk for colon adenomas and colon cancer.

Obesity is connected with a doubled risk of colon cancer (occurring more often in men than women). Starting at a body mass index >25 kg/m^2, a linear correlation between body mass index and risk of colon cancer was detected. Smoking is associated with a doubled risk of colon cancer. There is a positive correlation between alcohol consumption and colon cancer. The uptake of 100 g alcohol/week is connected with a 15 % increased cancer risk. Red meat and processed meat are also associated with a higher risk of colon cancer.

Cox-II inhibitors are associated with a decreased risk of colorectal cancer, but unfortunately their use is accompanied by increased cardiovascular morbidity. Therefore they are not generally recommended. Chronic use of aspirin decreases the risk of colorectal cancer (proven by cohort studies) but increases the incidence of gastrointestinal bleeding and is therefore also not recommended for the prevention of colorectal cancer.

25.4.2 Genetic Factors

Fifteen percent of patients with sporadic colorectal cancer show hereditary nonpolyposis colorectal cancer (HNPCC)–like genome defects: microsatellite instability (MSI) and loss of the MLH1 protein. In sporadic colorectal cancer, this is caused by a mutation of the *BRAF* gene. First-degree relatives of an index patient have a higher (1.6-fold) risk of developing colorectal cancer. In any tumor with MSI and an MLH1 defect, a *BRAF* analysis should performed to distinguish between sporadic colorectal cancer and HNPCC.

25.4.2.1 Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is associated with a mutation or loss of the FAP gene (also called the adenomatous polyposis [*APC*] gene). The risk of developing colorectal cancer is nearly 100 % in FAP. The onset of this polyp disease occurs in the second decade of life, and more than 100 polyps are characteristic.

Extracolonic intestinal manifestations (occurring in approximately 75 % of patients) include adenomas of the duodenum and the ampulla of Vater, both considered to be precancerous. Incidence of gastric adenomas is less than 10 % in FAP. Extraintestinal manifestations include desmoid tumors, thyroid carcinoma, medulloblastoma, hepatoblastoma, osteoma, epidermoid cysts, and pigment anomalies of the retina.

25.4.2.2 Attenuated Familial Adenomatous Polyposis

Patients with attenuated FAP (attenuated adenomatous polyposis coli [AAPC]) typically present with <100 polyps and at an older age, often the fourth decade. Extracolonic manifestations can occur. AAPC is caused by a heterogenous group of *APC* and *MYH* mutations. Proof of MSI, *APC*, and *MYH* can be helpful to differentiate AAPC from HNPCC.

25.4.2.3 MUTYH-Associated Polyposis

MUTYH-associated polyposis (MAP) is the most important differential diagnosis of FAP. It is diagnosed in 15–20 % of all *APC* mutation–negative colorectal adenomatoses. The phenotype of MAP is similar to that of AAPC. The lifetime risk of developing colorectal cancer is high among patients with MAP (70–80 %). Because MAP is an biallelic (autosomal-reces-

sive) germ-line mutation, the risk of children of index patients or heterozygotic carriers developing colorectal cancer is low.

25.4.2.4 Hereditary Nonpolyposis Colorectal Cancer

HNPCC is associated with germ-line mutations in six DNA mismatch repair (MMR) genes (*MLH1*, *MLH2*, *MSH2*, *MSH6*, *PMS1*, *PMS2*). Almost 90 % of the detected mutations are located in *MSH2* and *MLH1*.

Unlike for FAP, clinical diagnosis is difficult because HNPCC does not present with a distinct phenotype. Thus clinical criteria (Amsterdam I and Bethesda criteria; Tables 25.1 and 25.2) were defined for use as a screening tool for mutations. HNPCC is clinically diagnosed if the Amsterdam I criteria are met. The Amsterdam II criteria refer to extracolonic manifestations (endometrial, urothelial, and small-bowel carcinomas). Because many families today are small, a negative family history does not preclude HNPCC; the less-specific Bethesda criteria aim to determine a diagnosis in small families using clinical means. MSI is found in tumor tissue harvested from 80 to 90 % of patients who fulfill the Amsterdam I/II criteria and in 30 % of patients who fulfill the Bethesda criteria.

