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Colon Cancer

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Abstract

Colorectal cancers (CRCs) are commonly diagnosed malignancy in both men and women. Although it is a common disease, mortality rates decrease with widespread use of screening methods and novel developments in surgery. Physical examination, abdomen and pelvic computerized tomography, and chest imaging are necessary for preoperative staging and surgical planning of a newly diagnosed colon cancer. CRCs usually develop from adenomatous polyps. Although curative treatment of localized colon cancer is surgery, endoscopic polypectomy is sufficient when severe dysplasia or carcinoma in situ is detected on a polyp surface. Total mesorectal excision and neoadjuvant chemoradiotherapy in rectum cancers resulted in significant reductions in morbidity, mortality, and recurrence rates. Recently, complete mesocolic excision and central vascular ligation method has been described in the surgical treatment of colon cancer to achieve similar results. Unfortunately, metastatic colon cancer rate at presentation is approximately 20%. Surgery is a potentially curative option in selected patients with liver and lung metastasis. Pathologic stage of the tumor at presentation is the most important prognostic factor after resection. Therefore, early diagnosis of colon cancer by screening methods and new surgical techniques will lead to better results in survival rates.

Keywords: colon cancer, central vascular ligation, complete mesocolic excision, prevention, treatment

1. Introduction

Colorectal cancer (CRC) is the second most common cancer in women and third in men with an estimation of approximately 1.4 million new cases globally [1]. Men are more affected than women in most of the world with a higher incidence in North America and Europe and, lower incidence in South-Central Asia and Africa [1]. Although it is a common disease, mortality rates decrease with novel developments in surgery and widespread use of screening methods such as colonoscopy, computed tomography colonoscopy, fecal occult blood test. In the United States, decrease in CRC mortality rates has been shown in the Survey of Epidemiology and End Results (SEER) program [2]. Due to comprehensive researches about the biological and molecular characteristics of CRC, cancer pathogenesis has been well elucidated. Since CRC develops after a long process under the influence of both genetic and environmental factors, early diagnosis is possible and as a result there are better treatment outcomes and prognosis [1–3].

Colorectal cancer incidence rises steadily after the age of 50 years and most of the cases are diagnosed in 6th and 7th decades. The incidence under age 40 years is only 5% [3]. Although it is recommended to initiate screening studies at 50 years

age, suspicious symptoms like rectal bleeding, unexplained anemia, change in bowel habits, and weight loss should be investigated regardless of the individual's age. Approximately 80% of CRCs are sporadic, 15% are non-syndromic familial, and 5% are syndromic familial cancers [3–5].

CRC is more common in developed societies that consume high-calorie diets rich in animal fat, red meat, processed meat, sweets, refined grains, and alcohol. However a diet rich in fiber, vegetables, fruits, fish, dairy products, and olive oil is beneficial to prevent CRC [4, 5]. The consumption of vegetable fibers shortens the period of contact of the carcinogenic substances with the colon mucosa and at the same time increases the fecal volume and leads to the dilution of the harmful substances so that the adverse effect on the mucosa is reduced. The fat-rich diet stimulates bile acid and cholesterol synthesis in the liver, the amount of these sterols in the colon increases. Due to colon bacteria, production of secondary bile acids and other toxic metabolites are increased and causes negative effects on the colon mucosa [3, 6]. The intake of A, C, E vitamins, calcium, selenium, and carotenoids is thought to reduce the risk of developing CRC [5, 6]. The risk of developing CRC in obese and sedentary individuals also increases like other cancers [7]. Furthermore, chronic alcohol consumption and smoking have been reported to increase the risk of colon adenomas.

The risk of developing CRC in individuals with long-standing inflammatory bowel disease is significantly increased [8]. It is thought that chronic inflammation of the mucosa is a predisposing factor for CRC. Extent and the duration of the colitis is closely related with the development of CRC. While the cumulative risk of CRC in ulcerative colitis patients with pancolitis or left-sided disease is 1.6% at 10 years, it increases approximately 5 times at 20 years (8.3%), and 11 times at 30 years (18.4%) [9]. A similar risk for CRC is also associated with Crohn's disease. Screening colonoscopy for CRC has been recommended annually for patients with inflammatory bowel disease, 8–10 years after the first symptoms of the disease [10].

2. Pathogenesis

Most CRCs usually develop from adenomatous polyps that become dysplastic (adenoma-carcinoma sequence) (**Figures 1 and 2**). The epithelium of small bowel is constantly renewed. During this renewal process, progressive deterioration leads primarily to adenomatous polyps and later to dysplasia and invasive cancer. Hypothesis that CRC are a result of adenoma-carcinoma sequence are supported by findings such as frequent early carcinoma detection in large adenomatous polyps, detection of adenomas in patients 10 years before cancer in both sporadic and familial cases, and reduction of CRC incidence by removal of polyps in controlled trials [11].

CRCs occur by accumulation of epigenetic and genetic changes over time [12]. These changes transform normal glandular epithelium into adenocarcinoma. In hereditary forms of CRC, individuals are born with mutant genes. That means the mutant gene is present in one allele in the zygote from the beginning (germ-line mutation) but a second hit needed. Hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) are the best known types of hereditary CRC. Sometimes mutations develop after birth due to environmental factors (somatic mutation) and sporadic cancers occur [10–13].

Tumor suppressor gene mutations may remove an inhibitory signal while oncogenic mutations may cause overexpression of a gene or pathway [11]. These changes

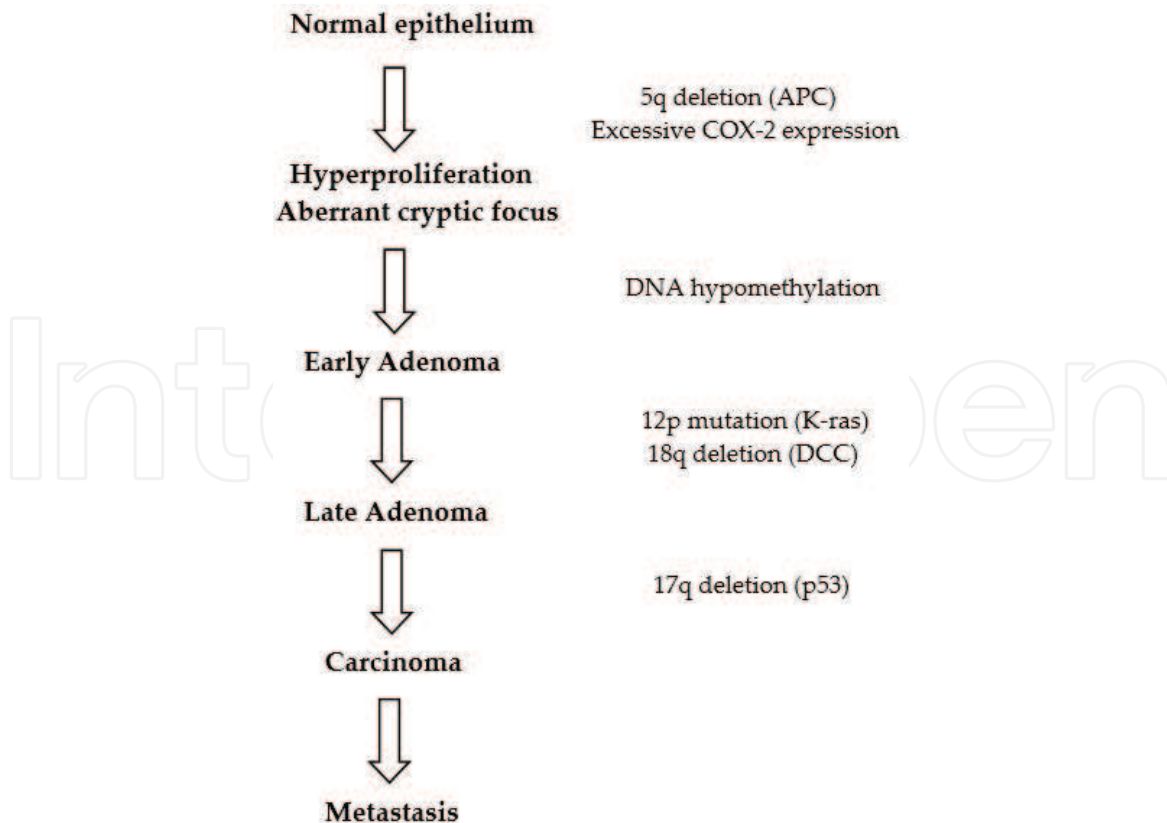


Figure 1.
 Adenoma—carcinoma sequence.

