Colon Polyps and Colorectal Cancer

Omer Engin
Editor

Second Edition

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Preface

Our published book entitled "Colon Polyps and the Prevention of Colorectal Cancer" is a great success, so we have prepared a second edition.

In the first edition, we explained colon polyps, the increased risks of colorectal cancer, factors of decreased colorectal cancer risk, and colonoscopic procedures, with related scientific knowledge.

In this new second edition, I and my colleagues have revised the first edition and added new chapters with related issues.

Our aim for this book is to prepare detailed presentations of all aspects of colorectal topics.

Why did we believe we should do this?

The patient with a colorectal cancer is opened with laparotomy (or laparoscopic surgery) and an ureter or uterus invasion with liver metastases is found. What can I do?

What should I have done in the preoperative period? Computerized tomography? Neoadjuvant chemotherapy or radiotherapy?

And what can I do during the operation? Ureter resection? Hysterectomy? Liver resection?

What shall I do in the postoperative period? Pathological diagnosis? Adjuvant chemotherapy or radiotherapy? Radiofrequency ablation for liver mass? Biliary stenting?

In our second edition, we aim to present all clinical knowledge related to colorectal cancer and its metastases in one volume. Detailed anatomical information is presented in our book. Information about colon polyps and about the relationship between polyps and cancer was examined. Methods used in diagnosis were written in the light of the latest information. Current surgical treatment of colon cancer is presented as open, laparoscopic, or robotic surgery. The ways in which colon cancer can spread are explained, and treatment options for liver metastases, including surgical options, are presented in detail. Urological metastases and urological injuries seen during surgery are examined in a separate chapter. Gynecological organ metastases are also explained in detail in a separate chapter. In the chemotherapy and radiotherapy chapters, information covers what can be done in colorectal cancer. What to do in cases of metastatic colorectal cancer is examined in the interventional radiology chapter.

We think this book will be useful to readers. All our authors have prepared their chapters meticulously with up-to-date medical information. We offer this book to you, valuable academicians, with wishes for fruitful reading.

Izmir, Turkey Omer Engin
2020

Contents

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Anatomy of the Colon, Rectum, and Anus

1

Semra Salimoglu, Gizem Kilinc, and Bulent Calik

Embryology of the Colon and Anorectic Area

A complete understanding of the colorectal anatomy is closely related to understanding its embryological development. The primitive gut develops from the yolk sac's endoderm. At the beginning of the third week of the fetus, the gut tube divides into three sections. Its sections are named from cranial to caudal as foregut, midgut, and hindgut. The development of the primary intestinal loop occurs with a rapid elongation of the midgut and its mesentery [1].

As a result of this rapid growth in the intestinal length and the simultaneous growth of the liver, the abdomen cannot accommodate all the intestines within itself for a temporary period of time. Thus, the intestinal loops go into the extraembryonic coelomic cavity within the umbilical cord in the sixth week. That is called as physiological umbilical herniation. During the tenth week, herniated intestinal loops begin to return to the abdominal cavity. Although the factors initiating this return are not known clearly, the regression of the mesonephyric kidney, the decline in the growth rate of the liver, and the actual enlargement of the abdominal cavity are considered to play a significant role. The distal 1/3 of the transverse colon, the descending colon, the sigmoid colon, the rectum, and the upper parts of the anal canal develop from the hindgut [2].

The endoderm of the hindgut is also the origin of the bladder and the mucosa of the urethra (Fig. 1.1a). In the later phases of the development, a transverse ridge which is called the urorectal septum arises in the angle between the allantois and the hindgut (Fig. 1.1b). This septum grows downward separating the cloaca into two sections as the primitive urogenital sinus in the anterior and the anorectal canal in

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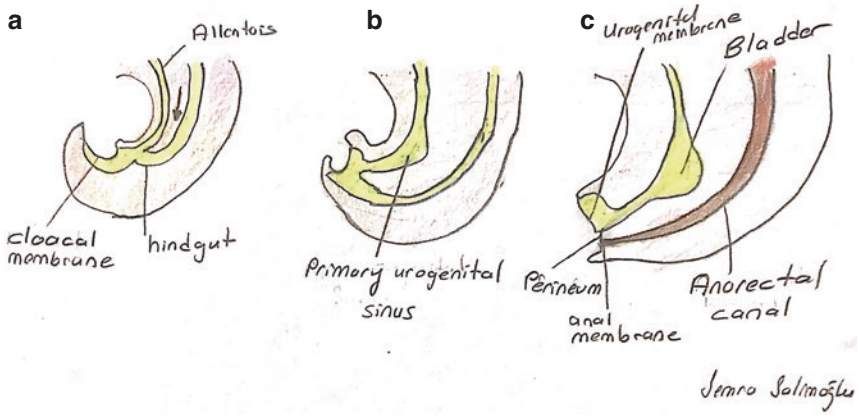


Fig. 1.1 Foregut-derived structures end at the second portion of the duodenum and are supplied by the celiac (coeliacus) artery (Fig. 1.2). The midgut extends from the duodenal ampulla to the transverse colon and takes blood perfusion from the superior mesenteric artery. The distal one-third of the transverse colon, descending colon, and rectum arise from the hindgut fold and take blood perfusion from the inferior mesenteric artery. Venous and lymphatic canals are the same as their arterial equivalents [3]

the posterior. In ninth week, the anal membrane ruptures and the rectum opens to the outside (Fig. 1.1c), which will create the anus later [3].

At the dentate line, endoderm-derived tissues come together with the ectoderm-derived "proctodeum." The development of the distal rectum is a little different. The cloaca is a specialized part of the primitive distal rectum which is composed of endoderm- and ectoderm-derived tissues. The cloaca continues to exist in the hindgut. However, around the sixth week, it starts to divide and separate into anterior and posterior urogenital canal and sphincter elements. With the caudal migration of the urogenital septum, urogenital and gastrointestinal canals become separated. Around tenth week, the descent of the urogenital septum is completed, and the external anal sphincter is formed from the posterior cloaca. By 12th week, the internal anal sphincter develops from the enlarged circular muscle layer of the rectum [3, 4].

The intestines occupy all around the abdomen. Over time, proximal colon meso is reabsorbed on the left side of the abdomen and takes a fixed state. Transverse colon and sigmoid colon mesos remain. Thus, the longest mesos are seen in the transverse and sigmoid colons. In embryological terms, cecum, the ascending colon, and the right half of the transverse colon originate from the midgut whereas the left half of the transverse colon, the descending colon, the sigmoid colon, and the anus originate from the hindgut. Clinically and practically, the first section is called the right colon and the second section is called the left colon [4, 5].

While explaining the colon, rectum, and anal canal anatomy, the pectinate line should be mentioned separately. The pectinate line is formed by the margins of the anal valves which are the small mucosal pockets between the five or ten folds of the mucosa that are known as the anal columns of Morgagni. It is the most critical mark

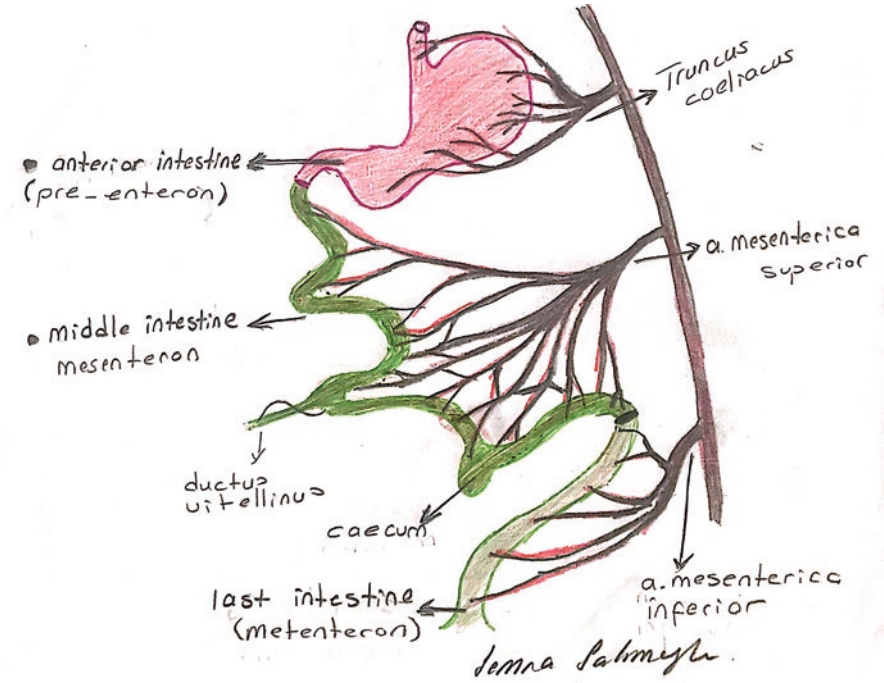


Fig. 1.2 Arterial supply of the digestive system in fetus

in the anal canal. It shows the transition location between the visceral and the somatic area. The course of arteries, veins, lymphatics, nerves and the character of the internal surface of anal canal change after the pectinate line. The anal canal has three histological sections. The cutaneous zone, which ends up to the anal verge, is covered by pigmented skin and contains hair follicles and sebaceous glands. The transitional zone which is located at the proximal part of the anal verge has sebaceous glands without hair follicles. It extends up to the pectinate line which is formed by the free edges of the anal valves [5].

The lower part of the pectinate line originates from ectoderm, and its inner surface is covered by stratified squamous epithelium. Its blood supply comes from inferior rectal artery and venous drainage goes through the inferior rectal vein. Lymphatic drainage goes to the inguinal lymph nodes. It is innervated by the inferior rectal nerves. The pathological type of the tumor of this area is squamous cell carcinoma. External and internal hemorrhoids develop as varicose changes. The upper part of the pectinate line is derived from the endoderm. Its epithelium is columnar epithelium. Arterial supply comes through the superior rectal artery, and the venous drainage goes through the superior rectal vein to the portal system. Lymphatics drain to the pelvic and lumbar nodes. The nerves are autonomous nerve fibers. The pathological tumor type is adenocarcinoma [6, 7].

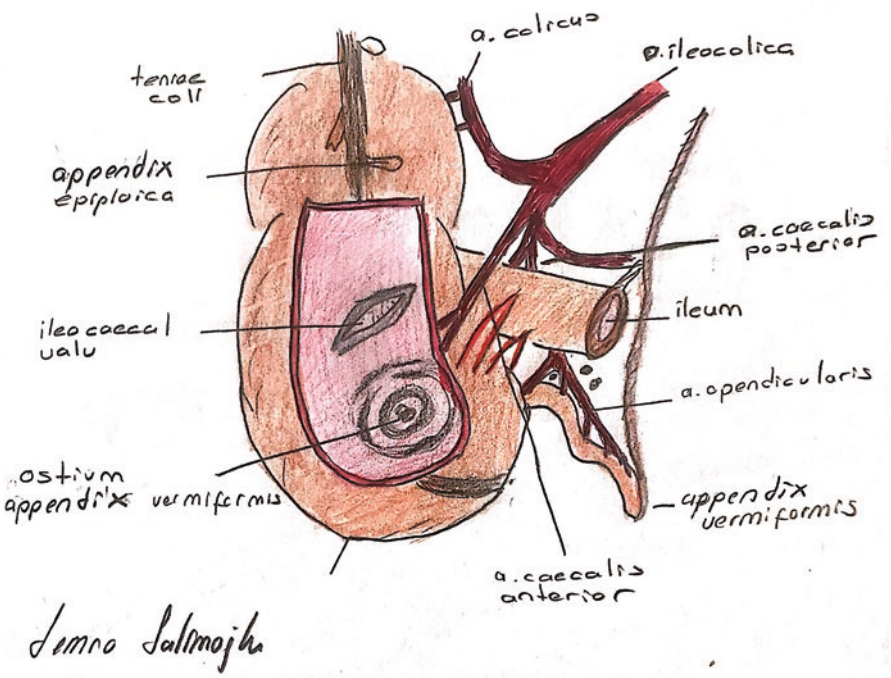


Fig. 1.3 Schematic appearance of the cecum and appendix

Colon, Rectum, and Pelvic Floor Anatomy

The colon is approximately in 120–200 cm length. The diameter of the cecum is 7.5 cm, and the colon becomes 2.5 cm at the point where the sigmoid colon ends. The terminal ileum drains into the cecum through a nipple-shaped structure called ileocecal valve [7–9].

Cecum is a large segment of the proximal colon with a diameter of 7.5 cm and a length of 10 cm (Figs. 1.3 and 1.4). Three longitudinal taenia arise from the cecum. The cecum is completely covered by peritoneum. It has a small meso which limits its movements. On the other hand, it can become very mobile with a long mesentery and be in an abnormal position. The ileocecal sphincter is placed where the terminal ileum binds to cecum. This prevents the contents of the ileum passing rapidly into the cecum. Although the cecum can enlarge to a great extent, dilatations greater than 12–14 cm may cause ischemic necrosis and perforation of the bowel wall. Surgery may be needed when cecal distention occurs due to obstruction or pseudo-obstruction [9, 10].

The appendix is placed at the posteromedial wall of the cecum and is located 3 cm below the ileocecal junction. The end of the anterior longitudinal taenia is always located at the tip of the appendix. The appendix is a blind-ended tube with an average length of 8–12 cm [10, 11].