General tumor risk in patients with HNPCC is considered to be 80–90 %, with colorectal cancer being the most common (at a median age of 44 years; uncommon before 25 years). The second most common cancer in patients with HNPCC is endometrial carcinoma; lifetime risk is 40–60 % at a median age between 46 and 48 years. Ovarian cancer occurs in 10–15 %; gastric cancer, mostly the intestinal tumor type, in 2–13 %; and small-bowel cancer in 1–4 % (around one-third occur in the duodenum). The relative risk for urothelial cancer in men with a mutation in the MMR germ line is 4.2; for women it is 2.2-fold higher.

Performing additional molecular (pathologic) diagnostics regarding HNPCC is recommended in every person fulfilling one Bethesda criterion. Diagnostic evaluation should include immunohistochemical staining of MMR protein expression and analysis of MSI.

Table 25.1 Amsterdam I criteria

1.	At least three relatives with histopathologically verified colorectal cancer; one must be a first-degree relative of the other
2.	At least two successive generations affected
3.	At least one of the relatives with colorectal cancer diagnosed at less than 50 years of age
4.	Familial adenomatous polyposis has been excluded

Table 25.2 Revised Bethesda guidelines

Tumors from individuals should be tested for MSI in the following situations	
1.	Colorectal cancer diagnosed in a patient who is less than 50 years of age
2.	Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, regardless of age
3.	Colorectal cancer with the MSI-H histology diagnosed in a patient who is less than 60 years of age
4.	Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under the age of 50 years
5.	Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

25.4.2.5 Hamartomous Polyposis Syndrome

Peutz-Jeghers syndrome and juvenile polyposis coli (familial juvenile polyposis) are rare hamartomatous polyposis syndromes. Peutz-Jeghers syndrome is an autosomal-dominant germ-line mutation of the *STK11/LKB1* gene. The cumulative lifetime risk for malignant tumors reaches 90 %; the risk for colorectal cancer is 39 % and is mostly commonly diagnosed at an age of 30–50 years.

25.4.2.6 Chronic Inflammatory Bowel Disease

Colorectal cancer risk is increased in patients with ulcerative colitis and is dependent on the manifestations, extent, and duration of the disease. The cumulative lifetime risk of developing cancer in patients with pancolitis is 2 % after 10 years, 9 % after 20 years, and 18 % after 30 years.

Crohn's disease is also associated with an increased risk for colorectal and small-bowel cancers, although it is less well defined. A 3.5- to 7-fold increase is suggested, specifically when the colon is involved in Crohn's disease.

25.5 Diagnosis

Colorectal cancer is diagnosed either as a result of a screening program or when a patient becomes symptomatic. Early colorectal cancer is often asymptomatic (especially if located in the right hemicolon) or presents with nonspecific symptoms; thus screening programs for early detection are of major importance. Since the late 1950s, a gradual shift toward right-sided or proximal colon cancers has been observed.

25.5.1 Screening in the Healthy Population

Screening for colorectal cancer aims for early detection and the removal of precancerous lesions in sporadic colorectal cancer developing in patients older than 50 years. Complete flexible colonoscopy is the gold standard in early detection of colorectal neoplasias. It shows the highest sensitivity and specificity. Two case-control studies demonstrated a 66–90 % reduction in colorectal cancer incidence by flexible colonoscopy. Negative colonoscopy should be repeated after a period of 10 years.

The protective effect of flexible sigmoidoscopy for distal neoplasms seems to last 6–10 years. However, a study of nearly 10,000 patients showed a 0.8 % detection rate for distal adenomas or carcinomas 3 years after negative sigmoidoscopy. The recommend control interval for sigmoidoscopy without pathological findings is 5 years.

The second recommended screening method is fecal occult blood testing (FOBT). The sensitivity of FOBT for confirmed colorectal cancer is 50 % and for polyps is around 10 %. The predictive value of a positive test averages 10 % for cancer. Any (single) positive test result must be followed by complete flexible colonoscopy. The efficacy of FOBT was demonstrated in four large, randomized trials in which colorectal cancer mortality was reduced by 25 % in individuals participating in an annual screening program. Biennial testing is less effective. FOBT is unnecessary in individuals participating in an regular colonoscopy screening program.