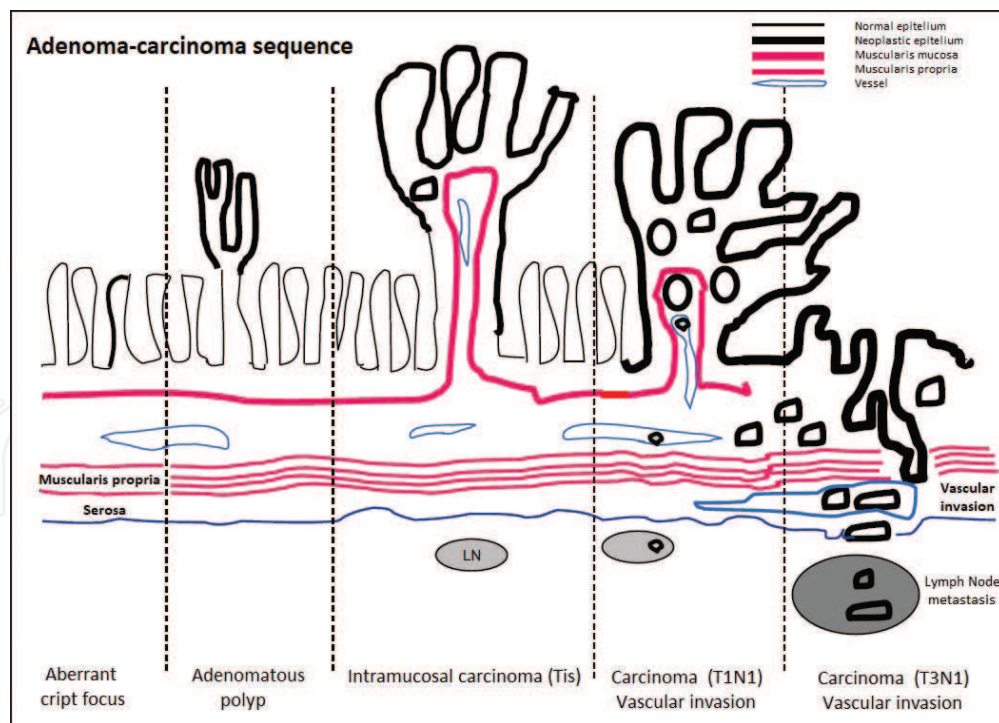


Figure 2.
 Adenoma—carcinoma sequence (figure taken from with permission of Prof. Kuzu, Turkish Society of Colon and Rectal Surgery; Colon and Rectum Cancers. Eds, Baykan A, Zorluoglu A, Gecim E, Terzi C. 2010).

that cause CRC, which is a different heterogeneous disease in each person, affect the phenotype of the disease, prognosis and response to treatment. Chromosomal instability, microsatellite instability, and the methylator phenotype are the three major molecular pathways that involved in CRC development.

Each pathway has unique characteristics, and multiple pathways may play a role in the development of CRC [12, 13].

2.1 Chromosomal instability

Chromosomes are unstable in chromosomal instability (CIN), because of a change in the chromosome structure or copy number (Loss of heterozygosity-LOH). CIN is the most common occurrence in CRC [13]. Approximately 80% of CRC patients have CIN. Vogelstein and Fearon described the classical adenoma-carcinoma sequence and their study supported that LOH was responsible for the sequence [14]. The main genes which play role in the carcinogenesis are the adenomatous polyposis coli (APC), K-ras, deleted in colon cancer (DCC), and P53 (**Figure 1**).

The APC is a tumor suppressor gene, therefore, mutation in both alleles are necessary for the initiation of the sequence. Mutated APC causes decreased production or lack of APC protein. Thus, translocation into the nucleus due to intracellular accumulation of β -caterin, which is controlled by the APC protein to regulate the WNT signaling pathway, causes alterations in cell signaling, proliferation, and adhesion [15]. The APC gene is first described in patients with FAP. However, it was then reported that majority of the sporadic CRC has the APC gene mutation and APC mutation is present in adenomas smaller than 0.5 cm [16].

K-ras is a cellular variant of RAS oncogenes and the most frequently mutated RAS proto-oncogene in CRC. Since K-ras is a proto-oncogene, mutation of only one allele is enough. K-ras gene encodes a G-protein (Guanine nucleotide binding protein) that is active when GTP bond state and inactive (GDP-bond state) after hydrolyzed by GTPase. This protein is involved in mitogen-activated protein kinase (MAPK) pathway which promotes cell growth and proliferation. RAS mutation results in an active GTP-bond protein, which is unable to switch off by GTPase, and leads to uncontrolled cell division. About 43% of non-hypermuted (Microsatellite stabile-MSS) CRC, which are nearly 80% of CRC, has RAS mutations [17].

DCC and SMAD4 mutations have been found in CRCs [18, 19]. Both are tumor suppressor genes. DCC gene product is thought to be involved in cell differentiation and adhesion in CRC [20]. DCC and SMAD4 (formerly PC4-deleted in pancreatic cancer) were both identified at 18q. SMAD4 mutations is thought to perturb TGF-beta signaling pathway which has an inhibitory influence on normal cell growth [19, 20].

TP53 gene on chromosome 17p encode P53 protein which arrests the cell cycle and facilitates DNA repair [21]. In all human cancers most of the mutations occur in TP53 gene. TP53 mutation occurs in about 75% of CRCs [14]. However it is not frequent in adenomas, therefore, it is considered to be a late event in CRC tumorigenesis and related with invasiveness [22, 23].

2.2 Microsatellite instability (MSI)

Microsatellites are non-coding DNA segments containing 1 to 4 repetitive nucleotide sequences. In normal individuals microsatellites are completely identical in all cells. But the failure of the DNA mismatch repair genes to function properly causes a change in the length of the microsatellite sites that are already prone to error during copying. This is called microsatellite instability. There are also short repetitive segments in various tumor suppressor genes (TSG), and accumulation of the mutations in TSGs due to the inactivity of MMR genes (most commonly MLH1 or MSH2) lead to the development of adenoma and subsequent carcinoma [21–23].

It is possible to detect microsatellite instability with current diagnostic procedures, as long as many cells carry the same abnormality, which means that the cells

belong to the clonal process. Clonal proliferation is a characteristic feature of the neoplastic process. And It should be understood that MSI is an indicator of a clonal neoplastic process [24].

Cancers arising through MSI pathway are approximately 15% of all CRC and tend to be hypermutated, therefore, are also termed the mutator phenotype [17]. However, prognosis is better than cancers arising through CIN pathway.

2.3 CpG island methylator phenotype (CIMP)

Another common pathway in CRC is epigenetic instability. Epigenetic alterations such as hypermethylation of DNA promoter regions can silence gene transcription and contributes to diseases like cancer. Methylation of cytosine is normally an essential process and controls multiple processes [25]. There are cytosine-guanine (CpG) dinucleotide enriched areas in promoter regions. These CpG enriched regions of genes are called CpG islands and normally maintained in an unmethylated state. Several tumor suppressor genes contain CpG repetitive sequences in the promoter region. Aberrant methylation of these CpG islands silences gene transcription and contributes to cancer process [25, 26]. This phenomenon is called CpG island methylator phenotype (CIMP). Especially methylation of the MMR gene, hMLH1 causes approximately 80% of MSI CRCs [27]. Almost all MSI-high (MSI-H), CIMP+ cancers without K-ras mutations have BRAF mutations. However, Lynch-related CRCs only have K-ras mutations [28, 29].