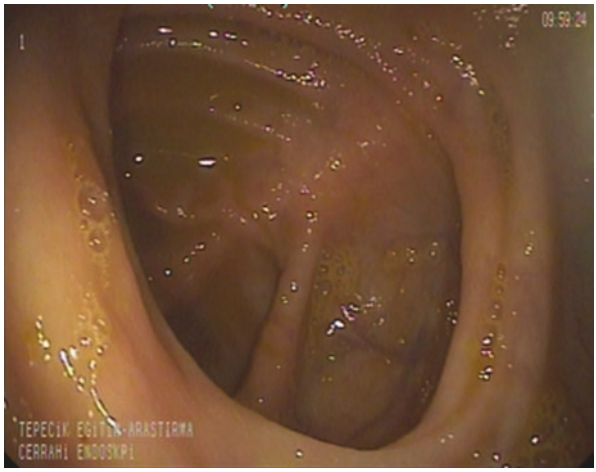


Fig. 1.4 Endoscopic view of the cecum

Localizations of the appendix by frequency are as follows:

1. Retrocecal-retrocolic, free or fixed
2. Pelvic or descendant
3. Subcecal, descending to the right
4. Ileocecal, ascending to the left of the ileum
5. Ileocecal, to the posterior of the ileum

Appendix mesentery derives from the posterior side of the mesentery of the terminal ileum. The mesentery attaches to the cecum and contains the appendicular artery. It takes its artery from the ileal branch of the ileocolic artery or the cecal artery (Fig. 1.3). The appendicular vein also follows the artery in the mesentery. Lymphatic drainage in the ileocecal region extends to the celiac lymph ganglia and cisterna chyli through the lymph ganglia in the appendical, ileocolic, and superior mesenteric artery. Appendicular neoplasms are uncommon. While adenocarcinoma is seen extremely rare (0.5%), carcinoids are the most frequent neoplasms. They are asymptomatic and most of them are smaller than 1 cm; therefore, they can be found by chance in tests. In these patients simple appendectomy is adequate. Surgery depends on the localization in tumors with 1–2 cm. If the tumor is invaded at the base of the appendix or mesentery, the treatment is right hemicolectomy. Appendectomy may be normally sufficient for tumors between 1 and 2 cm because distant metastases are rarely seen in these tumors. In order to decrease locoregional and distant metastasis, the treatment for tumors larger than 2 cm is a right hemicolectomy [12, 13].

The ascending colon is located between the cecum and the right hepatic flexure, with an average length of 15 cm. It is placed along the right side of the abdominal cavity from the cecum to the bottom of the lower right lobe of the liver. It is covered with a peritoneum on the anterior and on both sides. The back side is attached to the abdominal wall. Its lateral peritoneal connections are an

embryological junction between the parietal and visceral peritoneum. Twenty-six percent of individuals have mesentery. The upper part of the ascending colon turns left under the liver and then it turns downward to the medial to make the hepatic flexure on the lateral side of gallbladder. Mobility of this flexure changes between 2.5 and 7.5 cm in breathing. Toldt's white line represents the fusion of the mesentery and the posterior peritoneum. This boundary marker is a good guide in mobilizing the colon and mesentery from retroperitoneum [12, 13].

Transverse Colon

It is the part of the colon with a downward slope of varying degrees between hepatic flexure and splenic flexure. Its average is 40–50 cm and it is completely covered with the visceral peritoneum. It has a long mesentery. The transverse mesocolon attaches the transverse colon to the posterior abdominal wall and allows it to be the most mobile part of the colon. The large curvature of the stomach is connected to the transverse colon by the omentum. Just below the lower corner of the spleen, the transverse colon turns down and makes the splenic flexure. Splenic flexure is the most immobile part of the colon except for the rectum. The lateral surface of the splenic flexure is connected to the diaphragm with the phrenicocolic ligament at the level of the 10th and 11th ribs. This connection makes supportage to the spleen. The transverse mesocolon clings to the tail of the pancreas with its left end. Splenic flexure is deeper than hepatic flexure, and its angle is narrower than hepatic flexure. Also it is partially covered with stomach under the costal margin [13, 14].

The splenic flexura is typically accessed by dissecting the colon descending below the Toldt fascia. After that we can separate the omentum from the transverse colon and enter into the bursa omentalis. This maneuver allows flexure mobilization with minimal traction. The large omentum, which is attached to the upper edge of the transverse colon, consists of two layers of visceral and parietal peritoneum. It is clinically useful to prevent adhesions between surgical abdominal incisions and intestinal surface. The omentum can be mobilized and placed between the rectum and the vagina after the repair of high rectovaginal fistulas. It can also be used to fill the perineal space after rectum resection. It acts as a good patch in difficult situations such as duodenum perforation, where it is impossible to close inflamed and edematous tissues [13–15].

Descending Colon, Sigmoid Colon

It extends along the ventral face of the left kidney between the splenic flexure and pelvic ring and is approximately 25 cm in length. It is smaller than the ascending colon in diameter. It has a relatively thinner wall and stable at the pelvic entrance level. Deep muscle group (levator ani) plays the most important role in pelvic floor muscle structure. Pelvic organs are supported by the connections

they make with pubic bones, muscles, and connective tissue and are controlled by central and peripheral nerves. The term "pelvic floor" refers not only to the levator muscles but it also includes all the structures joining the support in the pelvic cavity. Pelvic floor consists of layers of muscles and fascia supporting the points where the vagina, rectum, and urethra open outside together with the abdominopelvic cavity. Pelvic floor gives active support to pelvic organs through muscular contraction and passive support via fascia and ligaments [14, 15]. The functions of the pelvic floor include preventing prolapse, maintaining continence, facilitating micturition and defecation, sexual function, and being a part of the birth canal in women. The pelvis floor attaches to the pelvis both directly and indirectly and has the top-down layers of endopelvic fascia, pelvic diaphragm, perineal membrane (urogenital diaphragm), and superficial layer [14, 15].

The sigmoid starts from the pelvic ring and ends in the rectosigmoid junction. The sigmoid colon is a small-diameter muscular tube on a long hanging mesentery usually forming an omega turn on the pelvis. The rectosigmoid junction is the part where the sigmoid mesentery ends at the third sacral vertebra level. The sigmoid colon is divided into two sections as the fixed and mobile segments. The pelvic segment is long and omega shaped continuing with the rectum at the bottom. Pelvic mesocolon is attached to the pelvis wall. The mesenteric line of attachment forms a reverse V shape. The sigmoid colon is 15–20 cm long and its terminal 10 cm portion can be seen during the proctoscopic examination. The mesosigmoid usually attaches to the left lateral wall of the pelvis, and the recess called the intersigmoid fossa is formed. It is an essential landmark for surgery as having the underlying left ureter. The two narrowest points of the GIS canal are the terminal ileum and the sigmoid [14, 16].

The Rectosigmoid Junction Has Six Anatomical Features

1. Narrowing in the diameter.
2. The absence of the peritoneal pattern below this point.
3. The absence of the real mesentery below the rectosigmoid.
4. Distribution of three longitudinal taenia over the rectum to form a constant longitudinal muscle layer in the rectosigmoid junction.
5. Appendices epiploicae are located in the sigmoid, but they are not found below the rectosigmoid junction.
6. Internally big morphological changes in the mucosa can be easily seen on sigmoidoscope.

The sigmoid is narrower than the ileum. Foreign bodies cause obstruction in either the terminal ileum or the sigmoid such as gallstone ileus, or obstructions associated with bezoars in patients with stomach resection. For example, a foreign body (bezoar etc.) that is passed from the terminal ileum without crushing may lead to obstruction and perforation in the sigmoid [16, 17].

Characteristics Distinguishing the Colon from the Small Intestine

1. Taenia coli (taenia libera, taenia omentalis, taenia mesocolica): These are three longitudinal muscular strips. They extend from the end of the cecum up to the rectosigmoid. They are formed by the longitudinal muscle fibers of the colon. They are 6 mm wide and are located at equal distance.
2. Haustral sacculations of the colon wall: These sacculations are formed by the adaptation of the longer bowel wall to the shorter longitudinal taenia.
3. Appendices epiploicae: They are the small fatty appendices of the peritoneum covering the external surface of the colon. They are relatively decent at the proximal part of the colon. Toward the sigmoid, they take an elongated and pedicled shape [15–17].

Rectum acts as a fecal reservoir together with the sigmoid colon. The rectum is 12–15 cm in length and lacks taenia and appendices epiploicae. It is settled in the pelvic concavity, and since its posterior surface remains outside the peritoneum cavity by attaching the presacral soft tissue, it is always completely extraperitoneal. The anterior face of the proximal one-third of the rectum is covered by visceral peritoneum. Peritoneal reflection is located at a 7–9 cm distance from the anal canal in men and 5–7.5 cm in women. This peritoneum-covered anterior area is called the pouch of Douglas or the pelvic cul-de-sac. The upper two thirds of the rectum is in association with the small intestine and the sigmoid colon in men, while the lower one-third associates with the prostate, seminal vesicles, vas deferens, ureter, and bladder in the front. In women, on the other hand, the lower one-third associates with the posterior vaginal wall in the front and the upper two thirds is related with the uterus, fallopian tubes, ovaries, small intestine, and the sigmoid colon [17, 18].

The rectum has three folds known as the Houston valves. The valve in the middle is folded to the left whereas the valves located above and below are folded to the right. These folds disappear in surgical mobilization which is an operation that gives an additional 5 cm length to the rectum. The posterior part of the rectum is firmly surrounded by a thick and adjacent mesorectum. This cover, which is usually in collagen form, is thicker in the posterior and thinner in the anterior. The fat tissue, veins, nerves, lymph glands, and lymph vessels located on the posterior and lateral sides of the rectum are surrounded by this cover and form the mesorectum defined by Heald. Presacral fascia (Waldeyer fasyası) is formed by the thickening of the parietal leaf of the endopelvic fascia. It covers the sacrum, coccyx, mid-sacral artery, and presacral vein. Between the two covers is located a cellular and veinless tissue. Some fascia leaves moving away from the Waldeyer fascia join the perirectal fascia right above the anorectal ring proceeding downward-forward at the sacral vertebral level. This extension in the tissue structure is called the rectosacral fascia or sacrorectal ligament. The section of the rectum posterior remaining under the peritoneum is covered by the perirectal fascia. Denonvillier fascia, which is located in front of the perirectal fascia and extends from the peritoneal reflection toward the urogenital diaphragm, is between the rectum and prostate and seminal vesicles in

men and between the rectum and vagina in women. Parietal fascia thickens in the right and left at the lower sections of the rectum. These anatomic formations located on the lateral pelvic floor wall with their ends at the side of the rectum supporting the rectum on both sides are called the lateral ligaments of the rectum. Although the middle rectal artery does not traverse these lateral ligaments, in 25% of the cases, it sends out small branches to one side or both sides. When these ligaments are cut, it has the risk of mild bleeding. A strong presacral fascia covers the sacrum and coccyx to contain the middle sacral artery, nerves, and presacral veins below. A postoperative damage to the presacral fascia may lead to bleeding caused by these veins which is difficult to control. This avascular fascia must be dissected very carefully during mesorectal dissection [17–19].

Anus is the last part of the digestive system extending 4 cm from the anorectal ring to the hairy skin of the anal line. In a normal individual, the anal canal is kept closed in the anteroposterior direction as a result of the tonic contractions of the anal sphincter. Its borders are attached with the fatty, connective, and muscular tissue to the coccyx. Ischiorectal fossa and contents (fatty tissue, hemorrhoidal branches, and nerves) are formed bilaterally, perineal body in the anterior, vagina in women, and urethra in men. The internal lining of the anal canal has changed in two main directions: mucosa is covered by columnar epithelium above. Below, it is covered by shaded colored squamous epithelium lacking hair and glands. The margin between the two linings is called linea pectinea or linea dentata. The valves along this line are formed by proctodermal membrane residuals. Each valve has a minor dent on it (Morgagni sinus, crypt, anal sinus). Musoca makes 8–14 longitudinal turns along the linea pectinea. Two adjoining colons come together at the linea pectinea level. The difference between the rectal columnar mucosa lining and the anal squamous lining has important clinical outcomes. For instance, diseases like ulcerative colitis affecting the rectal mucosa may progress up to the transition point while they do not reach the distal of the dentate line. Cancers in the dentate line proximal are typically adenocancer and those in the distal are squamous or cloacogenic. Anal canal epithelium has normal skin structure with apocrine glands. Inflammatory complications of the apocrine glands and hidradenitis suppurativa are observed. In addition, this difference varies in sensory perception affecting the surgical approach in anorectal diseases. For example, internal hemorrhoids can be treated with a rubber band application without requiring local anesthesia. External hemorrhoids, on the other hand, require local anesthesia on the sensitive perianal skin [18, 19].

Colon Wall Is Composed of Three Layers

The inner side of the colon is covered by a lining layer. The lining covering the inner side of the intestine is called the mucosa. This layer has the function of digesting and absorbing of the nutrients. The middle part contains the muscular layer. Nutrients are moved forward by this layer. The outermost layer of the bowel wall is the serosa layer. The surface of the serosa layer is smooth. This prevents the intestines from adhesion to each other within the abdominal cavity and the bowels

function within an order. The waste of the nutrients travels along the colon and is moved to the rectum, which is the terminal end of the colon where the stool is stored. When the stool stored here arouses the feeling of defecation, the individual defecates (sometimes the natural contractions and rhythm of the large intestine may change. Waste materials may progress quickly or very slowly. Stress, medications, pregnancy, disease, a constant feeling of defecation, lack of exercise, and a diet poor in fiber and liquid disturb the functions of the intestine) [19, 20].

The mouth where the colon opens outside is called the anus. This region has muscles that control stool. These stool-controlling muscles are called sphincters. There are two sphincters; one inside, one outside. The sphincter inside contains smooth muscle fibers and works involuntarily. The sphincter inside is called the internal anal sphincter. The one outside (external anal sphincter) has striated muscles and is controlled voluntarily [19, 20].