Randomized trials have demonstrated that some immunologic FOBTs are superior regarding the detection rate of advanced neoplasias compared with guaiac FOBT. The studies show some immunologic FOBTs (e.g., OC-Sensor) afford the same specificity (>90 %) but higher sensitivity.

The Advisory Committee on Cancer Prevention in the European Union suggested in 1999 that screening programs for colorectal cancer should use FOBT. Colonoscopy should be used to follow-up on positive findings. Screening should be offered to men and women aged 50 to approximately 74 years, with an interval of 1–2 years.

25.5.2 Screening in Populations at Increased Risk

Persons with increased risk for colorectal cancer due to certain predispositions comprise the following three groups:

- Increased family risk (genetic background unknown)
- Proven or potential risk of hereditary colorectal cancer
- Presence of chronic inflammatory bowel disease

First-degree relatives of patients with colorectal cancer are at increased risk of developing colorectal cancer. If an index patient older than 60 years develops cancer, the risk of developing cancer is only minimally increased for his or her relatives.

In patients with a family history of colorectal cancer or adenomatous polyps, advise screening colonoscopy beginning at age 40 years or 10 years younger than the youngest age at the diagnosis in the family. Screening should be repeated at 5-year intervals. This protocol should followed in two groups of patients:

Persons with a first-degree relative (parent, sibling, or child) with colon cancer or adenomatous polyps diagnosed at an age ≤60 years
Persons with two first-degree relatives diagnosed with colorectal cancer at any age

These screening recommendations must be considered provisional, as mortality-reduction studies are not yet available.

Colorectal cancer mortality is lower in patients with FAP who have been screened than in those who present with symptoms. Genetic testing should be performed at age 10 years; if a genetic mutation can be excluded, no further special screening is required. Annual colonoscopy from age 10–12 years should be advised in:

Persons with a genetic diagnosis of FAP
Persons with a risk of FAP in whom genetic testing has not been performed and/or a mutation cannot be excluded

In patients with attenuated FAP, treatment should be based on age, the number of polyps, and the histopathological findings. Colonoscopy should be performed annually throughout the patient's life if colectomy is not indicated. In persons from a family with attenuated FAP, the first colonoscopy should be at age 15 years; if there are no findings, the next colonoscopy should be performed in 5 years. From age 20 years, colonoscopy is recommend annually.

Colonoscopy can reduce risk and mortality from colorectal cancer in families fulfilling the Amsterdam criteria for HNPCC. Genetic testing for HNPCC should be offered to first-degree relatives of persons with a known inherited MMR gene mutation. Among persons with a genetic or clinical diagnosis of HNPCC, yearly or biennial colonoscopy should start at age 20–25 years or 10 years earlier than the youngest age at diagnosis of colorectal cancer in the family.

In asymptomatic biallelic *MUTYH* mutation carriers, colonoscopy is recommended at age 18–20 years. If there are no polyps these patients should undergo lifetime surveillance. In patients with MAP, colonoscopy should be performed annually.

History of Adenomatous Polyps (see Chap. 8.1)

In patients with a history of colorectal cancer, if synchronous neoplasm is excluded at the time of resection with curative intent, subsequent colonoscopy should be performed 2 and 5 years after surgery and every 5 years thereafter.

Colonoscopy with systematic four-quadrant biopsies at 10-cm intervals should be performed in patients with inflammatory bowel disease/ulcerative colitis presenting as long-standing pancolitis (>8 years) or left-sided inflammatory colitis (>15 years). If intraepithelial neoplasia is detected and confirmed, colectomy is indicated. No general recommendation can be given for patients with Crohn's disease.

No randomized controlled trials have studied surveillance colonoscopy in patients with ulcerative colitis or Crohn's colitis. A meta-analysis of case-control studies showed a reduction in the risk of colorectal cancer mortality in patients with ulcerative colitis following a surveillance program.

25.5.3 Symptoms

The majority of patients present with alteration in bowel habit, frank rectal bleeding, or anemia as a result of occult bleeding. Symptoms such as intermittent abdominal pain, nausea, and vomiting are often secondary to partial obstruction or peritoneal dissemination. Patients may occasionally notice a palpable mass, which is more common in right-sided colon cancer.