3. Hereditary colorectal cancers

3.1 Hereditary non-polyposis colorectal cancer (HNPCC)

HNPCC is the most common hereditary colorectal cancer. HNPCC is also termed Lynch syndrome. In Lynch syndrome, CRC and endometrial cancer risk are significantly increased as well as several other malignancies. It accounts for 3% of all colorectal cancers [30]. Lynch is an autosomal dominant disease. Mutations in DNA repair genes (mismatch repair-MMR) are detected in affected individuals. In Lynch syndrome there is a germline mutation. Since this mutation is only in one allele, a second hit is necessary (mutation, loss of heterozygosity, or epigenetic silencing). Colorectal cancer develops in 80% of patients around 40 years of age. The most frequently mutated MMR genes in HNPCC were MLH 1 (37%), MSH 2 (41%), MSH 6, and PMS 2. CRCs developed in Lynch syndrome are MSI-H tumors [30].

In patients with Lynch syndrome, the risk of synchronous and metachronous tumors is increased, and approximately 7% of patients have a second tumor at the time of diagnosis [31]. Metachronous tumors develop within 10 years in 16% of individuals who had previously undergone colon resection due to Lynch syndrome and within 30 years this rate reaches to 62% [32].

Lynch-associated CRCs also evolve from adenomas like most CRCs. However the adenomas are more often proximally located, and more likely to be larger and flatter. And as compared with sporadic adenomas, high-grade dysplasia and/or villous histology are more often detected. It is also known that the adenoma-carcinoma sequence progresses more rapidly in Lynch syndrome. Fortunately, the overall 10-year survival from CRC is 91% [33].

Tumors in HNPCC are more often found in the proximal colon than sporadic cancers. Unlike sporadic cancers, tumor in Lynch is poor differentiated and there is

peritumoral lymphocytic infiltration, and Crohn's-like reaction [34]. However, the prognosis is still better than sporadic colorectal cancer. The following three theories stand out for this reason: earlier diagnosis in HNPCC tumors, the genomic instability in HNPCC tumors leads to the continual increase of mutations and the loss of critical functions and metastatic ability of the tumor cell due to this mutation burden, and Crohn's-like lymphocytic infiltration around the tumor enhances host immunity by expressing IL-4, TNF-a [33, 34].

Two different forms of HNPCC have been described. Lynch Syndrome I is characterized with proximal colon tumor, young age, no extracolonic involvement. Generally same colonic segment is involved in other relatives. In Lynch Syndrome II, in addition to Lynch I, stomach, small intestine, pancreas, ovary, endometrium and urinary tract cancers may develop. The most important tool in diagnosing Lynch syndrome is family history of CRC or other cancers related with Lynch. Several family history-based criteria (Revised Bethesda Guidelines and Amsterdam II Criteria) have been used to determine the people at risk for HNPCC (**Table 1**) [34].

MSI is a characteristic of tumors in HNPCC and caused by a loss of DNA MMR. An MSI screening test is required for patients with a positive Bethesda criteria. Polymerase chain reaction is used to test for MSI by copying a panel of DNA sequences that contains nucleotide repeats [33–35]. Family members who meet the Amsterdam II criteria or revised Bethesda guidelines, or those with a diagnosis of endometrium cancer prior to the age of 50 years, or individuals with a MMR gene mutation in the first degree relatives are at risk for Lynch syndrome.

In Lynch syndrome, synchronous or metachronous cancer and polyp development are common. It is important to be cautious in this regard. Colonoscopy should be done every one or two years starting from the age of 20–25 [36, 37]. Gynecological examination and endometrial aspiration biopsy for endometrium cancer, and transvaginal ultrasonography for ovarian cancer should be done once a

Amsterdam II Criteria and Revised Bethesda Guidelines

Amsterdam II Criteria [35]

All criteria must be met:

- Three or more individuals with colorectal cancers or HNPCC-related cancers, and one of them being a first-degree relative of the other two,
- Two or more successive generations are affected,
- At least one relative has colorectal or HNPCC-related cancer diagnosed before the age of 50 years.

Revised Bethesda Guidelines [34]

One or more of the following criteria must be met:

- Colorectal cancer diagnosed before the age of 50 years,
- Synchronous or metachronous colorectal cancer or other HNPCC-related tumors*, regardless of age,
- Colorectal cancer with MSI-high histology** diagnosed before the age of 60 years
- Colorectal cancer diagnosed in one or more first degree relatives with HNPCC-related tumor, and one of them being diagnosed before the age of 50 years,
- Colorectal cancer in 2 or more first- or second-degree relatives with HNPCC-associated tumors, regardless of age.

HNPCC: hereditary nonpolyposis colorectal cancer; MSI: microsatellite instability.

**HNPCC-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel.*

***Presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring cell differentiation, or medullary growth pattern.*

Table 1.
Amsterdam II Criteria and Revised Bethesda Guidelines.

year starting from the age of 30–35, or 3–5 years prior to the age of a relative diagnosed with HNPCC [37]. Upper gastrointestinal endoscopy should be done once every 2 years starting from the age of 30–35, with gastric biopsy and treatment for *Helicobacter pylori* infection when found on biopsy. Renal ultrasound, urine analysis and cytology should be done every year starting from the age of 30–35 [36, 37].

3.1.1 Treatment

Prophylactic colectomy is not considered in patients without CRC. Tumor is usually located in the proximal colon. Total abdominal colectomy—ileorectal anastomosis is recommended in patients with Lynch syndrome. Considering the quality of life in elderly patients, or in patients who are not eligible for total colectomy a segmental colectomy may be recommended according to the location of the tumor [36]. However patients who undergo segmental colectomy are at increased risk for subsequent CRC as compared to patients with total abdominal colectomy—ileorectal anastomosis [38, 39]. Prophylactic hysterectomy and oophorectomy should be recommended at the time of colorectal surgery. However, it may be recommended for women who aged 35 years or older after family planning [39].

3.2 Familial adenomatous polyposis (FAP)

It accounts for 1% of all colorectal cancers and is an autosomal dominant disease. FAP is characterized by the presence of hundreds of adenomas in the colon (**Figure 3**). It is a broad spectrum disease with extraintestinal manifestations. It usually occurs after puberty and is diagnosed at a mean age of 29 years. Colorectal cancer develops at an average age of 39 years. Colorectal cancer is unavoidable in patients who do not undergo surgery. FAP is 80% familial, and 20% sporadic [40].

Mutation in the APC (adenomatous polyposis coli) gene, which is located at the q21 locus of chromosome 5, is responsible for FAP (5q deletion) [40, 41]. Mutations in codons close to the 3' and 5' ends of the APC gene lead to attenuated FAP (AFAP), while mutations in the middle, between codons 169 to 1393, result in FAP. Generally, there is less than 100 polyps in AFAP. Unlike FAP, life-long risk for CRC development in AFAP is approximately 70%, and polyps and CRCs develop later in life than FAP. In AFAP, tumors mostly do not develop in the rectum and are characterized by a more proximal distribution in the colon. If germline mutation is absent in these patients, MMR gene mutation should be considered for HNPCC elimination [41]. In

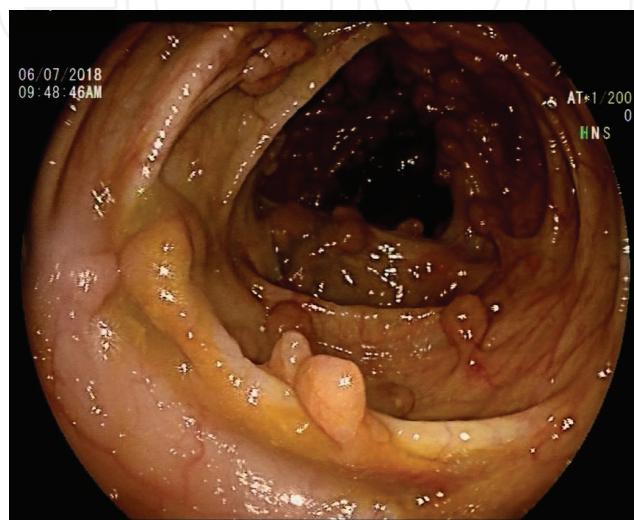


Figure 3.
Colonoscopic familial adenomatous polyposis (FAP).