Arterial Supply, Venous and Lymphatic Drainage

Arterial supply of the cecum is provided by anterior and posterior cecal artery. Veins accompany arteries and are drained into superior mesenteric vein. The appendix receives its blood supply from the appendicular artery, a branch of the posterior cecal artery. The arterial supply of the ascending colon is provided by the two branches of the superior mesenteric artery called ileocolic artery and right colic artery. Veins accompany arteries and flow into the superior mesenteric vein. The proximal 2/3 of the transverse colon arterial supply comes from middle colic artery which is a branch of superior mesenteric artery. The distal 1/3 is supplied by left colic artery which is a branch of the inferior mesenteric artery. Veins accompany arteries and flow into the superior mesenteric vein and inferior mesenteric vein. The descending colon is supplied by the branches of left colic artery and sigmoid artery which are the branches of the inferior mesenteric artery. Veins accompany arteries. The terminal branch of the inferior mesenteric artery, the superior rectal (hemorrhoidal) artery, reaches the upper rectum within the colon meso, entering into the rectal wall as small branches divided into two sub-branches as right and left. The middle rectal (hemorrhoidal) artery (it is reported to be absent in 40–80% of the cases in the specimen studies carried out) is a sub-branch of the internal iliac artery which supplies the 1/3 of the lower rectum and the upper part of the anal canal. It progresses along the lateral ligament and reaches the rectum. The inferior rectal (hemorrhoidal) artery arises from the internal pudendal artery, passes the ischiorectal fossa and reaches the anal sphincters. The main artery of the rectum is the superior rectal artery. Although superior and middle rectal arteries are ligated during the rectal mobilization the perfusion of the rectal stump is not affected due to the submucosal collateral network. The middle sacral artery arises 1 cm above the aortic bifurcation, progresses downward passing in front of the last two lumbar vertebra, sacrum, coccyx, and behind the aorta, left common iliac artery, presacral nerve, superior rectal artery, and the rectum (Fig. 1.5). Its terminal branches reach the anococcygeal raphe and the anal canal [20, 21].

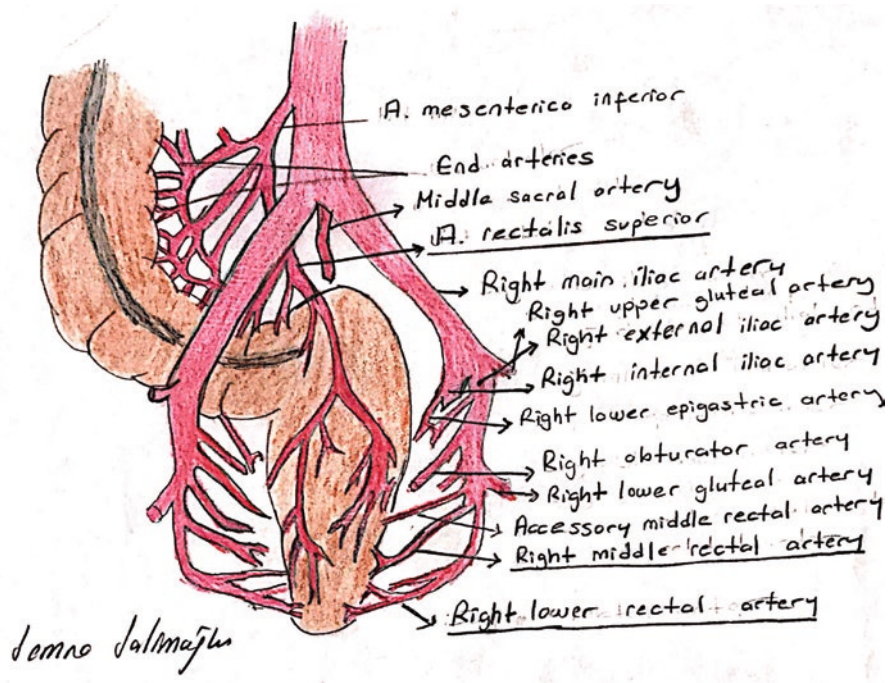


Fig. 1.5 The arterial supply of the rectum

As for the venous circulation, superior hemorrhoidal vein flows into the portal system through inferior mesenteric vein. Middle hemorrhoidal vein and inferior hemorrhoidal vein drain into the systemic circulation through the internal iliac vein. Thus, a portal-systemic natural shunt is formed around the anal canal. The importance of this shunt is that if portal hypertension develops for any reason in patients, venous distention and further rectal varicosis can occur in the distal part of the portal system (that is the anal canal) and that should not be confused with hemorrhoidal disease. From an epidemiological point of view, it was seen that in patients with portal hypertension the incidence of hemorrhoidal disease is not different from the normal population. Rectal varices account for only 1% of the gastrointestinal bleeding seen in patients with portal hypertension. The upper hemorrhoidal plexus is located in the submucosa, in the section above the linea dentata of the anal canal. The external hemorrhoidal plexus lies below the linea dentata of the anal canal beneath the skin. The two plexuses are connected to each other. Enlargements in the internal plexus form internal hemorrhoids while enlargements in the external plexus form external hemorrhoids [20, 21]. The arterial supply of the anal canal is provided by the inferior rectal (hemorrhoidal) artery arising from the internal pudendal artery. It supplies the arterial circulation of the section below the pectinate line. Its venous circulation is through the middle and inferior rectal veins to the internal iliac vein and then to the inferior vena cava. This

bilateral drainage of the anal canal is responsible for the differences in the metastases of the tumors developing in this region (Fig. 1.5).

SMA and IMA Have Three Main Connections

1. The marginal artery of Drummond (parabolic arcade) is located at a distance of 1–8 cm to the colon wall with a parallel progression. (The marginal artery may end at the superior rectal artery). Two to six sigmoid branches are collateralized with the left colic artery for forming an arch that supplies blood to the sigmoid colon.
2. The central anastomotic artery: The larger and centrally located artery.
3. Riolan's arc is the anastomosis between the left colic artery as a branch of the IMA and the middle colic artery as branch of the SMA. It acts as a vital canal when the principal arteries of the colorectal area are occluded. The presence of an enlarged Riolan's arc in imagings supports the occlusion of one of the major mesenteric arteries (Fig. 1.6) [21, 22].

Venous drainage of the colon (Fig. 1.7), as stated above, accompanies the arteries. On the left, veins come together forming the superior mesenteric vein. Veins from descending colon, sigmoid colon, and superior rectal area form the inferior mesenteric vein. This drainage continues toward the portal system. The middle and inferior rectal veins join the internal iliac veins which are a part of the systemic circulation [21, 22].

The Lymphatics of the Colon

They are divided into four groups: epicolic lymphatics are below the serosa of the bowel wall, paracolic lymphatics are above the marginal artery, intermediate lymphatics are along superior and inferior mesenteric arteries, and the lymphatics are in the radix of the principal superior and inferior mesenteric artery. The last group includes the mesenteric root nodes (which also collect the lymph coming from the small intestine), aortic nodes, and the left lumbar nodes (Figs. 1.8 and 1.9). They all drain into the cisterna chyli. A wide resection of the colon should involve the whole segment supplied by a major artery. This would resect a large part of the lymphatic drainage of the segment. The lymphatic drainage of the cecum flows into the superior mesenteric lymph nodes. The lymphatic drainage of the appendix flows into the superior mesenteric lymph nodes through the mesoappendix lymphatics. The lymphatic drainage of the ascending colon flows into the nodes extending along the blood vessels and then to the superior mesenteric lymph nodes. The lymphatic drainage of the transverse colon follows the same path as well. Two-third proximal part of the colon lymphatics flow into the superior mesenteric lymph nodes, and 1/3 distal part of the colon lymphatics drain into the inferior mesenteric lymph nodes. The lymphatic drainage of the descending colon also follows the vessels and drains into the inferior mesenteric lymph nodes. Lymphatics follow the arteries (Fig. 1.10).

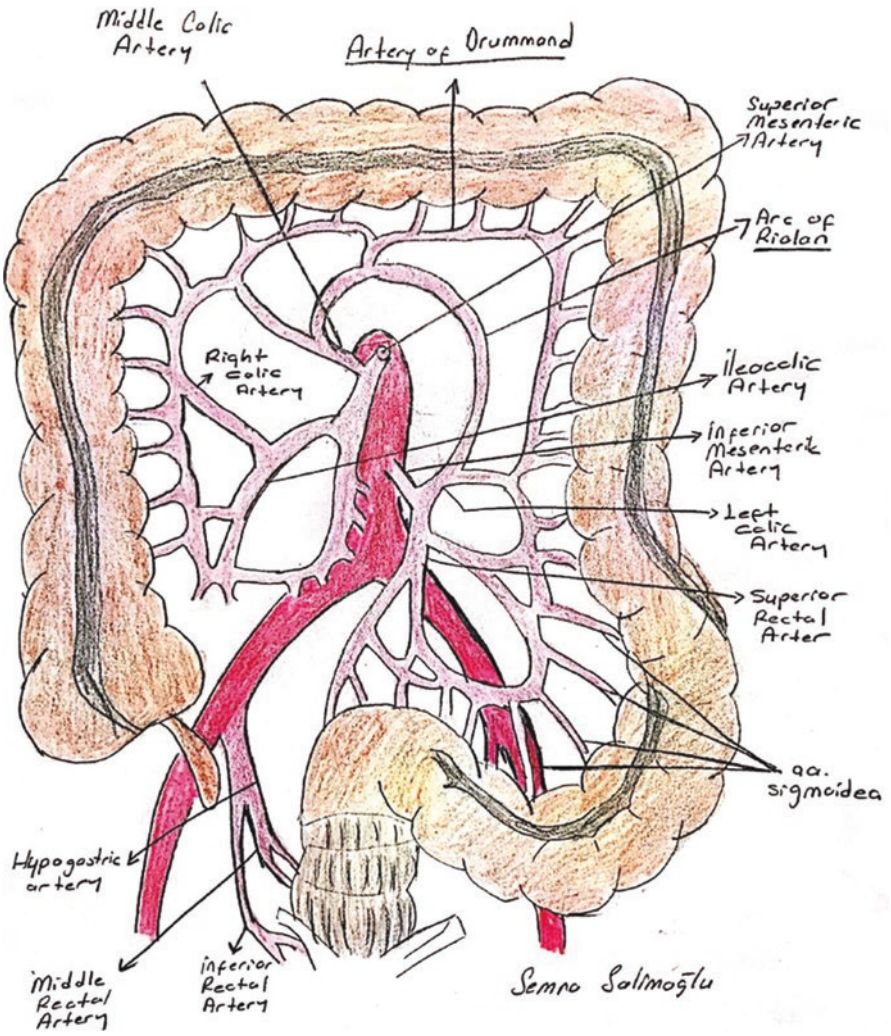


Fig. 1.6 Arterial supply of the colon

The lymphatics of the upper 1/3 and middle 1/3 section of the rectum drain into the inferior mesenteric lymph nodes. The lymphatics of the lower 1/3 part of the rectum drains into the inferior mesenteric lymph nodes. The lymphatic drainage of the part of anal canal below the linea dentata is toward the perianal lymphatic plexus and then to the inguinal lymph nodes (Figs. 1.8 and 1.9) [20, 21]

The extramural lymphatic drainage is separated by the pectinate line. The distance from the anal opening to the pectinate line is approximately 2 cm. The margin separating the intramular lymphatic drainage is at the level of the middle rectal valve located 8 cm above the anal opening.