Intestinal obstruction is most commonly associated with cancer of the sigmoid colon. This may lead to acute colonic perforation if the ileocecal valve is competent. If the valve is incompetent, presentation is less dramatic, with increasing constipation and abdominal distension noticed over many days, ending in a typical symptomatic ileus.

Perforation of colon cancer may be acute or chronic. It may occur at the site of the tumor or more proximal in the distended part of the colon. Perforation may extend into the retroperitoneum, bladder, or genital tract, with fistula formation.

25.5.4 Diagnostic Strategies

Diagnosis is established by colonoscopy and biopsy. The precise location of the neoplasm must be documented and the base of any suspicious polyp tattooed at the time of snare excision. Careful clinical examination for regional lymphatic and distant metastatic disease should be performed.

To exclude liver metastasis, ultrasonography or multislice computed tomography (CT) are the imaging techniques with highest sensitivity (63–86 % and 75–83 %, respectively) and best specificity (98 % and 98 %, respectively). CT has advantages in assigning metastases to anatomic structures such as liver veins, hilar vessels, and the caval vein, which is necessary to estimate resectability. However, magnetic resonance imaging is the optimal tool to evaluate the extent of liver metastasis. To exclude synchronous malignancies, the entire large bowel should be examined if the lumen is not obstructed. If colonoscopy is not possible or complementary information is required, virtual colonography (based on CT or magnetic resonance tomography) or radiography with water-soluble contrast (if there is a risk of perforation) is mandatory.

25.6 Differential Diagnosis

The most common differential diagnoses are:

Diverticular disease with stenosis or phlegmon
Inflammatory bowel disease
Colonic ischemia
Infection
Other malignancies

25.7 Staging

Clinical staging aims to determine the local and distant extent of the disease according to the clinical TNM system (see Chap. 23). Staging requires local assessment of the tumor and screening for metastatic disease. The clinical classification, cTNM, is the basis for clinical decision making and determines the therapeutic algorithm.

25.7.1 Clinical Staging

History, including family history (Amsterdam and Bethesda criteria)
Physical examination

25.7.2 Investigations

- Colonoscopy
- Chest radiography
- CT of the abdomen and pelvis
- Positron emission tomography, which is indicated in the following scenarios:
  - Candidates for resection of isolated colorectal cancer metastases to prevent unnecessary laparotomy
  - Restaging of possible local recurrence or metastatic disease

25.7.3 Laboratory Testing

Elevated levels of serum carcinoembryonic antigen (CEA) that do not normalize after surgical resection imply persistent disease and the need for further evaluation. A postoperative increase in CEA during follow-up indicates a potential recurrence. A liver chemistry panel should also be performed.

25.8 Treatment

Primary treatment for colon cancer is surgical resection of the primary tumor and lymph nodes. Open and laparoscopic approaches are equally safe in experienced hands. The term *curative resection* (R0) should be used when there is histological confirmation of complete excision without residual tumor.

25.8.1 Curative Intent

25.8.1.1 Operative Intervention

Any operative intervention should start with intraoperative staging by inspection and palpation of the liver. As long as a sufficient preoperative diagnostic test (magnetic resonance imaging, CT) is performed, intraoperatively only subserosal metastases (>2 mm) may additionally be detected (by palpation and inspection). In addition, intraoperative liver sonography provides high sensitivity and has a very high positive predictive value (−100 %).

Operative intervention aims to achieve a curative resection. If adjacent organs are involved, en bloc resection is indicated. In colon cancer (unlike rectal cancer), the need for a radical approach has not been proved in prospective randomized trials. However, based on histopathological results, prospective observational studies, and theoretical concepts, surgeons performing colon cancer resections should adhere to the following principles of radicality:

A 2-cm safety margin is sufficient with regard to microscopic tumor spread but insufficient for lymphatic spread (as regional lymph drainage exceeds this distance).

Lymph node metastases travel along the vascular supply, primarily with the paracolic supply, up to 10 cm from the macroscopic edge of the primary tumor. Thus at least 10 cm of the colon should be removed if vascular division is radicular.