FAP, one inherited mutant allele is not enough to cause carcinoma. Carcinoma develops when the second allele of APC and other necessary gene mutations occur [42].

Extraintestinal manifestations of FAP include gastric, duodenal, and periampullary polyps, and less common manifestations such as epidermoid cysts, desmoid tumors, osteomas, and brain tumors. Gastric and duodenal polyps occur in about half of affected individuals. Most of the gastric polyps are hyperplasia of the fundus glands, rather than adenomatous polyps and their malignancy potential is limited [43]. However duodenal polyps are adenomatous. They are present in approximately 90% of FAP patients and should be considered premalignant [44, 45]. Periampullary tumor risk is higher in FAP patients. In patients who undergo total colectomy, the most important cause of cancer-related death is duodenal adenocancer. Adenomatous polyps and cancer are rarely found in the jejunum and ileum of FAP patients. Other rare extraintestinal malignancies in FAP patients are extrahepatic bile duct, gallbladder, pancreas, adrenal, thyroid, and liver cancers [45].

The likelihood of a desmoid tumor is increased especially in mutations in the 3' end of the APC gene [46]. Most of the desmoid tumors occur within the first 5 years in patients who have undergone abdominal surgery, presumably as an inflammatory response [47, 48]. In addition to abdominal surgery and APC mutation, pregnancy, female sex, and family history are other risk factors for desmoid tumors [49, 50]. Although desmoid tumors are slow growing, non-metastatic mesenchymal tumors, they may cause complications such as pain, bowel, and ureter obstruction by compressing and encasing adjacent structures [50].

An interesting marker for FAP is congenital hypertrophy of the retinal pigment epithelium (CHRPE), which can be determined by ophthalmoscopy in about 75% of patients [51]. Fundus examination with ophthalmoscopy reveals oval, pigmented lesions with regular borders in the retina. Lesions may be bilateral and multiple. CHRPE can be used as a clinical diagnostic tool in the screening of FAP and Gardner syndrome [51].

FAP has two subtypes with their own extracolonic manifestations. Gardner's syndrome is a variant of FAP and characterized by desmoid tumors, colonic polyps, osteoma, soft tissue sarcomas, and CHRPE [52]. Also, although very rare, an adenomatous polyposis coli may be associated with malignant tumors of the central nervous system (especially medulloblastoma and/or glioma), known as Turcot syndrome [53]. Turcot is the true variant form of FAP and has a familial character. Colonoscopy and brain scanning tests should also be performed on family members. APC mutations are also responsible for both syndromes.

Screening for FAP should be performed in individuals with an APC mutation and in individuals who are first-degree relatives of those with FAP, or who have >10 cumulative colorectal adenomas, or colorectal adenomas in combination with extracolonic features such as duodenal adenomas, desmoid tumors, osteomas, etc. [53, 54].

Screening for CRC should begin during puberty and flexible sigmoidoscopy, or genetic testing for APC mutations should be performed every 6 months or year. When positive genotype is detected by genetic screening, or adenomatous polyps are detected by sigmoidoscopy, full colonoscopy should be performed to evaluate the spread of the disease. Several polyps should also be sampled to confirm histology. First-degree relatives of FAP patients, who do not have a genetic diagnosis, may be removed from aggressive follow-up and included in standard general population screening programs if there is no polyp detected until 40 years of age on screening [54]. Screening of the upper gastrointestinal tract should be performed at the time of diagnosis, or before 25 years of age. In later periods, it should be done while the colon is being evaluated. Thyroid cancer is rarely seen in patients with FAP. Studies have shown that thyroid

cancer reaches up to 2.6% and thyroid nodules up to 51.7%. Therefore, it is recommended to screen thyroid gland by ultrasonography once a year [55, 56].

3.2.1 Genetic testing

Identification of the APC mutation and its type in a patient diagnosed with FAP facilitates screening of other family members as well as recognition of possible phenotypic lesions that may result from different APC mutations. Commonly accepted indications for genetic testing include FAP cases, FAP in first degree relatives, APC mutation in first degree relatives, at least 10 cumulative colorectal adenomas, extra-colonic involvement of FAP and multiple adenomas with colorectal cancer family history but without a FAP trait in the family [36].

3.2.2 Treatment

3.2.2.1 Medical treatment and chemoprevention

In cases with FAP non-steroid anti-inflammatory drugs (NSAIDs) are thought to achieve regression in number and size of polyps [57, 58]. The most commonly used agents for this purpose are sulindac and celecoxib. The role of chemopreventive agents in FAP patients is controversial, because the effects of these agents on cancer prevention are unclear.

3.2.2.2 Surgical treatment

Prophylactic colectomy should be performed in all cases with FAP. The timing of surgery is planned according to the number of polyps, number of adenomas, presence of dysplasia, size of polyps, symptoms and characteristics of the patient. In cases with mild to moderate polyposis and no other risk factors (low risk of cancer), surgery can be done at mid-puberty. However patients should continue to undergo annual CRC surveillance with colonoscopy while awaiting colectomy. Surgery should be performed in patients with severe polyposis, dysplasia, and polyp greater than 5 mm and in symptomatic cases without any time loss after diagnosis [58].

Surgical treatment options include subtotal colectomy with ileorectal anastomosis (IRA), total proctocolectomy with ileal pouch-anal anastomosis (IPAA), or total proctocolectomy and permanent ileostomy. Total proctocolectomy and permanent ileostomy is preferred in cases of rectal tumor that involved the sphincter complex, and in cases which IPAA is not technically feasible. Functional outcomes (quality of life) and the risk of developing rectal cancer, which is the result of leaving the rectum in place, are important in the selection of anorectal anastomosis or IPAA. Patients with a few rectal polyps which can be controlled endoscopically are ideal for IRA. Chemoprevention is recommended for these patients in the post-operative period. Since colon cancer mostly develops in proximal colon in AFAP patients, total abdominal colectomy and IRA is ideal for this group [58–60].

Risks of developing rectal cancer in the 10th and 25th years in patients undergoing IRA are 4–8% and 26–30% respectively [59, 60]. It is known that adenoma or cancer may develop in patients with IPAA, even in those with end ileostomy [61]. Therefore, the remaining rectum or pouch should be examined endoscopically at 6 months or 1 year intervals after whichever method is preferred (IPAA, IRA). IRA should be avoided in cases with family history of desmoid tumor, and IPAA should be preferred. Because in the case of a cancer or polyposis that may develop later in the rectum, revision of IRA to IPAA would be technically very difficult due to mesenteric desmoids that may develop [54].

3.3 MutYH-associated polyposis (MAP)

The number of polyps may range from 0 to 1000, but it is known that MAP usually contains less adenomatous polyps than FAP. MAP is an autosomal recessive disease. There is a biallelic mutation of the MutYH (MYH) gene on chromosome 1 [62]. MAP usually occurs in fifth or sixth decade with a polyp number of 10–100 [62, 63]. There are insufficient data on extraintestinal manifestations. However, gastric and duodenal polyps may be found in individuals with MAP. Unlike FAP, there is no association with desmoids, osteomas, and CHRPE in MAP [63].