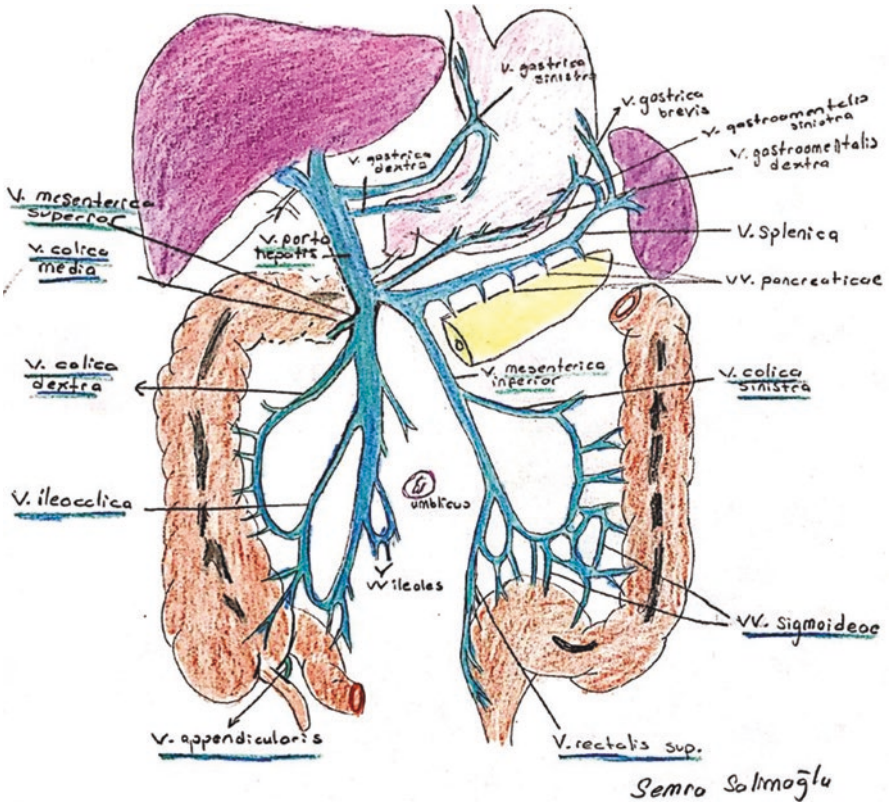
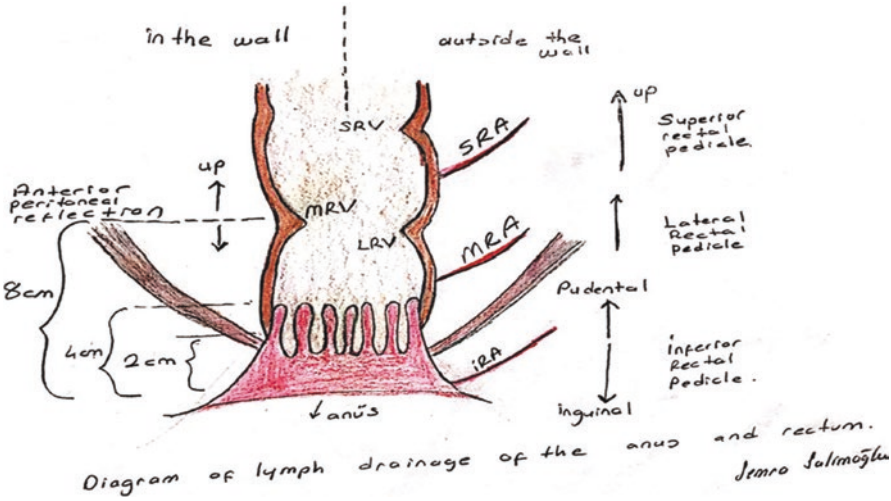


Fig. 1.7 Venous drainage of the colon

Downward spread of rectum lesions is extremely rare. Only 2% of them spread downward. Anterior resections should go at least 2–3 cm distal of the lesions. The invasion of the lymph node with metastatic cancer is a significant prognostic factor for colorectal cancer. The correct pathological evaluation is essential for staging, which is decisive in the treatment of patients. While the lymphatics of the colon and proximal 2/3 of the rectum eventually open to the sisterna chile through the para-aortic lymph nodes, the distal rectum and anal canal lymphatics can drain both to the para-aortic lymph nodes and the internal iliac and superficial inguinal lymph nodes. Although the dentate line clearly shows the level at which the lymphatic drainage is separated, studies have shown that in color injections allied even from a 10 cm distance to the dentate line, lymphatics could drain via the lymphatics of the neighboring organs such as the vagina and the round ligament of the uterus (Figs. 1.8 and 1.9). The drainage of the proximal part of pectinate line is to the inferior mesenteric lymphatics. Distal part of the line drains to the inguinal nodes (Fig. 1.10) [21, 22].



IRA:Inferior rectal artery
MRA:Middle rectal artery
SRA:Superior rectal artery
LRV:Lower rectal valve
MRV:Orta rectal valve
SRV:Superior rectal valve

Fig. 1.8 Diagram of lymph drainage of the anus and rectum. *IRA* inferior rectal artery, *MRA* middle rectal artery, *SRA* superior rectal artery, *LRV* lower rectal valve, *MRV* middle rectal valve, *SRV* superior rectal valve

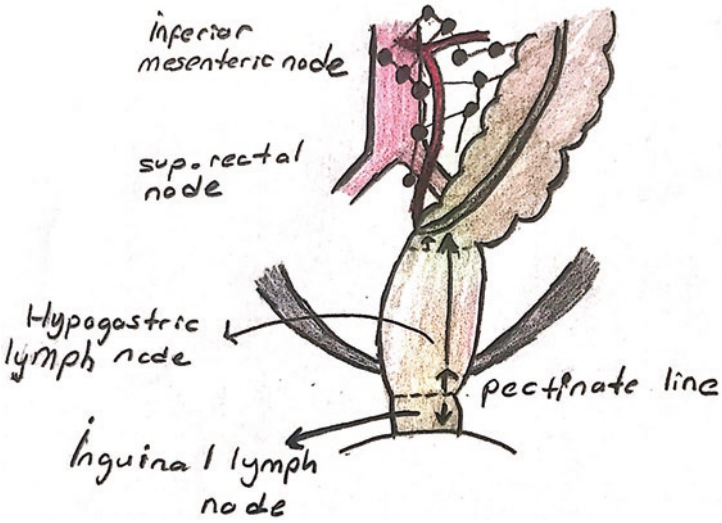


Fig. 1.9 Diagram of lymph drainage of the anus and rectum (*S. Salimoglu*)

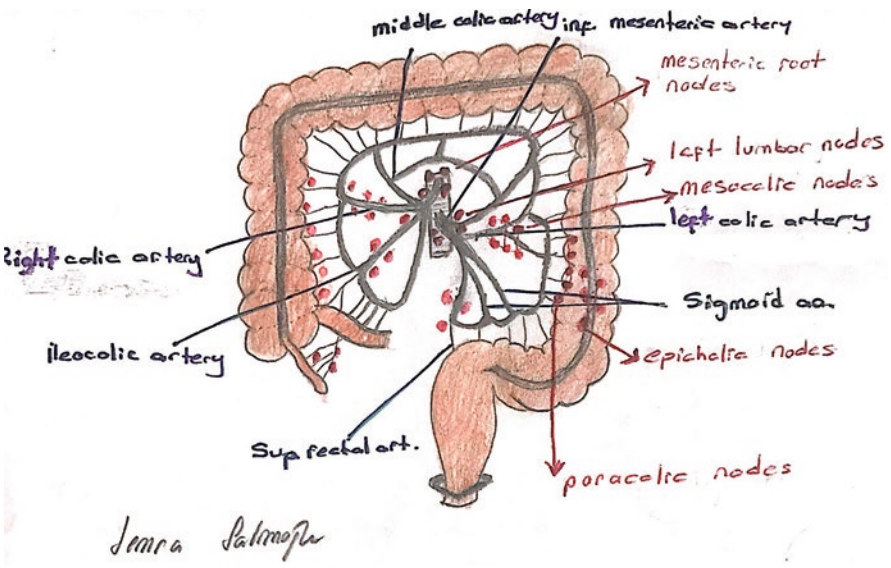


Fig. 1.10 The lymphatics of the colon

Innervation of the Colon, Rectum and Anal Canal

Preganglionic sympathetic fibers come from the T6–T12 synapses in the preaortic ganglion. Postsympathetic fibers progress along the blood vessels to reach the right and transverse colon. The parasympathetic innervation of the right and transverse colon come from the right vagus nerve. Parasympathetic fibers follow the SMA branches, making a synapse within the bowel wall. The left colon and the rectum take their sympathetic stimuli from the L1–L3 preganglionic lumbar splanchnics. They form synapses in the preaortic plexus located above the aortic bifurcation, and postganglionic extensions follow the branches of the IMA and the upper rectal artery to reach the left colon, sigmoid, and rectum. The innervation of the rectum is composed of sympathetic and parasympathetic nerves. Sympathetic nerves taken from the thoracic columnar segments come together below the inferior mesenteric artery and form the inferior mesenteric plexus. These purified sympathetic nerves go down to the superior hypogastric plexus right below the aortic bifurcation and to the pelvis making a bifurcation and form the hypogastric nerves. The lower rectum, bladder, and genital organs take their innervations from the hypogastric nerves. Inferior mesenteric plexus damage is seen following the high attachment of the inferior mesenteric artery. The sacral third, fourth, and fifth parasympathetic roots merge and form the nervus erigentes (located behind the Waldeyer's fascia). However, they might get hurt at the point they join the pelvic plexus (high attachment and connection of the lateral ligament to the lateral). They combine with the hypogastric nerves at the rectum anterior and lateral forming the pelvic plexus and progress along the lateral wall of the pelvis. Periprostatic plexus originates from the pelvic plexus and the complex

fibers in this plexus innerve the rectum, internal anal sphincter, bladder, prostate, and penis. The pudendal nerves (S2, S3, S4) provide the penis and clitoris with sensory stimulus via the dorsal nerve. Both parasympathetic and sympathetic nerves are needed for penile erection. Since parasympathetic nerves increase blood flow in the corpus cavernosum and cause vasodilatation, they cause erection. Sympathetic nerves cause erection by making vasoconstriction. Also they cause contraction of the seminal vesicle, ejaculation ducts, and prostate which cause ejaculation [23, 24].

The periprostatic plexus might be damaged during rectal surgery. Bladder dysfunction and/or impotence may be seen in the damage of the pelvic autonomic nerves. The internal anal sphincter is innerved by both the sympathetic and parasympathetic nerves. The internal anal sphincter has a constant tonus that increases as rectal pressure increases. Internal sphincter tonus increases again when the rectum is empty. The external anal sphincter and levator ani muscles are innerved by the inferior rectal branch of the internal pudendal nerve (S2, S3, S4), and the perineal branch of the fourth sacral nerve. In case of any distention of the rectum, the internal sphincter loosens, the external sphincter can voluntarily contract, and in this case it can remain for about 1 min. Superficial heat, coldness, pain, and tactile senses below the dentate line are innerved by the perineal branch of the pudendal nerve and the inferior rectal nerve. Above the dentate line, the senses of ligation or mucosal stimulation of the internal hemorrhoids are possibly done by the parasympathetic fibers. Resection of the sacrum by protecting the sacral nerves can be performed during pelvic tumor surgery. Protection of at least one fiber of the third sacral nerve would be sufficient for an acceptable anal continence. On condition that the upper three roots of one side and the upper two roots of the other side are protected, a near-normal continence can be obtained. If all the sacral fibers are lost on one side while those on the other side are protected, continence could be maintained; if S3 roots are damaged on both sides, the patient has incontinence. The upper half of S1 is necessary for the stability of the spine and pelvis. Bladder and erection dysfunction may be as high as 45% following rectal surgery [23, 24].

In colon surgery, the margins of resection may vary by the location of the lesion in malign diseases. It has to cover the whole area supplied by a major artery along with the lesion itself. The anatomy of vessels and lymphatics should be well understood. In cancer surgery, vessels must be tied where they originate. It is essential to avoid ureteral injury. In order not to cause internal hernia, defects in the mesentery must be closed. In elective operations, intestinal cleaning should be done properly. This is limited in emergent operations, but requires utmost care. There are two important points in intestinal clean up. The first one is cleaning the fecal content (mechanical preparation) and using antibiotics against colon bacteria. A poorly prepared colon has the risk of anastomotic leakage [23–25].

Ten Golden Rules of Good Colon Surgery

1. Intestinal cleaning should be performed properly.
2. Intravenous antibiotics should be given during and after the surgery for 24–48 h.

3. Nasogastric tube and Foley catheter should be used.
4. The anatomy of the vessels and lymphatics should be understood well. During cancer surgery, vessels should be resected where they come out.
5. A good anastomosis technique involves the following:
   (a) Intestinal segments cut at ends should be pink in color, soft and flexible in form, and mild bleeding must be monitored. In addition, there should be arterial blood flow with visible pulsation at the incision margin of both intestine segments. Since hematoma formation along the anastomosis line or at the mesentery would reduce blood flow, mobilization, resection, and anastamosis should be performed with utmost care on the intestine and mesentery.
   (b) All the fatty tissue at the field of anastomosis should be cleaned without removing the appendices epiploicae and mesenteric margin.
6. Tension on the anastomosis line should be prevented.
7. Anastomosis should be covered with omentum if possible.
8. The whole surgical intervention and its modifications should be known.
9. Urethral injury should be avoided.
10. Mesenteric defects should be closed to avoid internal hernia. Complete seromuscular joining must be ensured in anastomosis. All the stitches should be passed through the submucosa as well making the connective tissue here support the power of anastomosis. Anastomosis leakages usually occur at the antimesenteric part of the intestine. This probably happens due to insufficient cleaning of the mesenteric fatty tissue. If manual stitching technique is to be used, all the layers of the intestine must be inverted so as to avoid narrowing. It is important not to use excessive force while pulling tissues together by placing the sutures because it could lead to the development of strangulation on the bowel wall due to pressure and the resulting anastomosis dehiscence. Similarly, blood (or serum) accumulation in the anastomosis neighborhood does not only decrease circulation, but it also forms a focus of infection. The following localized sepsis may cause abscess development and anastomosis dehiscence. It is critical to make sure that no occlusion or narrowing is present in the distal prior to anastomosis [25, 26].