The extent of resection is determined by the vascular supply and the consequently defined area of lymphatic drainage. In principle, if the tumor is located between two major vessels, both should be divided centrally (Figs. 25.1, 25.2, 25.3, 25.4, and 25.5).

Complete mesocolic excision in patients with colon cancer improved overall survival and progression-free survival in some cohort studies. This complex surgical procedure provides more radicality but may be connected with higher morbidity. It should performed only by excellent trained surgeons with expertise in colon surgery.

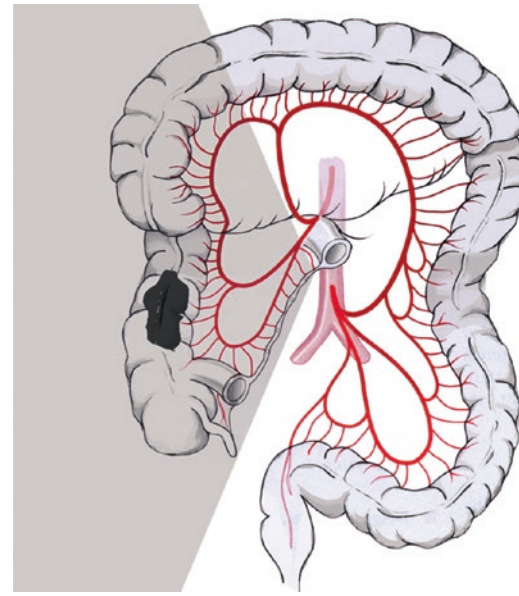

Fig. 25.1 Cancer: ascending colon. Right-sided hemicolectomy with central ligation of the ileocolic artery and the right colonic artery

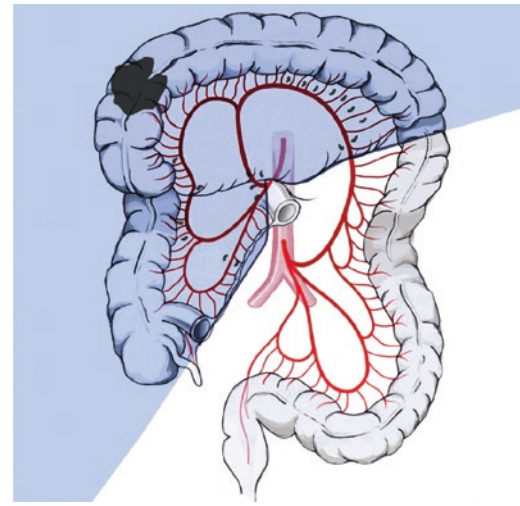

Fig. 25.2 Cancer: hepatic flexure. Extended right hemicolectomy with central ligation of the ileocolic, right colonic, and middle colic arteries

Special Considerations

When patients present with multiple colon cancers, total colectomy is not mandatory, in principle. The extent of the resection should follow the principles of radicality, as described earlier.

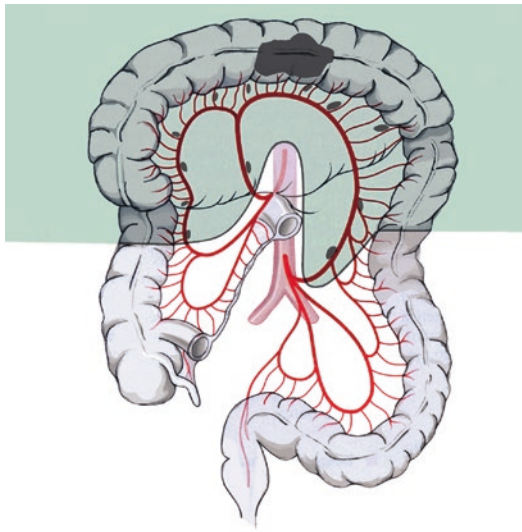

Fig. 25.3 Cancer: transverse colon. Transverse colon resection with central ligation of the middle and left colonic arteries