MAP should be suspected in individuals with 10 or more cumulative adenomas as in other adenomatous polyposis syndromes. Germline MYH testing is recommended to those who have a family history of colorectal cancer or polyposis in recessive pattern, or who have a clinical FAP or AFAP phenotype but a negative APC mutation test result. In patients with biallelic MUTYH mutations, the cumulative lifetime risk of developing colorectal cancer is 75% in men and 72% in women by age 70 [64]. Most of the patients with MAP are diagnosed when they have cancer, but it is recommended to perform a colonoscopy every one to two years to individuals with known biallelic mutations, starting at 25–30 years of age [36].

CRC, adenomatous polyp with high-grade dysplasia that cannot be removed endoscopically, and a great number of polyps that cannot be controlled endoscopically are indications for surgery. It is recommended to remove the newly developed polyps by performing at least annual colonoscopy in patients not eligible for surgery. Surgical options include subtotal colectomy with IRA, total abdominal colectomy, or proctocolectomy with IPAA [63, 64].

4. Clinical findings of colon cancer

Patients frequently present with changes in bowel habits, rectal bleeding, anemia, and abdominal pain accompanying these findings. Patients may also suffer from weight loss, fatigue, nausea, vomiting, obstruction and perforation [65–69]. Clinical findings vary according to the tumor location. Abdominal pain, which can be seen in all localizations, is the most common clinical manifestation. The most common symptoms in right colon tumors are blunt, permanent lower quadrant pain and anemia of iron deficiency due to occult hemorrhage, fatigue, and anorexia and weight loss. Sometimes, a mass can be palpated in the lower right quadrant [24, 68, 69].

In the left colon, the diameter is smaller (especially sigmoid colon) and the content is solid. In addition, left colon cancers are scirrhous and annular. Therefore, obstructive symptoms are common. Obstruction may lead to perforation and peritonitis. According to Laplace's law, the most likely location of perforation as a result of obstruction of the sigmoid colon is the cecum of which the diameter is largest. A change in bowel habits and a progressive decrease in stool diameter may be the first symptoms. While rectal bleeding may be a finding as occult blood in feces on the right side, it may occur as hematochezia on the left side. In the presence of iron deficiency anemia in an adult male or postmenopausal woman, the diagnosis of colon cancer should be absolutely ruled out [67–70].

Patients may also present with metastatic disease. At the time of presentation, metastatic disease is detected in approximately 20 percent of patients in the United States [70]. Advanced, or often metastatic disease should be suspected in case of the presence of abdominal distention, ascites, early satiety, right upper quadrant pain, periumbilical nodules, or supraclavicular lymphadenopathy.

Colon cancer can spread in 4 different ways; directly through the neighborhood, lymphatic route, hematogen route, and through the peritoneal cavity by

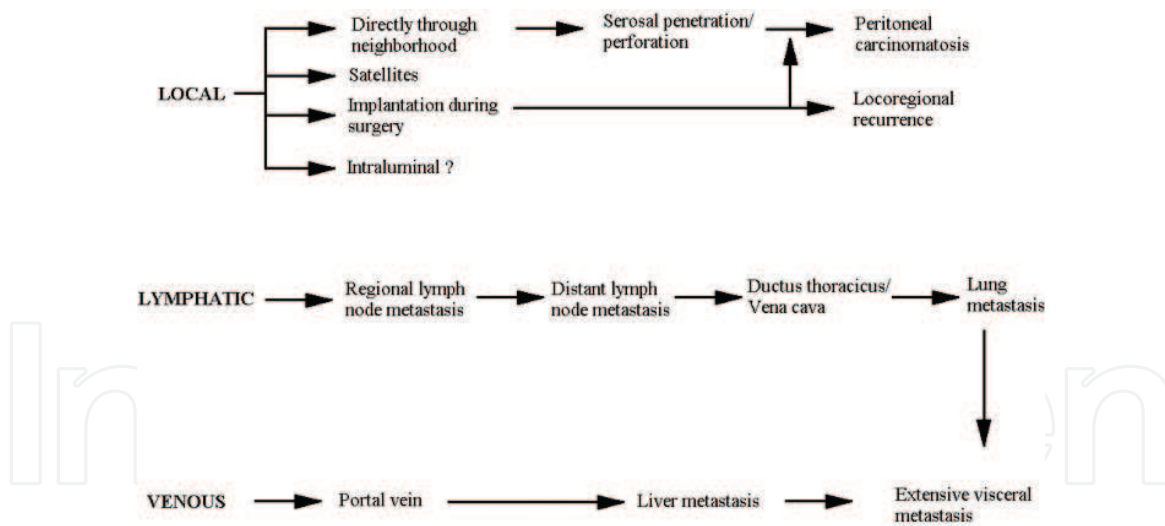


Figure 4.
Colon cancer dissemination.

gravity (seeding) (**Figure 4**). It should be remembered that tumor may also spread by implantation due to manipulation at the time of surgery. The most common metastasis is in the regional lymph nodes. The most important factor determining lymph node involvement is the T category. While lymph node metastasis is 5–20% in T1–T2 tumors, in T3–T4 tumors lymph node involvement increases to more than 50%. Tumor differentiation, presence of lymphovascular invasion and tumor size are other factors. Hematogenous spread occurs with portal system and the most common site for metastasis is the liver. The other common sites for metastasis after liver is the lung and bones. Seeding is caused by the placement of free tumor cells in the omentum, periton (peritoneal carcinomatosis), rectovesical pouch (Blumer's shelf tumors), and ovary (Krukenberg tumors) [70, 71].

5. Diagnosis and preoperative evaluation in colon cancer

Colon cancer may be suspected from vague but suspicious symptoms and signs, or sometimes, especially asymptomatic CRC, may only be revealed by routine screening. Anamnesis, physical and rectal examination are valuable in diagnosis. If there is a suspicion of CRC in the patient after anamnesis and physical examination, the first diagnostic test should be colonoscopy or flexible sigmoidoscopy. In addition, barium enema and computed tomography colonography (CTC) may be performed, if necessary.

The most accurate and preferred diagnostic test for colon cancer is colonoscopy since it can be used for detecting and sampling of lesions along the large bowel, examination of lesions by direct observation, treatment in appropriate patients, and detection of synchronous tumors. Synchronous CRCs occur in 4–5% of patients [71, 72]. In some individuals, a minority of neoplastic lesions are nonpolypoid and flat, and may be more challenging to detect by colonoscopy. However colonoscopy is still more sensitive in this situation than barium enema or CTC [72].

Flexible rectosigmoidoscopy can be used for diagnostic purposes as well. It is mostly recommended for screening of CRC every 5 years, starting at the age of 50 with annual fecal occult blood test. In recent years there is an increase in right-sided or proximal colon cancers. Because of this and the likelihood of synchronous CRCs, it should be considered that flexible sigmoidoscopy may be an inadequate test for diagnosis of a patient suspected of having a CRC [72, 73].

Computerized tomography is the most frequently used test for staging purposes. Positron emission tomography has no place in routine staging and screening. However, in suspicious cases, tumor and fibrous tissue are well separated. Abdominal ultrasonography has no place in the diagnosis of colon cancer [71].

Routine laboratory tests including complete blood count, liver function tests, etc. have no role in diagnosis. However, in the presence of iron deficiency anemia in an adult male or postmenopausal woman, colon cancer should be ruled out. Although liver function tests has no role in diagnosis of liver metastasis, the increase in liver enzymes in patients with colon cancer should be taken into consideration to scan for metastasis [71, 72].

It is known that some tumor markers, especially CEA (carcinoembryonic antigen), are associated with CRC. Nevertheless, tumor markers such as CEA and CA 19-9 appears to have a low diagnostic yield to diagnose primary CRC, since these markers have low sensitivity for early-stage disease and may also increase in some benign diseases. However, both markers have prognostic significance. High CEA suggests the presence of metastasis. In addition, after appropriate treatment increase in CEA level in follow-up should be assessed in favor of recurrence or metastasis [73].