Histology of the Colon

The whole of the gastrointestinal canal has some structural characteristics. In the center there is a lumen varying in diameter. This lumen is surrounded by a wall consisting of four layers. These layers are the mucosa, submucosa, muscularis, and serosa from inside out (Fig. 1.11). Mucosa is composed of the epithelium, lamina propria, and muscularis mucosa. Lamina propria is a connective tissue rich in blood and lymph vessels. Muscularis mucosa is made up of a circular muscle inside and a longitudinal outside separating the musoca from submucosa. Mucosa is also called the membrane. Submucosa is a loose connective tissue containing a large number of blood and lymph vessels as well as a submucosal nerve plexus (Meissner). The muscularis layer is composed of two muscle layers. The internal part of this muscle is circular and the

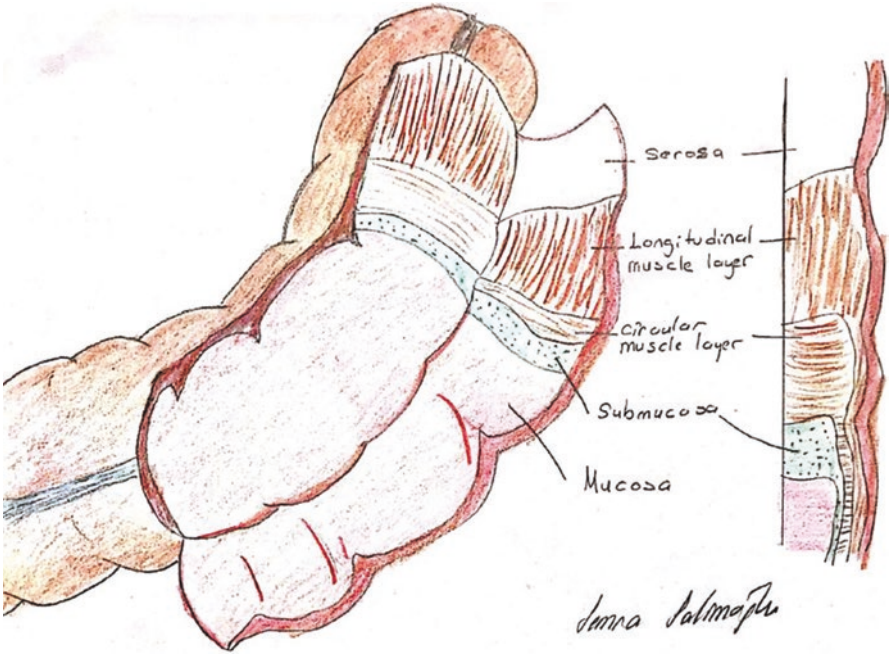


Fig. 1.11 Histologic layers of the colon (*S. Salimoğlu*)

external part is longitudinal. Between these two muscle layers is the myentric (Auerbach's) nerve plexus and the loose connective tissue containing blood and lymph vessels. Serosa is covered by a thin and loose connective tissue [27, 28].

Mesothelium is covered by a single-fold flat epithelium. Colon mucosa does not contain layers except rectum. This portion of the bowels does not have villi. Intestinal glands are long and characterized by a large number of goblet and absorptive cells with a small number of enteroendocrine cells. The absorptive cells have cylindrical and short irregular microvilla. This matches very well with the main functions of the organ and allows for water absorption, stool consistency regulation, and mucus secretion. Mucus has a watery gel form which not only lubricates the intestine surface but also covers bacteria and particulate material. Lamina propria is rich in lymphatic cells and nodules. Nodules are usually found within the submucosa. The reason for the high amount of the lymphoid tissue is the dense population of bacteria in the colon. Muscularis is composed of longitudinal and circular muscle layers. Different from the small intestine, longitudinal muscle fibers come together in the form of three thick longitudinal strips called taenia coli. There are small tissues called appendices epiploicae formed by the fatty tissue in the intraperitoneal section of the colon [27, 28].

There is a range of longitudinal folds in the anal region which are called the rectal columns of Morgagni. At 2 cm of the anal opening, lamina propria contains a large blood vessel plexus an extraordinary enlargement of which forms hemorrhoids. Differentiation and proliferation of the cells located 1/3 below the colon mucosa glands occurs approximately every 6 days. Colon mucosa is responsible for digestion and

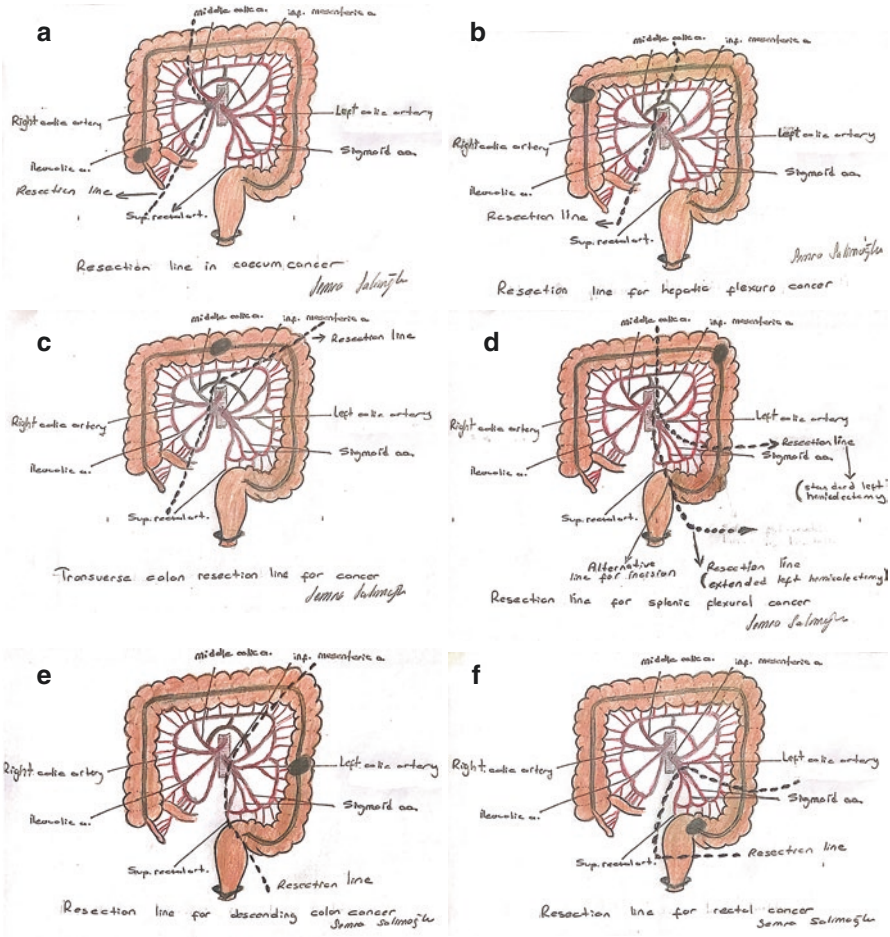


Fig. 1.12 (**a**) Cecum cancer. (**b**) Hepatic flexura Ca. (**c**) Transverse colon Ca. (**d**) Splenic flexura Ca. (**e**) Descending colon Ca. (**f**) Rectal Ca

blood absorption of nutrients. The muscle layer in the middle pushes the nutrients forward. Serosa layer has a smooth surface. This prevents intestinal adhesion in the abdominal cavity and intestines function in an order. Waste material travels along the large intestine and is taken to the rectum, the terminal section of the large intestine where stool is stored. When the waste stored here arouses the feeling of defecation, the individual defecates (sometimes the natural contractions and rhythm of the colon may change). Stress, medications, pregnancy, disease, a constant feeling of defecation, lack of exercise, and a diet poor in fiber and liquid disturb the functions of the intestine. The region where the colon opens outside is called the anus. This region has muscles that control stool. These stool-controlling muscles are called sphincters. There are two sphincters: one inside and one outside. The sphincter inside contains smooth muscle fibers and works involuntarily. The sphincter outside is called the external anal sphincter. The one outside has striated muscles and is controlled voluntarily [28, 29].

In colorectal tumors, incision lines depending on the location of lesion is important for a safe tumor surgery (Fig. 1.12a–f). With a better understanding of the importance of proximal, distal, and radial margin and lymphadenectomy, the concept of therapeutic resection has improved considerably. Resection in colon cancers is usually performed based on vascular anatomy in order to endure the removal of the whole lymphatic region. For a successful lymphadenectomy, generally colon resection performed from 4 to 5 cm distance should include the whole area supplied by a major artery together with the lesion itself [30, 31].

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Anesthesia in Colonoscopy

2

Ergin Alaygut

Introduction

In the last decade, the need for and the value of the anesthesia increased proportional to the increase in the number and complexity of endoscopic procedures. The aging population, the presence of the important comorbidities, and the need for an effective, reliable, and timely provision of the patient care lay a big burden on the anesthesiologists [1].

As there was no need for anesthesia for the most gastrointestinal interventions in the former years, the endoscopy rooms had been not designed according to the anesthesia requirements [2]. However, in developed countries, most of the lower gastrointestinal interventions are performed under anesthesia [3]. Colonoscopy, which is one of the lower gastrointestinal interventions, may cause physical and emotional disturbances like fear, anxiety, and embarrassment [4]. Although the diagnostic colonoscopy can be carried out without sedation, colonoscopy under sedation provides better results and improved patient comfort, and the endoscopists are more satisfied with the diagnostic quality [5]. For a safe, comfortable, and technically successful endoscopic intervention, the sedation level should be optimized and the pharmacological properties of the used sedative agents should be well known for the titration of the targeted sedation level [6].

Pre-anesthesia Evaluation Before Colonoscopy

During the pre-anesthesia evaluation, allergies and all drugs including the non-prescription products used by the patient should be investigated. The prior hospitalizations, surgeries, and adverse events encountered after the sedation and anesthesia

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should be discussed. The examination of the airway—even there is no need for the airway instrumentation, heart, lungs, and nervous system should be performed in all patients. A good preoperative evaluation will ease the solution of the pre-interventional medical problems and cancellations [7].

The physical examination before the implementation of sedation or anesthesia involves the vital sign assessment, heart and lung auscultation, and the evaluation of the consciousness level and airway anatomy. The examination of the patient before the anesthesia implementation is important for the preparation of the anesthesia plan. Although some parts of the preoperative assessment are standardized, some parts can be personalized according to the patient, time of the assessment, and the type and the site of the intervention [8].

During the preoperative period, the informed patient consent, which includes information about the sedation procedure, its alternatives, risks, benefits, and limitations, should be obtained from all patients [9].

Which patients need anesthesia consultation?: The anesthesia becomes more difficult and the anesthesia-related complications increase with the number of comorbidities. Therefore, anesthesia consultation is critical in some patient groups [10] before the interventions performed outside the operation room (Table 2.1).

ASA Classification Used for the Evaluation of the Sedation Risk [11]

ASA Classification

- ***Class I:*** Normal and healthy.
- ***Class II:*** Mild systemic diseases only without substantive functional limitations (controlled hypertension, controlled diabetes mellitus without systemic sequel).

Table 2.1 Patient groups needing anesthesia consultation

ASA (*American Society of Anesthesiologists*) 3–4 patients
Expected difficult airway
Serious pulmonary disease
Obstructive sleep apnea
Coronary artery disease (previous myocardial infarct, angina, valvular disorder)
Congestive heart failure
Patient with pacemaker/internal cardiac defibrillator
Elderly patients
Obesity (BMI > 35)
Pregnancy
Substance addiction
Failed sedation
Unsuccessful positioning of the patient during the procedure
Chronic opioid use
Anesthesia-related serious events in the medical or family history (malign hyperthermia)
Patients requesting an anesthesiologist

- ***Class III:*** Moderate or severe systemic disease without substantive functional limitations (stable angina, diabetes mellitus with a systemic sequel).
- ***Class IV:*** Severe systemic disease concomitant with persistent life-threatening conditions (e.g., severe congestive heart failure, end-stage kidney failure).
- ***Class V:*** The patient is sick and under serious risk of death within 24 h (with or without intervention).
- ***E: Emergency:*** In addition to the diagnosis of the underlying ASA condition (I–V), a patient, who undergoes an emergency procedure, is defined with appendix "E."

In a study conducted in more than one million patients, who had undergone endoscopy and colonoscopy, it was confirmed that the ASA classification was consistent with the risk classification of the gastrointestinal endoscopies. The linear correlation between the increase in the ASA score and the development of the unexpected cardiopulmonary events during endoscopy had also been demonstrated [12].

The Tests Required Before Anesthesia

Tests are usually not needed. A laboratory analysis should only be considered after the completion of the physical examination and anamnesis and if the anesthesiologist believes that the test may have an influence on the anesthesia method. For example, if there is a history of recent bleeding, a hemoglobin level of 8 g/dl and a necessity for a hemogram to decide on a pre-interventional blood transfusion [13].

Besides, under suitable circumstances, a pregnancy test is needed in all women in the child-bearing age, as some sedatives may have teratogenic properties [14].

A preoperative ECG may be useful in elderly patients. ECG should be used in patients with comorbidities (e.g., heart diseases, dysrhythmia, diabetes mellitus, hypertension, and electrolyte disorders), particularly if symptomatic, more complicated and long-lasting procedures are planned. Although a routine, preoperative ECG is not recommended, it should be useful if the administration of droperidol is planned, as this drug has the potential to prolong QT-interval [15].

The Cardiovascular System

Although anesthesia is not a must in the procedures implemented outside the operation room, a need for general anesthesia, surgical intervention, or urgent resuscitation and even referral to the operation room may arise. The American College of Cardiology and American Heart Association Guidelines drew attention to the acute myocardial ischemia (within 7 days after the onset), labile or severe angina, decompensated heart failure, serious valvular disorders, or critical arrhythmias among all important cardiovascular diseases in patients, who will undergo non-cardiac surgery [16].

The baseline blood pressure and heart rate should be recorded, and these parameters should be maintained within an interval of ±10% during anesthesia. The preoperative coronary vascularization or the priority of the planned intervention should be determined in the preoperative period [10].

The Pulmonary System

Regarding the preoperative respiratory risk factors, advanced age, chronic obstructive pulmonary disease (COPD), smoking (current and previous), heart failure, high ASA score, impaired sensorium, functional addiction, and obstructive sleep apnea are among the main risk factors for hypoxia and desaturation [17]. In patients with active respiratory disease, the intervention should be postponed for 6 weeks to decrease the respiratory risks. Patients with an obstructive sleep disorder should be asked to bring along their continuous positive airway pressure device [10].

The Airway Evaluation

The Mallampati classification (Fig. 2.1) should be carried out to evaluate the risk of difficult intubation. There is a relationship between difficult intubation and mallampati score [18].