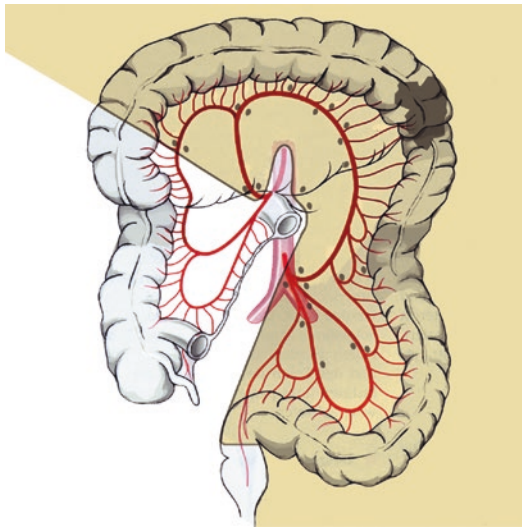

Fig. 25.4 Cancer: splenic flexure. Extended left hemicolectomy with central ligation of middle colic and inferior mesenteric arteries

However, many advocate subtotal colectomy and ileorectal anastomosis.

Synchronous distant metastases can be resected at the same time as the primary tumor or later. Simultaneous liver resection may be connected with high mortality rate in patients aged >70 years. Multiple synchronous liver metastases

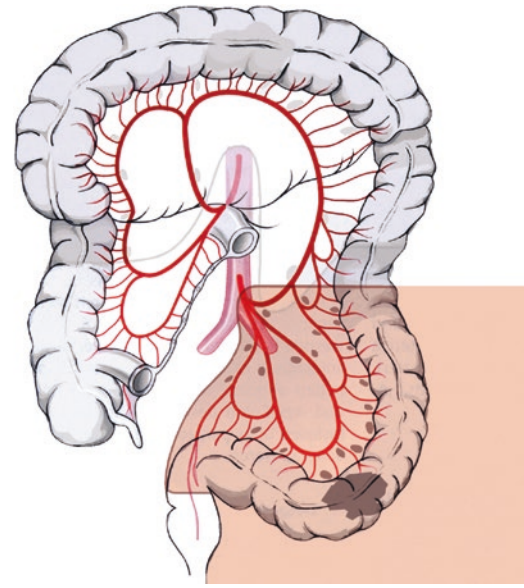

Fig. 25.5 Cancer: sigmoid. Sigmoid resection with central ligation of the inferior mesenteric artery

should be treated using a two-stage concept. In synchronous metastasis with an asymptomatic primary tumor, whether to go for the liver first with or without neoadjuvant chemotherapy should be discussed.

In emergencies, a radical procedure should be performed, if possible. In the case of obstruction, intraluminal stenting can be used for bridging in select cases. If perforation is excluded, obstruction can be considered urgent, not emergent, unless the ileocecal valve is competent and the cecum is at risk of perforation. In the majority of cases with obstruction, the disease is at an advanced stage and neoadjuvant treatment is indicated. For that reason, a diverting stoma may a good option in cases without perforation.

When cancer occurs in patients with FAP, a radical procedure should be attempted via restorative proctocolectomy. If complete resection (R0) is not achievable, limited procedures can be considered. In cases with insufficient anal sphincter, stoma creation can be suggested. Lifelong surveillance is mandatory if a subtotal colectomy with ileorectal anastomosis is feasible. The patient must be counseled accordingly. Subtotal colectomy with ileorectal anastomosis

is acceptable for cancer in patients with attenuated FAP with limited manifestation in the rectum.

For patients with HNPCC with cancer, oncological resection may be performed as in sporadic colonic cancer; however, prophylactic subtotal colectomy may be considered in patients known to have a genetic mutation.

Restorative proctocolectomy is indicated if anal sphincter function is adequate for cancer in patients with ulcerative colitis.

Local/Limited Procedures

A local procedure for colon cancer should be considered oncologically adequate only if, after complete full-thickness resection (R0), tumor stage is confined to pT1, grade is good or moderate (G1–2), no lymphatic (L0) or vascular invasion (V0) has occurred, and the tumor diameter is less than 3 cm.