6. Staging

The local features (size, invasion, lymph node involvement) of the tumor are important in determining the resection margin. Therefore, preoperative clinical staging should be done properly. Physical examination and radiological tests are used for accurate clinical staging. It should not be forgotten that the accuracy of radiological detection of the stage is 85–90%, even in the best hands. Definitive staging can only be performed by pathological examination [74].

Pathologic staging in colorectal cancers is based on tumor depth, lymph node involvement, and the metastatic status. Dukes and Astler-Coller classifications are no longer used, instead the TNM staging system is preferred [74]. The most recent (8th edition) revision of the TNM staging classification contains few changes compared with the earlier edition (7th edition). T categories have been revised. Tis in the AJCC 8th edition refers only to intramucosal carcinoma, a lesion with involvement of lamina propria with no extension through muscularis mucosae. T4 is defined as tumor exceeds the visceral peritoneum either by continuous invasion or perforation of the tumor. N categories have not changed. Lastly, the M category has been expanded, with the addition of M1c for peritoneal metastases. Therefore, a new stage, IVc, have been added in stage grouping.

Stage of the disease is the most important prognostic parameter that determines the type of surgery and postoperative treatment options in colorectal cancers. Because of the different lymphatic drainage on the intestinal wall, colorectal cancer gains potential to make metastasis only when there is submucosal invasion. For this reason, colorectal carcinoma is diagnosed only in the presence of submucosal invasion [74].

Dukes staging:

Dukes A: Tumor is limited in the bowel wall.

Dukes B: Invasion through the bowel wall but no lymph node involvement.

Dukes C: Lymph node involvement.

Dukes D: Distant metastasis.

Modified Astler-Coller staging:

A: Tumor is limited to mucosa.

B1: Muscularis propria is invaded but not exceeded.

B2: Invades through muscularis propria (subserosal dissemination).

- B3:** Lesion involves adjacent organs.
- C1:** B1 + lymph node involvement.
- C2:** B2 + lymph node involvement.
- C3:** B3 + lymph node involvement.
- D:** Distant metastasis.

7. Treatment

Colon cancers mostly develop from polyps. Although curative treatment of localized colon cancer is surgery, endoscopic polypectomy is enough when carcinoma in situ or severe dysplasia presents on the polyp surface. However, surgery should be considered for the treatment of colon cancer especially in patients a polyp that cannot be removed endoscopically, and if there is continuity in resection margin after polypectomy [75].

In the last decade, there have been major changes in colorectal cancer management. Total mesorectal excision and neoadjuvant chemoradiotherapy in rectum cancers resulted in significant reductions in morbidity, mortality, and recurrence rates. Recently, complete mesocolic excision (CME) and central vascular ligation (CVL) (open or laparoscopic) has been described in colon cancer treatment to achieve similar oncological results. In 2007, Hohenberger published the first article on CME with CVL for colon cancer and which was later published in English [75, 76]. The aim of CME with CVL method is to create an intact protective mesocolic fascia and avoid tumor spread within peritoneal cavity by dissection of the visceral fascia from the parietal (retroperitoneal) plane (**Figure 5**). The origin of colonic vessels is well exposed and ligated centrally at their origin using this technique. The specimens are characterized by a greater distance from the tumor to the high vascular tie, higher distance from the closest bowel wall to the high vascular tie, longer length of the colon and larger area of mesentery. Thus, maximum lymphatic tissue harvest is achieved [76, 77]. Increase in the patients who have a high number of lymph nodes, decrease in perioperative morbidity, reduction in local recurrence, and advancement in colon cancer-specific survival rate have been shown in recent studies regarding CME [76, 78–80]. This technique is a matter of controversy in colon surgery. Because longer operating times, autonomic nerve injury, and major vascular damage are disadvantages of routine implementation of CME. Although the technique has improved oncologic data, routine implementation of CME may decrease health-related quality of life (QoL) [76, 80].

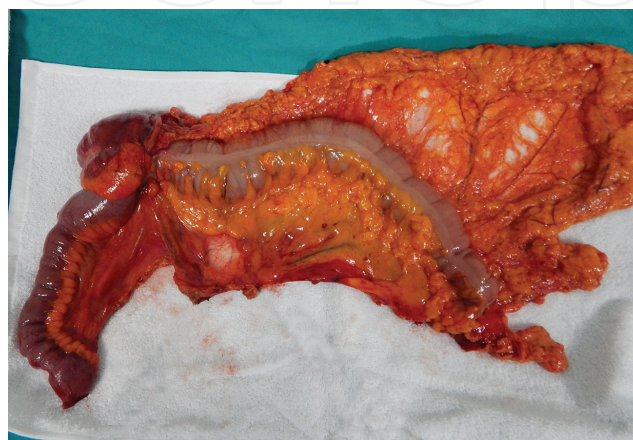


Figure 5.
Complete mesocolic excision and central vascular ligation for the treatment of extended right hemicolectomy specimen.

Surgical resection of the tumor is the main curative treatment option. The colon segment where the tumor is located, the mesentery that contains the lymphatic drainage, and, if there is invasion, adjacent organs should be removed in one piece without deteriorating tumor integrity. If the tumor cannot be removed surgically, palliative surgical procedures such as limited resections, proximal diversion ostomies (colostomy, ileostomy), or bypass surgeries may be applied to relieve symptoms or prevent possible complications [79]. Right hemicolectomy (extended or not), transverse colectomy, left hemicolectomy (extended or not) sigmoid colectomy, and subtotal or total colectomy are preferred for surgical treatments of colon tumors according to involved bowel segment. Surgical intervention may be performed conventional (open) or laparoscopic, provided that it conforms to oncologic principles [80].

7.1 Cecum and ascending colon tumors

Right hemicolectomy is performed as a standard surgical treatment option in the right-sided colon tumors. In this operation, right branch of the middle colic, ileocolic, and right colic vessels are ligated as high as possible. The ascending colon, the hepatic flexure, the first third of the transverse colon, and distal part of the terminal ileum is resected (**Figure 6**). Then, ileocolonic anastomosis is performed between ileum and transverse segment of the colon.

7.2 Hepatic flexure tumors

To remove the entire lymphatic network, CVL of the middle colic, right colic, and ileocolic vessels is performed. This operation is called extended right hemicolectomy (**Figure 7**). When compared to the left hemicolectomy, the amount of transverse colon that is resected increases and only distal 1/3 of the transverse colon is left. An anastomosis should be avoided in areas of unreliable blood supply such as splenic flexure. In this case resection margins should be expanded and splenic

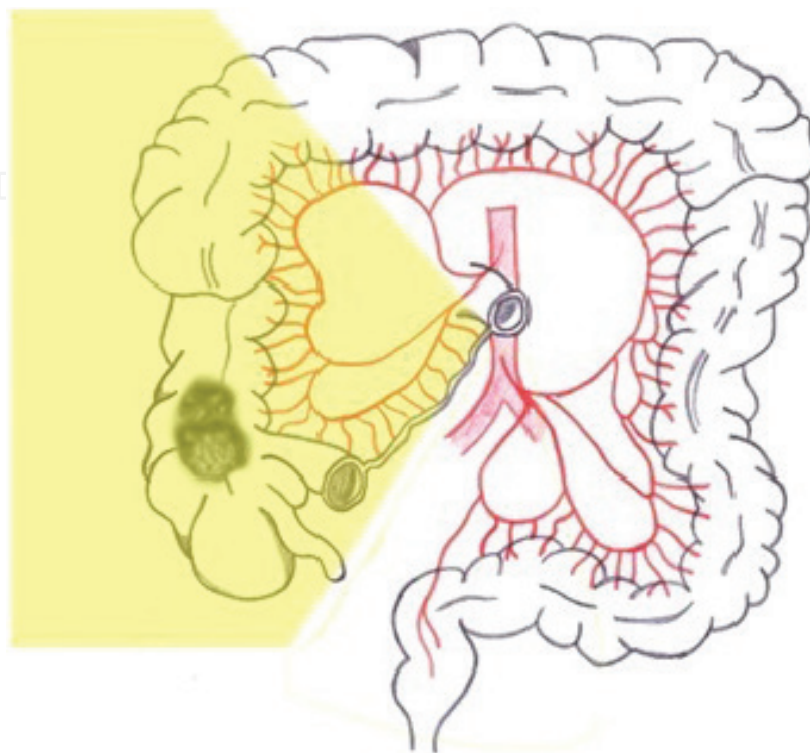


Figure 6.
Resection margins in cecum and ascending colon tumors.