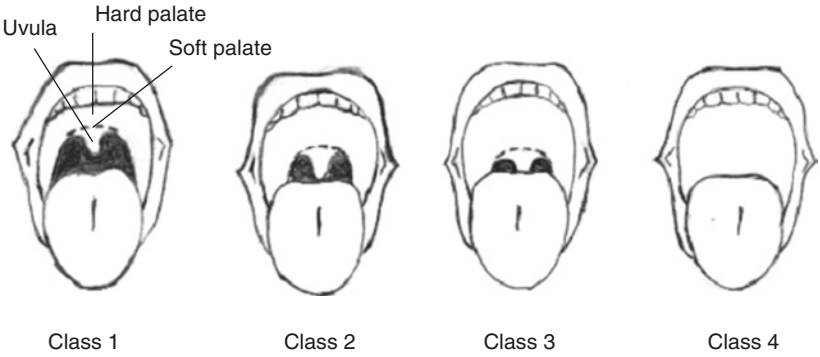
Airway and the risk factors related to the aspiration should be closely monitored. Even though an anesthesia device is not needed, a breathing circuit to provide positive-pressure respiration (e.g., Mapleson C), laryngoscope, face mask, oral and nasal airway, laryngeal mask airway (LMA), endotracheal tubes in different sizes, emergency drugs should be kept ready. As the places of the endoscopic interventions are usually not close to the operation rooms, bougies, stylets, video laryngoscopes, and carbon dioxide detectors should also be available. The availability and the functionality of this equipment should be checked before every intervention [19].

Predictors of Difficult Mask Ventilation and Difficult Intubation

Increased risks of both ventilation and intubation can be predicted in some patients with the following characteristics: increased body mass index (>30 kg/m^2), history of snoring and sleep apnea, presence of beard, missing teeth, age over 55, Mallampati score III or IV, limited mandibular protrusion, and male gender [20].

Preoperative Fasting

According to the ASS principles introduced for adult patients, a 6-h fasting period is recommended after a light meal or non-clear liquid or an 8-h fasting period after a fatty meal or meat-containing food [21].



Class I: Uvula, soft palate and hard palate visible
Class II: Major part of uvula, soft palate and hard palate visible
Class III: Base of uvula, soft palate and hard palate visible
Class IV: Only hard palate visible.

Fig. 2.1 Mallampati classification of mouth opening. *Class I*: Uvula, soft palate and hard palate visible. *Class II*: Major part of uvula, soft palate and hard palate visible. *Class III*: Base of uvula, soft palate and hard palate visible. *Class IV*: Only hard palate visible

Maintenance of Anesthesia

Although the endoscopic interventions are usually carried out under sedation, they can be performed also without sedation depending on the advantages like the low cost, lower risk, higher performance, and faster return to daily activities [22]. Male patients and patients with higher education levels and lower anxiety scores are more motivated for a colonoscopy without sedation [23]. However, it should be kept in mind that sedation and anesthesia are important tools to increase the efficiency of colonoscopy [24].

Choosing the Suitable Technique

The suitable sedation level for a certain colonoscopy procedure can be achieved with the titration of the agents with rapid onset and short duration of action. The anesthetic agents used in colonoscopy should cause minimal respiratory depression and enable rapid recovery. Most of the colonoscopies can be performed under mild and conscious sedation. However, the passage through the terminal ileum or colonic strictures caused by the inflammatory bowel disease may cause severe pain. Deeper sedation is required in such cases. If the colonoscopy patient has other gastrointestinal disorders, the anesthesia team should evaluate the aspiration risk and secure the airway with an endotracheal tube if needed [25].

Although most of the gastrointestinal interventions can be carried out under sedoanalgesia, the risks of the monitored anesthesia may be higher than general anesthesia, as the morbidity and mortality may increase if the airway patency is not secured [26, 27].

The sedation depth is defined in four stages between minimal sedation and general anesthesia [28].

1. ***Minimal Sedation or Anxiolysis:*** **Response**: Normal response to verbal stimulation**/Airway:** Airway not affected**/Spontaneous breathing:** Not affected**/Cardiovascular function:** Not affected.
2. ***Moderate Sedation or Analgesia:*** **Response:** Purposeful response to verbal and tactile stimulation**/Airway**: No intervention needed**/Spontaneous breathing:** Sufficient**/Cardiovascular function**: Usually preserved.
3. ***Deep Sedation or Analgesia:*** **Response:** Purposeful response to repeated painful stimulation**/Airway**: Intervention may be needed**/Spontaneous breathing:** May be insufficient**/Cardiovascular function**: Usually preserved.
4. ***General Anesthesia:*** **Response:** No response to painful stimulation**/Airway:** Intervention is usually needed**/Spontaneous breathing:** Usually insufficient**/Cardiovascular function**: Maybe impaired.

Monitoring

The recent developments related to patient safety in anesthesia depend partially on the improvements in patient monitoring. The basic monitoring recommended by ASA, which must be followed in all interventions performed under anesthesia, consists of electrocardiography (ECG), blood pressure (invasive and non-invasive), end-tidal capnography, oxygen saturation, and body temperature [29].

For both moderate and deep sedation, the level of consciousness and vital signs should be evaluated and recorded periodically depending on the type and dose of the administered drugs, the duration of the intervention, and the patient's general condition. The level of consciousness and vital signs should be checked at least

1. Before the procedure
2. After the administration of the sedative/analgesic agents
3. Every 5 min during the intervention
4. During the first recovery period
5. Just before leaving the intervention room [30]

The staff monitoring the patient under deep sedation should carry out this process continuously without interruption [31].

ECG

The ASA guidelines recommend ECG monitoring in patients who have cardiovascular disease or arrhythmia and undergo moderate sedation [32]. Although the necessity of the ECG monitoring is not clear, it is recommended in elderly patients with lung disease and in the interventions with known prolonged duration [30].

Pulse Oximeter

It is usually placed on the fingertip. The nail lack may prevent the reading of saturation depending on the impairment of the penetration of light, which is emitted from the tip of the probe, into the tissue [33].

The limitations:

- As pulsatile blood flow is needed to measure oxygen saturation, shock, severe vasoconstriction, and low cardiac output may lead to inaccurate readings [34].
- Particularly supplemental oxygen may lead to delayed detection of the hyperventilation due to the delayed development of desaturation [35]. Therefore, the patient should be closely monitored; respiratory monitoring with auscultation or capnography should be not neglected [36].
- It should be kept in mind that the routine administration of supplemental oxygen decreases the severity of the oxygen desaturation during the endoscopic interventions performed under sedation [37].

Capnography

Capnography is a non-invasive method, which detects the deteriorated or depressed respiratory activity and visualizes the partial carbon dioxide pressure during the respiratory cycle with graphs [38]. The capnography trace has a rectangular shape in intubated patients (Fig. 2.2). Capnography is especially recommended in patients undergoing deep sedation and in patients undergoing moderate sedation without breathing monitoring [32].

In patients who were sedated with propofol in the endoscopy room, capnography was found useful not only in the early detection of hypoventilation but also in the reduction of hypoxemia rate [39]. Studies failed to demonstrate the benefit of capnography in patients who underwent routine upper endoscopy and colonoscopy and were sedated with opioids or benzodiazepines [40, 41].

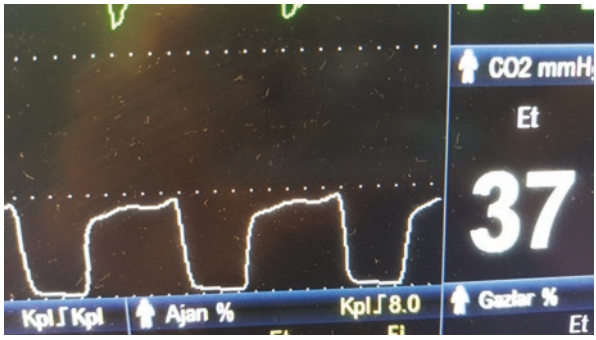


Fig. 2.2 Image of capnography

Non-invasive Blood Pressure

Blood pressure should be monitored with manual or automatic measurements every 5 min [36].

Supplemental Oxygen

ASA and ASGE (American Society for Gastrointestinal Endoscopy) announced that supplemental oxygen should be administered in patients undergoing moderate sedation and in all patients undergoing deep sedation [31, 32]. Supplemental oxygen should also be administered if hypoxemia is predicted or during its emergence [30]. In addition, it has been demonstrated that supplemental oxygen decreases the severity of desaturation that may emerge during the endoscopy [37]. Desaturation is critical especially in patients with a history of coronary artery disease as it is demonstrated that supplemental oxygen decreased the ST-elevation and depression in ECG [42].

Airway Maintenance

No matter where—if anesthesia is administered—a breathing circuit to provide positive-pressure respiration (e.g., Mapleson C), laryngoscope, face mask, oral and nasal airway, laryngeal mask airway (LMA), endotracheal tubes in different sizes, emergency drugs should be kept ready, even though an anesthesia machine is not needed. As the endoscopic intervention units are usually not close to the operation rooms, bougies, stylets, video laryngoscopes, and carbon dioxide detectors should also be kept available [19].

The goal of the anesthesia in patients undergoing endoscopic examination is the maintenance of spontaneous breathing with no or little support, protection of the airway, and the establishment of an unreactive patient. Manipulations such as chin lift, chin thrust and neck extension, devices used to protect the airway are not indicative of the unsuccessful anesthesia technique. The gastroenterologists should be prepared to intervene anytime an airway problem emerges [43].

Although the prone position is useful for the prevention of airway obstruction depending on the prevention of the drop of the tongue to the anterior, it limits the access to the airway. Unlike in the operation room, the procedure has to be immediately canceled and the patient has to be intubated. The airway maintenance is rather difficult in the prone position compared to other positions [1]. In the endoscopy room, which is a restricted area after all, the anesthesia machine, monitors, and other equipment make the management of anesthesia more difficult (Fig. 2.3).

Regarding the patient's airway, the following examination should be done during the preoperative period:

- Oral patency
- Mallampati score

- Thyromental distance
- Condition of the teeth
- Cervical mobility
- Records of the previous anesthesia administrations [10]

The need for an airway intervention increases along with the increase of the sedation depth. Screening the patients for the applicability of a face mask is useful in this regard. In patients with difficult mask ventilation, the risk of intubation increases four times [44].

ASA reported that airway maintenance may be difficult in the following conditions:

1. Problems encountered in the previous anesthesia and sedation implementations
2. History of stridor, snoring, or sleep apnea
3. Dysmorphic facial appearance (e.g., Pierre-Robin syndrome)
4. Oral anomalies (oral opening smaller than 3 cm, toothlessness or protruded incisors, elevated palate, large tongue, tonsillar hypertrophy, absence of uvula)
5. Cervical anomalies (obesity involving cervical and facial structures, short stature, limited cervical extension, decreased hyomental distance (<3 cm), a mass lesion in the neck, cervical vertebra disorder or trauma, tracheal deviation, advanced rheumatoid arthritis)
6. Jaw anomalies like micrognathia, retrognathia, trismus, or malocclusion [31]

Fig. 2.3 Patient under sedation in the prone position

Aspiration Risk

In the preoperative period, patients should be informed about the risk of aspiration, which is a possible complication during sedation or monitored anesthesia. Particularly the increased use of propofol in colonoscopy raised concerns about the increased aspiration risk. The incidence of aspiration during the colonoscopy under sedation is between 0.10% and 0.14% [45].

The patients should fasten for 8 h in cases of hiatal hernia, long-term diabetes, pregnancy, severe ascite, intestinal obstruction except for water and required medication [21]. As it is known that deep sedation depresses the upper respiratory reflexes, patients applied for colonoscopy may be under the risk of aspiration and aspiration pneumonia particularly if deep sedation is implemented [45].

Regarding the risk of the pulmonary aspiration caused by the gastric content, if the gastric emptying is not functioning properly or in cases of emergency, it is important to determine beforehand:

1. The level of the targeted sedation
2. Whether a delay of the procedure is necessary or not
3. Whether the airway patency can be maintained with the endotracheal intubation [46]

Patient Position

Furthermore, as the light is usually dimmed in the endoscopy room, the patient's position may prevent the direct observation of the airway and the visual monitoring of the chest wall movements and air exchange may be prevented by the position of the endoscopy monitors and endoscopist [47]. If there are concerns about airway maintenance, the safest method is the endotracheal intubation and continuation of the endoscopic intervention under general anesthesia. Besides, the visibility of the monitors and intravenous patency should be checked before the positioning of the patient [48].

Choice of the Anesthetic

Agent considering the sedation implementation in the endoscopy units, drugs with rapid onset, and short duration of action, which do not cause cardiovascular instability and do not increase the risk of postoperative nausea and vomiting, should be preferred [49].

1. **Midazolam**: Midazolam is an anxiolytic that may cause antegrade amnesia. Following a usual administration of an intravenous bolus injection of 0.5–2 mg midazolam [50]. One milligram is administered via the intravenous route every 2–5 min to achieve a sufficient sedation level [48]. This water-soluble drug has

a short duration of action. Its effect starts in 30–60 s. The maximum effect is achieved in 3–5 min. This effect lasts 20–80 min. Its effects disappear following the redistribution [7]. If it is used as a monotherapy, the risk of respiratory depression is relatively lower. It contributes to the inhibition of the vomiting, even though it has no analgesic properties [51]. Besides, the central effects of the benzodiazepines on the GABA receptors can be competitively antagonized with flumazenil. Furthermore, midazolam-related paradoxical reactions (disinhibition and aggression) are also antagonized with flumazenil [48]. Apnea may emerge if it is combined with opioids. Its dose should be reduced in the elderly and obese patients, and in patients with liver and/or kidney failure [52].