25.8.1.2 Postoperative Histopathological Evaluation/ Histopathological Reporting

To ensure correct histopathological classification, the following information must be answered in the report:

Location of the primary tumor
Type of tumor
Level of invasion (pT)
Tumor grading (G)
Status of local lymph nodes (pN)
Number of examined lymph nodes (≥12 are recommended)
Number of lymph nodes with tumor involvement
Distance of resection margins
Completeness of tumor removal (R)
Invasion of lymphatic and vascular vessels (L, V)
MSI (in HNPCC)

25.8.2 Adjuvant Treatment

The prerequisite for adjuvant therapy is complete removal of the primary tumor (local R0). The indication is based on histopathological staging, especially nodal status (pN), determined by the examination of at least 12 lymph nodes. Positive immunocytological detection of isolated tumor cells and/or positive cytological findings from peritoneal lavage are not considered indications. Arguments for adjuvant therapy in addition to tumor classification are special intraoperative risk factors such as T4 stadium, tumor perforation, fewer than 12 nodes examined, and/or an emergency situation.

25.8.2.1 Contraindication for Adjuvant Therapy in Colon Cancer

All items are primary contraindications for adjuvant treatment. Incomplete removal is explicitly mentionened because this situation may be improved by additional surgery.

Union for International Cancer Control (UICC) stage I

Poor performance status

Liver cirrhosis (Child-Pugh score of B or C)

Cardiac insufficiency (New York Heart Association heart failure classes III or IV)

Preterminal and terminal renal failure

Reduced bone marrow function

Inability to participate in follow-up

25.8.2.2 UICC stage II (relative contraindication)

In special risk situations (see Sect. 25.8.2.1), adjuvant treatment in UICC stage II disease may be discussed, but based on available data, adjuvant therapy should not be recommended in general for patients with UICC stage II disease. If chemotherapy is given, it should be administered only within controlled studies.

Good general health status provided a patient age older than 70 years is not a contraindication for adjuvant treatment.

25.8.2.3 Neoadjuvant Treatment

Neoadjuvant chemotherapy, radiotherapy, and radiochemotherapy are not generally indicated in colon cancer. In nonobstructing tumors with distant metastases, neoadjuvant treatment may be an option to control the disease before resection. Moreover, it should be discussed whether the first treatment (resection) of (liver) metastases is

advisable; however, this should be performed only when following controlled study protocols.

Adjuvant Treatment Protocols

Adjuvant chemotherapy is advised for patients with stage III colon cancer (R0). Several randomized clinical trials demonstrated a significant reduction in recurrence and improved overall survival after 5-fluorouracil (5-FU)– and folinic acid–based adjuvant therapy. In the meantime, other studies demonstrated that a 5-FU/folinic acid and oxaliplatin regimen significantly improves disease-free survival.

In patients with contraindications to oxaliplatin, fluoropyrimidine monotherapy is advocated. Oral administration is recommended. Because of its high toxicity, bolus administration should not be used.

Adjuvant chemotherapy is not indicated for patients with stage II colon cancer (R0). As mentioned earlier, in a setting implying increased risk of recurrence it may be considered, but then should be used only within controlled studies.

Several chemotherapy regimens are commonly used:

Leucovorin- 5 Flurouracil + oxaliplatin (MOSAIC trial): 200 mg/m^2 folinic acid (2-h infusion on days 1 and 2), plus 5-FU (400 mg/m^2 bolus followed by 600 mg/m^2 [22-h infusion on days 1 and 2), plus 85 mg/m^2 oxaliplatin (2 h on day 1); 1 cycle every 2 weeks, for a total of 12 cycles.

5-FU/folinic acid regimen: 500 mg/m^2 folinic acid (1- to 2-h infusion), plus 2,600 mg/m^2 5-FU (24-h infusion) once a week for 6 weeks (days 1, 8, 15, 22, 29, and 36). A second cycle should start at week 8; a total of two cycles is recommended.

Mayo regimen: 20 mg/m^2 folinic acid (intravenous), plus 425 mg/m^2 5-FU (intravenously for <5 min) on days 1–5 in weeks 1, ,4 and 8; three additional cycles occur at 5-week intervals thereafter.

Oral 5-FU prodrug regimen: capecitabine 1250 mg/m^2 twice daily on days 1–14; repeated every 3 weeks for eight cycles.

Toxicity

Typical side effects of chemotherapy are neuropathy (oxaliplatin) and neutropenia, diarrhea, and alopecia (irinotecan).