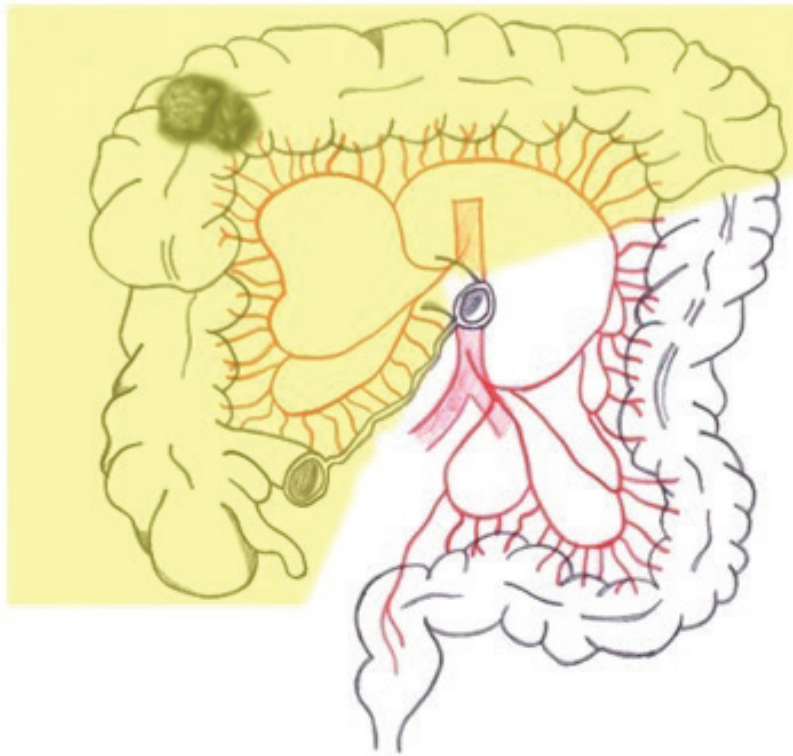


Figure 7.
Resection margins in hepatic flexure tumors.

flexure should be removed as well. Finally, anastomosis is created between the ileum and the proximal end of the remaining colon.

7.3 Transverse colon tumors

The choice of surgery type in transverse colon tumors may be a matter of debate. The arterial supply of the transverse colon is provided by right colic and left colic and middle colic arteries. Ischemia usually does not occur in the anastomosis at the hepatic flexure due to branches from ileocolic and right colic arteries, even if middle colic artery is centrally ligated. However when middle colic artery is ligated, arterial supply of splenic flexure is only provided by left colic artery and there is an ischemia risk in the anastomosis at the splenic flexure. Therefore, transverse colectomy could be performed by CVL of the middle colic and left colic vessels for mid-transverse colon tumors. In this procedure, distal ascending, hepatic flexure, transverse, splenic flexure, and proximal descending colon are resected (**Figure 8**). Moreover, it is recommended surgical resection of the ascending colon and cecum to perform ileosigmoidal anastomosis because it is technically difficult to create an anastomosis between ascending and sigmoid colon. Consequently, it is necessary to consider both the arterial circulation and the lymphatic drainage in the selection of the operation type in transverse colon tumors.

7.4 Splenic flexure tumors

Extended left hemicolectomy is recommended for splenic flexure tumors, as lymphatics may drain to the lymph nodes along the inferior mesenteric artery (IMA) and middle colic artery. The central ligation of the middle colic artery and IMA requires to remove all entire bowel from the proximal transverse colon to the proximal rectum. At the end of the surgical procedure, an anastomosis is performed between proximal transverse colon and proximal segment of the rectum (**Figure 9**).

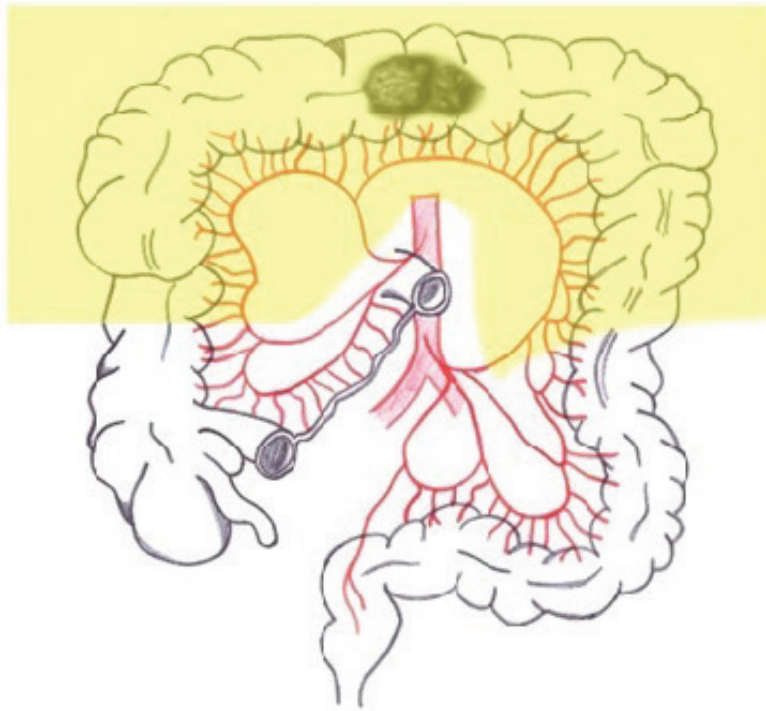


Figure 8.
Resection margins in transverse colon tumors.

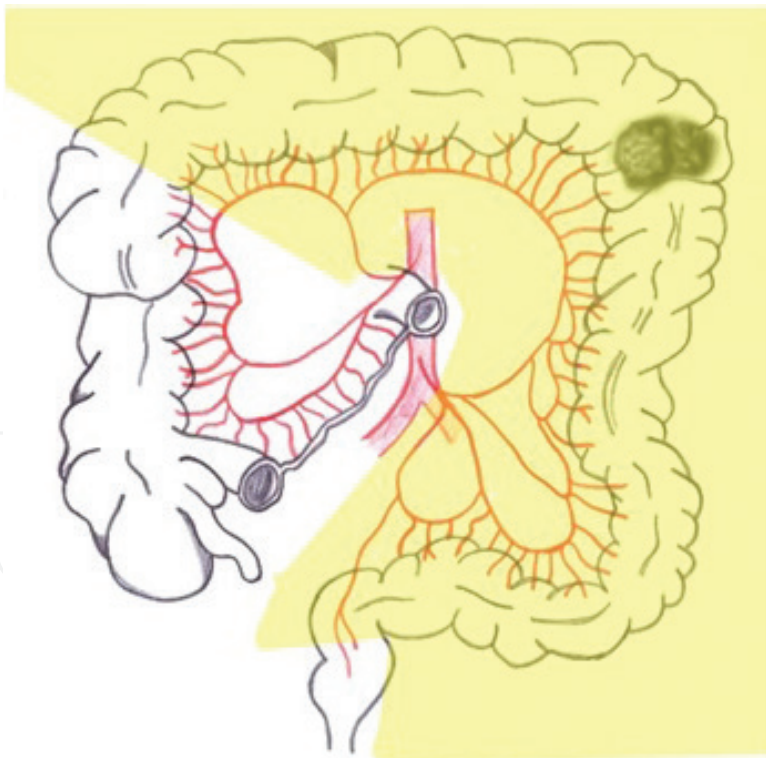


Figure 9.
Resection margins in splenic flexure tumors.