It can be used as a monotherapy or combined with meperidine, opioids, ketamine, and propofol [53, 54]. The most common side effects are confusion, delirium, dizziness, motor discoordination, cognitive, and mental impairment [7].

2. **Remimazolam:** Its properties are similar to midazolam except for a shorter duration of action [55]. Remimazolam provides rapid onset and shorter sedation similar to midazolam [56]. Although its organ-independent metabolism and rapid onset of action are considered as advantages compared to other benzodiazepines, studies demonstrated that it had depressant effects on the respiratory system [57].
3. **Propofol:** Propofol, which is a phenol derivative, is an ultra-short acting hypnotic agent. No dose adjustment is needed in patients with moderate-to-severe liver or kidney failure, but the dose should be reduced in the elderly and patients with cardiac dysfunction [58]. As the sedation depth can be changed with the dose titration, it is suitable for the use in the endoscopy units [59]. The infusion rate between 25 and 75 μg/kg/min is adequate for moderate sedation in elderly patients without any critical disease [60]. Its effects start in 30–60 s and last 4–8 min. As it depresses particularly the breathing, it is rather recommended for the use of the staff experienced in airway maintenance [61]. The most common and severe complications are dose-depended hypotension especially in hypovolemic patients and transient apnea following the induction doses [62]. However, as the dose of propofol can be reduced during the combined use with other sedative agents, the adverse cardiovascular effects will decrease [63]. Propofol is widely used as a monotherapy or combined with opioids, benzodiazepines, and other sedatives for sedation during colonoscopy [64]. The recovery and re-establishment of the cognitive functions occur rapidly. Although it has antiemetic properties, its effects cannot be reversed like in benzodiazepines [5, 65]. Regarding sedation during colonoscopy, its powerful amnestic properties and decrease in the emetogenic effect related to the insufflation during colonoscopy are its most advantageous characteristics [25].
4. **Fospropofol**: It is the water-soluble prodrug of propofol but has different pharmacokinetic and pharmacodynamic properties [66]. It is rapidly hydrolyzed to propofol by the alkaline phosphatases. It has a rapid onset of action and its effect lasts 15–30 min [67].
5. **Ketamine**: It has anesthetic and analgesic properties. In patients undergoing colonoscopy, it was demonstrated that the addition of low-dose ketamine

(0.3 mg/kg) to midazolam-fentanyl-propofol improved the hemodynamic parameters, the propofol consumption is reduced, and less supportive airway maneuvers were needed [68]. If the previous sedation was unsuccessful, adjuvant ketamine was useful for the establishment of moderate sedation [69]. Ketamine is usually combined with midazolam to prevent its hallucinogenic effects. Ketamine decreases the suppressing effects of propofol on the cardiopulmonary system. It is administered with a bolus dose of 0.1–0.3 mg/kg until the targeted effect is achieved. The maximum recommended dose is 1 mg/kg in healthy adults [70, 71]. As it stimulates salivation, combined use with anticholinergic agents is recommended. It can be safely used in patients with opioid addiction. If it is combined with propofol, the ketamine dose and the dysphoria risk are reduced [7].

6. **Dexmedetomidine:** It provides anxiolytic, sedative, and analgesic effects without respiratory depression. However, it may cause hypotension and bradycardia [72]. It can be safely used for sedoanalgesia during colonoscopy [73]. Although it may be preferred in patients, in whom hypoventilation should be avoided, as it has a minimal effect of the respiratory impulse, it is effective in colonoscopy in combination with fentanyl or other drugs [72]. As the patient can be easily awakened from the sedation caused by dexmedetomidine and it causes minimal respiratory depression, it may be suitable for patients with obesity and obstructive sleep apnea [7]. Dexmedetomidine is administered with a loading bolus dose of 0.5–1 mg/kg in 10 min and then infused with a dose of 0.2–0.7 μg/kg/h [48].
7. **Opioids:** In the postoperative period, respiratory depression is the most important side effect of opioids. Even in low analgesic doses, it may depress the spontaneous ventilation, and even the respiratory responses to hypercarbia and hypoxemia. The depression of the respiratory functions can be aggravated by the natural sleep and hypnotic agents through a synergistic mechanism [74].
   (a) **Fentanyl**: Fentanyl is a short-acting synthetic opioid widely used as an analgesic. Depending on its rapid onset and short duration of action, it is a better choice compared to other opioid analgesics [75]. In spite of its analgesic and sedative properties, it has no amnestic property [1]. The initial dose is between 50 and 100 μg, and this dose may be supported with 25–100 μg bolus administrations in individual cases [48]. It may cause muscular rigidity [75].
   (b) **Alfentanil**: Alfentanil has a faster onset (1–2 min) and a shorter duration of action (5–10 min after bolus injection) compared to fentanyl and has a short half-life; consequently it can be beneficial in the treatment of acute pain [76].
   (c) **Remifentanil:** It has a rapid onset and short duration of action. Therefore it has to be administered with continuous infusion. There is no risk of accumulation even in long-lasting infusions [1]. The cardio-respiratory side effects can be minimized with low doses of remifentanil (0.4 μg/kg loading dose and 0.04 μg/kg/min infusion dose) [77].

(d) **Meperidine:** It can be titrated in low doses for the targeted sedation level. However, it is rarely used as a result of its slower metabolism than fentanyl and active metabolite (normeperidine) [25]. The initial dose is 25–50 mg IV and can be repeated every 2–5 min with a dose of 25 mg IV [50]. It is metabolized in the liver and excreted from kidneys. In patients with kidney failure, muscular fasciculations, and seizure may emerge as a result of the accumulation. It is contraindicated in patients with a hypersensitivity to meperidine and MAO inhibitors [7].

8. **Nitrous oxide:** The comparison of nitrous oxide and oxygen with the conventional sedation in colonoscopy showed that they were comparable for pain and discomfort, but the duration of hospitalization and recovery was shorter [78, 79].
9. **Volatile anesthetics**: The combined use of sevoflurane and nitrous oxide may be preferred due to the rapid recovery of the motor functions and quicker discharge [80].
10. **Ketorolac:** In patients undergoing colonoscopy under sedation, ketorolac has the advantage of long-lasting analgesic effect. However, it should be cautiously used in patients with renal disorders, bleeding disorders, large polyp resection, and stricture dilatation [81].
11. **Adjuvant medications**: Diphenhydramine, promethazine, and droperidol, which can be combined with benzodiazepines and opioids, increase the sedative effect but cause longer recovery periods. The efficacy of droperidol has been demonstrated especially in patients, who will undergo difficult-to-treat therapeutic endoscopy [82, 83]. The efficacy of a typical benzodiazepine and narcotic combination can be supported with diphenhydramine, promethazine, and droperidol. These drugs increase the efficacy of the benzodiazepine + narcotic combination and may cause deeper sedation levels and probably longer recovery periods. It was shown that the addition of diphenhydramine to the benzodiazepine + narcotic combination improved the sedation and decreased pain in colonoscopy patients [84].
12. **Antagonist drugs:** The specific antagonists of the opioids (naloxone) and benzodiazepines (flumazenil) should be available in every endoscopy unit. As the duration of action of the antagonist drugs can be shorter than benzodiazepines and opioids, an observation room equipped with monitors may be necessary for longer monitoring of patients, who will have a prolonged recovery period [31].

Anesthesia-Related Complications

Sedation in colonoscopy may increase morbidity and rarely mortality, and these risks will increase depending on the type, dose, administration route of the sedative agents, and age and comorbidities of the patient [85, 86].

It was found that patients with a physical ASA score III and IV were under a higher risk of desaturation during endoscopy compared to patients with an ASA score I and II [87]:

Sedation, colon distension, and mesenteric tension may lead to hypoxia, hypoventilation, arrhythmias, hemodynamic disturbances, abdominal discomfort, and vasovagal reactions. A relatively deeper sedation level may ease the completion of colonoscopy by the endoscopists but may also increase the risks of aspiration pneumonitis and pneumonia [88]. The incidence of aspiration, which is one of the complications of sedation, is between 0.10% and 0.14% in patients undergoing colonoscopy. It was suggested that this risk increased with propofol [45].

The anesthesiologist should be prepared for complications like the vagal reaction to the insufflation (atropine or glycopyrrolate), bleeding, or colon laceration [48].

The airway obstruction, which is one of the most common complications, emerges usually due to the deep sedation level and distant location of the patient and anesthesiologist. Deep sedation maybe not recognized in darkened endoscopy units. As oxygen is usually administered with a nasal tube or mask and the decline in sPO_2 will develop after a while, the detection of hypoventilation and respiratory standstill may be delayed. The paradoxical breathing may be helpful in such cases [89]. An emergency trolley with a defibrillator, emergency medication, and equipment should be ready for the cardiopulmonary resuscitation in case of anesthesia given anywhere except for the operation room. The staff responsible for anesthesia should know the location of this equipment and be experienced in the use of a defibrillator.

Informed Consent

Patients should be informed about the mild, moderate, and deep sedation or changing consciousness levels during general anesthesia. Patients may prefer to be awake during the procedure or not to remember even the entry into the endoscopy unit. Patients' informed consent should be obtained following a detailed discussion of the possible risks and alternatives. The consent should involve also loss of consciousness and endotracheal anesthesia, as the sedation level will have a continuous course and a switch to a deeper sedation level may be required. Patients may express their concerns about general anesthesia, but they should be also informed that general anesthesia and intervention to the airway may be necessary during the procedure [25].

Post-anesthesia Care

Every patient who underwent anesthesia should be monitored afterward. Phase 1 and phase 2 care in the post-anesthesia care unit (PACU) including hemodynamic monitoring, airway monitoring, oxygenation and respiratory support, diagnosis, and treatment of nausea/vomiting along with the pain control should be provided. Before leaving the unit, criteria for the ambulation, liquid, and urine volume should be checked. Protocols for postoperative gastrointestinal problems like acute pancreatitis, bleeding, and intestinal perforation should be available [76].

The scoring systems like the Modified Aldrete Scoring System are suitable for the monitoring of the recovery period. While the patient is in the recovery period, it

should be kept in mind that resedation may develop, if the antidotes like flumazenil or naloxone have been administered after the endoscopic intervention [90].

After the procedure, patients are referred by the experienced staff to a recovery room that is equipped with sufficient monitoring and resuscitation devices [91]. As serious side effects emerge within the first 30 min in sedated patients, they should be monitored in the recovery room at least for 30 min [92]. Patients are discharged from the recovery room according to their Aldrete score, which assesses respiration, saturation, blood pressure, consciousness, and activity. Patients are recommended to avoid driving, using machines, and taking juristic and binding actions until the establishment of full recovery [93]. It should be also kept in mind that patients who were referred from the clinics may be returned to their clinics or may be referred to ICU under certain conditions, and the recovery rooms of the endoscopy units are different from the recovery rooms of the operation rooms [25]. In emergencies, protocols necessary for the activation of the acute care team should be available. Moreover, there should be preplanned procedures for the patients, who should be immediately referred to the ICU [7].

Cardiopulmonary Resuscitation

Cardiac arrest is uncommon during colonoscopy. The increased use of propofol (has a narrow therapeutic window), complicated procedures, and increased rates of comorbidities are among the factors, which increase the risk of cardiac arrest during the endoscopic procedures under monitored anesthesia [94]. In the endoscopy units, life-threatening events, which require CPR (cardiopulmonary resuscitation), may be encountered before or even after the intervention. Especially patients with gastrointestinal bleeding should be closely monitored, as they are under a higher mortality risk in cases of life-threatening events [95]. Not only anesthesiologists but also other specialists should know what to do in these rare but fatal events. Cardiac arrest may emerge also in the clinic during the postoperative period and an urgent intervention may be needed. The treatment is implemented in three steps, which cannot be sharply separated from each other: basic life support, advanced life support, and long-term life support.

Basic Life Support

It involves ventilation and chest compression without the use of additional devices. The basic life support has four elements [96, 97]:

1. Initial assessment and asking for help (to prevent cardiac arrest)
2. Early CPR (to save time)
3. Early defibrillation (to re-run the heart)
4. Care after the resuscitation (to improve quality of life)

Advanced Life Support

This phase includes the use of all devices required for resuscitation. In cases of cardiac arrest during colonoscopy, staff experienced in CPR should be ready and the presence of monitored venous patency and the availability of required devices are the critical prerequisites of advanced life support. In cases of cardiac arrest, the endoscopic intervention should be immediately terminated and compression should be initiated while the patient's position is corrected. The compression/ventilation ratio should be 30:2. The chest compression should be performed with the base of the hand to the middle of the chest while the elbows are kept straight (in a 90° vertical position) at a rate of 100–120. The depth of the compression should be 5–6 cm and the chest should be allowed to expand after each compression movement. As it is a tiring procedure, the rescuer should be changed every 2 min. If the patient's arrhythmia is suitable for defibrillation (ventricular fibrillation and pulseless ventricular tachycardia), compression/ventilation (five times in 2 min) with a ratio of 30:2 should be continued at least for 2 min following the first shock sent with the defibrillator. If the patient has pulseless electrical activity and asystole, the compression/ventilation should be continued with a ratio of 30:2 for 2 min without defibrillation. If a rhythm, which is suitable for a defibrillation shock, emerges during the CPR, compression/ventilation should be continued for 2 min following the defibrillation process. Pulse and rhythm should be checked every 2 min. However, time used for the pulse and rhythm control should not exceed 10 s. In patients with a rhythm not suitable for defibrillation shock, 1 mg IV adrenaline should be administered as soon as cardiac arrest is diagnosed and the treatment should be continued with 1 mg IV adrenaline injections every 3–5 min. In rhythms suitable for the defibrillation shock, following the defibrillation, 1 mg IV adrenaline is injected while the chest compressions are started and continued in doses of 1 mg IV every 3–5 min. In rhythms suitable for the defibrillation shock, 300 mg IV amiodarone or 100 mg IV lidocaine should be administered after the implementation of the third shock; if the arrhythmia persists, an additional 150 mg IV amiodarone or 50 mg IV lidocaine can be injected following the implementation of the fifth defibrillation shock [96, 97].