25.8.3 Palliative Treatment

Depending on the patient's situation, various modes are used for palliative treatment (e.g., surgery, endoscopic interventions, radiotherapy, chemotherapy, and interventional radiology). Surgery should be attempted even with only palliative intent to minimize the risk of complications from the primary tumor, such as stenosis, bleeding, and tumor infiltration of adjacent organs. In a French randomized, multicenter trial, a risk reduction of 58 % in overall survival was shown for resected compared with nonresected patients.

If resection of the primary tumor is not indicated, bowel passage can be reestablished by local treatment, bypass procedures, or stoma creation. If the tumor is not resectable, therapeutic options depend on the patient's general status and comorbidity. Strategies include:

- Turn unresectability into resectability (especially in liver/lung metastases)
- Prolong progression-free survival
- Provide the best supportive care

Several combinations of chemotherapy with palliative are advocated, depending on the patient's general condition and tumor characteristics (e.g., a *KRAS* mutation). The following regimens are used: 5-FU/folinic acid/irinotecan infusions and 5-FU/folinic acid/irinotecan/oxaliplatin infusion. In patients with comorbidities or contraindications for oxaliplatin or irinotecan, less toxic regimens with capecitabine or uracil/tegafur (5-FU prodrug) are good alternatives.

Various regimens of 5-FU with irinotecan and/or oxaliplatin are used as second- and third-line treatments. Depending on KRAS status, they are usually combined with antibodies against the vascular endothelial growth receptor or epidermal

growth factor receptor (bevacizumab, cetuximab, panitumumab).

25.8.4 Special Considerations: Metastases and Local Recurrence

Patients with resectable metastases of the liver or lung should undergo primary resection. Positron emission tomography/CT is advocated, as disease is subsequently upstaged in 30% of patients. Patients presenting with liver metastases that are not amenable to radical resection should be treated with systemic chemotherapy. Resectability must be evaluated by a surgeon with expertise in liver surgery. Surgical resection is superior to interventional procedures and therefore the method of choice. The role of all interventional procedures has not been proven yet. Radiofrequency ablation is an option in all patients who do not qualify for surgical resection (unresectability, poor general condition, recurrence following liver surgery). Selective internal radiation therapy may be used in disseminated liver metastases without other therapy options. Laser-induced interstitial thermotherapy should be evaluated in studies only.

Isolated bone metastases with pain should be treated with local radiation. A single, high-dose application seems to be equivalent to fractioned radiation.

In local recurrence, the reintervention aims for radicality. If an R0 resection is not achievable, reintervention aims to relieve symptoms and avoid complications such as stenosis, bleeding, obstruction, and ileus.

In patients with limited peritoneal carcinosis, cytoreductive surgery followed by hyperthermic intraperitoneal chemotherapy is an option. Treatment should be administered within a study protocol or at least a register. The following criteria should be fulfilled:

- Preoperative Peritoneal Carcinosis Index <20
- No extra-abdominal metastases
- Resection must achieve R0 or R1 status
- Treatment in a specialized center

25.8.5 Current Treatment Recommendations

- The mainstay of therapy is surgery with curative intent, in particular colon resection with lymphadenectomy (guided by vascular supply).
- Histopathological evaluation should include at least 12 lymph nodes.
- Adjuvant chemotherapy is indicated in UICC stage III disease.
- Surgery is the treatment of choice for resectable distant metastases.

25.9 Follow-Up

The follow-up regimen should be adapted to the tumor stage. In UICC stage I disease after R0 resection, the risk of recurrence is low. Colonoscopy in years 2 and 5 can detect secondary tumors early. The regimen should be modified in cases of increased risk of recurrence (e.g., G3/4, L+, V+, tumor perforation) and should include regular follow-up with CEA levels measured every 6 months (up to year 5), ultrasound or CT of the abdomen and pelvis every 6 months for 2 years, and chest radiography every year.

In patients with HNPCC after hemicolectomy, colonoscopy is indicated every year if adenomas were present; after subtotal colectomy, sigmoidoscopy is advised every second year. In patients after colectomy with ileal pouch–anal reconstruction, pouchoscopy is indicated yearly and duodenogastroscopy every 3 years (annually in patients with adenomas).

Suggested Reading

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