7.5 Descending colon tumors

Left hemicolectomy is recommended in patients with ascending colon tumor. IMA is centrally ligated without preserving the left colic artery. Splenic flexure, descending and sigmoid colons are removed. Then, anastomosis is established between transverse colon and proximal rectum (**Figure 10**).

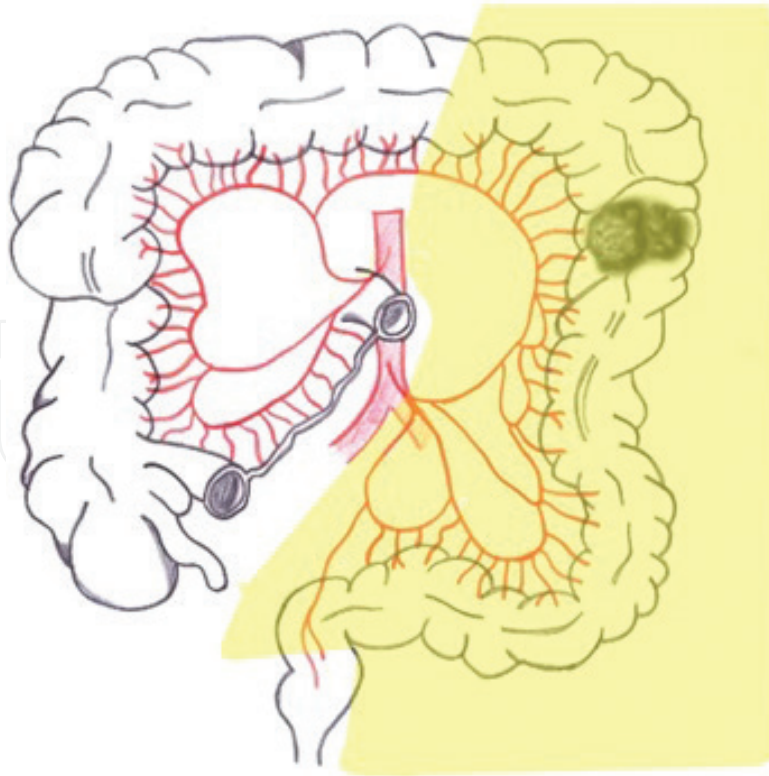


Figure 10.
Resection margins in descending colon tumors.

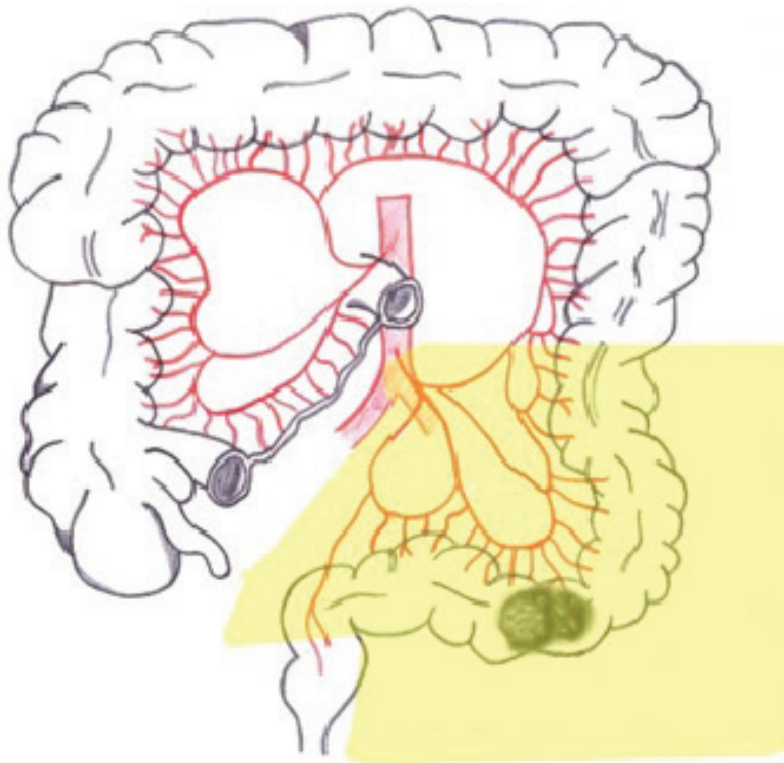


Figure 11.
Resection margins in sigmoid colon tumors.

7.6 Sigmoid colon tumors

The appropriate operation for these tumors is sigmoid colon resection. IMA is centrally ligated while left colic artery is preserved. Sigmoid colon is then removed and colorectal anastomosis is created (**Figure 11**).

8. Prognosis

Pathologic stage at presentation is the strongest prognostic factor. In patients with stage 1 colon tumor, the 5-year survival rate is approximately 90% while it drops to 15% in stage 4 patients [2]. Despite a curative surgery and modern adjuvant treatments, recurrence develops in approximately 40% of stage 2 and 3 patients [81]. Almost all recurrences develop within the first 5 years, and most of them are seen within the first 3 years [82].

Besides pathologic staging, the most important prognostic factors for CRC are histologic grade of differentiation, extramural tumor deposits, lymphovascular and perineural invasion, the preoperative carcinoembryonic antigen (CEA) level, MSI, and *RAS* and *BRAF* mutations. The local extent of disease independently influences survival [83, 84]. However tumor size has no significant impact on prognosis [84, 85]. One of the adverse prognostic factors is residual tumor after resection [86, 87]. There are three types of R designation for residual tumors in non-metastatic patients: R0 resection, complete resection of the tumor with histologically negative margins, R1 resection, incomplete tumor resection with positive microscopic margin involvement, R2 resection, and incomplete resection with macroscopic margin involvement [74].

Regional lymph node metastasis is the other important determinant of prognosis after distant metastasis. Lymph node involvement is alone an indication for post-operative adjuvant therapy to reduce the metastasis risk. Although the number of positive lymph nodes involved is a crucial predictor of outcome [74, 88], relationship between total number of the lymph nodes and the prognosis is not well understood. However, increased number of total lymph nodes in the surgical specimen may be an indicator for the quality of the surgical procedure [88].

Tumor deposits are separate nodules of tumor within the pericolic fat or mesentery. In the TNM staging they are staged as N1c which means there are no regional lymph nodes involved but the subserosa, mesentery, or nonperitonealized pericolic tissues contains tumor deposits(74). These deposits are strong adverse prognostic determinants, and there is a relation between extramural extranodal tumor deposits and extramural venous invasion [89, 90]. Lymphovascular involvement which is tumor invasion into veins, especially extramural veins, or lymphatics is thought to be an adverse prognostic factor [91–93]. Perineural invasion is also associated with an elevated risk of recurrence and poor prognosis [94, 95].

Several studies have provided evidence that preoperative high CEA levels have adverse impact on prognosis for colon cancer. It has been determined that higher CEA levels increase overall mortality and even prognosis is similar or worse in patients with higher CEA levels but lower stages when compared to patients with higher stages but lower CEA levels according to AJCC TNM staging [96, 97].

Metastatic disease is another significant clinical problem in patients with CRCs. The liver, lungs, lymph nodes, and peritoneum are the most frequently involved organs. Major developments in chemotherapy have increased survival rates in a serious manner, but 5-year survival rates are below 20% without resection or ablation of metastasis. Five-year survival rates are 36–58% in patients undergoing partial hepatectomy for hepatic metastases [98–102]. Lung involvement is less common than liver metastasis, but in carefully selected patients metastasectomy is a favorable option for treatment [102].

Conflict of interest

The authors declare that there are no conflicts of interest.

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