Defibrillation

The sternal paddle (or electrode) is placed on the right upper part of the sternum below the right clavicle and the apical paddle is placed on the midaxillary line at the left side of the left nipple. A 150–200 J biphasic, 360 J monophasic shock is given as the first shock and then the defibrillation process is continued with 150–360 J biphasic—360 J monophasic shocks.

The reversible causes in CPR:

The reversible causes should be evaluated again and again during CPR. These causes are abbreviated as 4H/4T:

- Hypoxia
- Hypovolemia
- Hypothermia

- Hypo/hyperkalaemia. Metabolic disorders
- Tension pneumothorax
- Tamponade (cardiac)
- Thrombosis (pulmonary or coronary)
- Toxins [96, 97]

In conclusion, the anesthesia implementations outside the operation room became more important due to the recent increase in the number of the endoscopic procedures and the number of more complicated and complex interventions. A detailed investigation of the patient and planned procedures and preparation of a reliable anesthesia plan will be instructive for the anesthesia providers.

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Colonoscopy

3

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Colonoscopy is a procedure used for the diagnosis and treatment of all colonic segments and their diseases from anus to cecum with flexible instruments which is specially manufactured with light and camera.

Colonoscopy is a minimally invasive procedure which is used in diagnosis and treatment. The complication rate is extremely low when it is performed by an experienced doctor or team and with good equipment. Compared with virtual colonoscopy and enema opaque colon graphy, colonoscopy is seen more specific in recognizing colon polyps and colon malignancies. Colonoscopy does not require very large machines or facilities like tomography; therefore, it can be performed in endoscopy offices or centers.

The importance of colonoscopy has been understood better from past to present. Colonoscopy devices have become more modern than in the past, and imaging quality has improved. Today, as a result of colonoscopy, life expectancy has increased thanks to preventive and therapeutic medicine.

Description of Colonoscopy

Colonoscopy is the examination of the colonic mucosa, and it is also possible to examine the terminal ileum during colonoscopy. It is useful to briefly review the anatomy of the colon before explaining this definition broadly. The colon starts from the right iliac fossa at the end of the small intestine, and this is the widest part of the colon called as cecum. It continues from the cecum to the liver and is called the ascending colon. Then it forms hepatic flexura under the liver. It moves right to

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the spleen and takes the name of the transverse colon. It forms a flexura below the spleen and is defined as splenic flexura. The colon descends from the splenic flexura to the sigmoid colon and is called the descending colon. The descending colon is followed by the sigmoid colon, rectum, anal canal, and the anus [1, 2].

The examination of the entire colon is performed as retrograde with colonoscopy. In the colonoscopic examination, only the inner surface of the colon can be seen and evaluated. Colonoscopy cannot obtain information about the lesions within the colon wall, but the lesions can be noticed if it grows in the colon wall and reaches the size to cause protrusion of the colon mucosa. It should be known that in colon cancer, the characteristics of the mucosal lesion can be identified with colonoscopy. But, the level of involvement of the colon wall, which layers of the colon wall are involved, and serosal invasion cannot be identified with the colonoscopic examination. For these definitions other imaging methods such as endoscopic ultrasound, MRI or computerized tomography may be done [3, 4].

Indications and Contraindications for Colonoscopy

Colonoscopy is a minimally invasive and expensive procedure, and it has complications and therefore needs a skill for use. For these reasons, it must be done to selected patients [5].

Colonoscopy indications can be counted as iron deficiency anemia, lower gastrointestinal system bleeding, lower abdominal pain, chronic constipation, uncomplicated diarrhea, evaluation of known ulcerative colitis and Crohn's disease, colorectal cancer screening in patients with inflammatory bowel diseases, follow ups after polypectomy, follow-ups after colorectal cancer surgery, colorectal cancer screening, colonic masses, intraluminal colonic pathologies and undefined weight losses etc. [5–7].

Contraindications are classified as absolute and relative contraindications in the literature.

Absolute contraindications can be defined as intestinal perforation, acute peritonitis, complete or high-grade intestinal obstruction, patient's refusal to the procedure, toxic megacolon, fulminant colitis, patients who can give consent but not cooperated during the procedure. Relative contraindications are classified as bleeding disorders, thrombocytopenia, platelet dysfunction, neutropenia, previous bowel surgery, patients at risk of bowel perforation (Ehler Danlos syndrome, Marfan syndrome, etc.), acute diverticulitis, cardiac infarction history, pulmonary embolism, very large abdominal aortic aneurysm, pregnancy (second or third trimester), and hemodynamic instability [8–10].

We want to examine these indications in sub-topics.

Colonoscopy Indications

Colonoscopy in Iron Deficiency Anemia

The World Health Organization (WHO) defines anemia as the insufficiency of the number and the oxygen binding capacity of red blood cells to meet the physiological

functions of the body. The most common cause of anemia is iron deficiency. Malignancies are other reasons that we should consider in anemia. It should be kept in mind that malignancy is more common among the causes of iron deficiency anemia in older ages. WHO considers normal hemoglobin levels above 13 g/L in adult men and 12 g/L in women [11]. Also the normal values accepted for hematocrit are reported as 36–46% in women and 38–48% in men [12]. Normal red blood cell count is reported as 4.5–6.5($\times 10^{12}$/L) in men and 3.9–5.6($\times 10^{12}$/L) in women [13].

Iron deficiency anemia can occur as a result of chronic or acute blood loss into the colon lumen. Anemia due to chronic blood loss can occur as a result of macroscopic or microscopic bleedings into the colon lumen. Microscopic bleedings that cannot be seen by eye can be detected with occult blood test in stool. In iron deficiency anemia, low serum iron capacity and low iron storage protein ferritin levels can be detected in serum [14].

Intracolonic hemorrhages that cause iron deficiency anemia may occur from benign or malignant causes. Colonoscopic examination is a diagnostic and therapeutic method used effectively in differential diagnosis.

Colonoscopy in Lower Gastrointestinal System Bleedings

Bleeding from the distal part of the treitz ligament is called lower gastrointestinal bleeding. It accounts for 20% of all major gastrointestinal bleedings. Colonic diverticulum, vascular ectasia, and colonic ischemia are among the most common etiologies of lower gastrointestinal bleeding. Other causes include inflammatory bowel diseases, Meckel's diverticulum, neoplasms, anorectal diseases, infectious colitis or enteritis, radiation colitis, idiopathic ileocolonic varices, Dieulafoy's lesion, bleeding after polypectomy, trauma, and hematologic diseases. In these diseases with bleeding, colonoscopy can be used in both diagnosis and treatment [15–19].

Colonic Diverticular Disease

Diverticulum can be seen in small intestines, cecum, and colon. The number of colon diverticules can be one or more than one. Colonic diverticulum is commonly seen in sigmoid colon and presence of multiple diverticules in colon segments is named as diverticulosis coli. Diverticulosis coli may be a part of the Saint's triad which is a disease associated with hiatus hernia, cholelithiasis, and diverticulosis coli. If the diverticule that contains all layers of the colon is called real diverticulum, and these diverticules are thought to be congenital and usually occur in the right colon. At the point where the vessels enter the colon wall, a weakness occurs and the mucosa and submucosa herniate from this weakness. If the diverticule that occurs with this physiopathology, it is called pseudodiverticule. These pseudodiverticules are usually located in the sigmoid and left colon. Increased intra-colonic pressure, age progression, decreased dietary fiber intake, and mucosal fragility are responsible for pseudodiverticule formation. Bleeding, diverticulitis, and diverticulum perforation are among the expected complications in patients with

diverticulum. Diverticular hemorrhage may start suddenly and present as painless and massive [20–22].

Endoscopic band ligation, epinephrine injection, or endoscopic clipping can be applied in cases that diverticula hemorrhage do not stop spontaneously with medical treatment. Endoscopic band ligation is safe, effective, and superior to endoclip application. During colonoscopic procedures, we should be careful to avoid colon perforation [23, 24].

Vascular Ectasia (Angiodysplasia)

Vascular ectasias are arteriovenous malformations that are mostly seen after the age 60. It is frequently located in the right colon in elderly patients. In a study of Moore et al., type 1 lesions are mentioned as small solitary lesions that are usually seen in elderly patients and are usually located in the right colon. It is defined as angiodysplasia or vascular ectasia and it is considered to be acquired. Type 2 lesions are congenital submucosal lesions of the small intestine and usually seen in younger than 50 years. Type 3 lesions include hereditary hemorrhagic telangiectasias and are associated with respiratory and cutaneous lesions [25, 26].

Dieulafoy's lesion is one of the causes of acute bleeding. In Dieulafoy's lesion, the abnormal submucosal artery is typically protruded from the defect in the mucosa. Hematochezia and melena can be seen in this disease [27, 28].

Heyde's syndrome is a syndrome which causes recurrent gastrointestinal bleeding and contains the triad of calcific aortic stenosis, acquired coagulopathy, and bleeding due to angiodysplasia [29–31].

Medical treatment, colonoscopic procedures, selective embolization, and surgical resection in resistant cases are among the methods in treatment.

Bleedings Due to Chronic Ischemia

Ischemic colitis due to ischemia can be reversible or irreversible. It can hold only the mucosa or the whole colon wall. Ischemic colitis is commonly seen in the left colon, whereas it is rarely seen in the whole colon [32, 33]. It is frequently seen in elderly patients. It may develop spontaneously or without major vascular obstruction.

In ischemic colitis due to occlusion, midgut ischemia may result in right colon ischemia. Left colonic ischemia may also develop after aortic surgery. Predisposing risk factors for ischemic colitis include cardiac failure and arrhythmias, shock, thromboembolic events, hypercoagulability, vasculitis, and mechanical colon obstructions (tumors, adhesions, etc.). Cases without necrosis may be transient or chronic. Sudden-onset abdominal pain and bloody diarrhea may occur. It can be diagnosed by colonoscopy, and over inflation should be avoided to avoid perforation during the procedure. Petechial hemorrhages occur in the early times of the ischemia, and pale edematous mucosa occurs between these hemorrhages. In the subacute period, segmental erythema, ulceration, and bleeding foci can be seen. With increased

severity of ischemia, cyanotic, gray, or black mucosa is observed. In chronic ischemia, strictures, decreased haustration, and mucosal granularity can be seen [34–37].

In treatment, medical treatment is usually applied but surgical treatment may become necessary for peritonitis [38, 39].

Lower Gastrointestinal System Bleeding Due to Inflammatory Bowel Diseases

There are two types of inflammatory bowel disease: ulcerative colitis and Crohn's disease [40].

Massive hemorrhage, toxic megacolon, and colonic perforation may be seen in ulcerative colitis; and surgical intervention may be required for bleeding that cannot be controlled by medical treatment [41–43].

Crohn's disease is a granulomatous disease that presents with transmural and focal inflammation. The ileum and colon are frequently involved. Endoscopic methods may be sufficient for bleeding control if bleeding is limited [44, 45].

Bleeding Due to Meckel's Diverticulum

Meckel's diverticulum is a congenital anomaly that can be find in the gastrointestinal tract. It is usually localized within 100 cm proximal of the ileocecal valve. Meckel's diverticulum may contain ectopic gastric mucosa or ectopic pancreatic tissue. Peptic ulceration due to ectopic gastric mucosa may cause painless bleeding. Angiography, scintigraphy, and double-balloon endoscopy can be used for diagnosis. Surgical intervention may be required when medical treatment is insufficient [46–49].

Lower Gastrointestinal Bleeding Due to Neoplasms

Lower gastrointestinal system bleeding may occur in benign or malign colon neoplasms. Malignant neoplasms may be a primary malignancy of colon or metastatic colon neoplasm. Neoplasm hemorrhages can be seen as acute or chronic microscopic bleeding. Polypectomy is performed in bleeding polyps. If acute bleeding does not stop with medical treatment, surgical treatment may become necessary [28, 50–53].

Lower Gastrointestinal System Bleedings Due to Anorectal Diseases

Occult or macroscopic bleeding may occur in anorectal diseases. These anorectal diseases include hemorrhoids, anal fissure (acute or chronic), perianal fistula, rectal colitis ulcerosa, rectal varices, rectal malignancies, polyps, rectal ulcers, perineal,

and anorectal injuries. After sclerotherapy to the varices in the esophagus, massive bleeding may occur from the varices in the rectum. In that situation, colonoscopy is recommended for diagnosis and treatment [19, 54–60].

Lower Gastrointestinal System Bleeding Due to Infectious Colitis or Enteritis

Infectious colitis can be seen with different clinical findings from asymptomatic disease to fulminant toxic colitis. The effective microorganisms can be bacteria, fungi, parasites, and viruses. Hematoshesis can be seen in infectious colitis whereas massive hemorrhage is rare. Colonoscopy may be required for diagnosis and treatment [61–63].

Lower Gastrointestinal System Bleeding in Radiation Colitis

Radiation colitis may develop after pelvic radiotherapy and it can be acute and chronic. Acute radiation enteritis may cause mucosal ulceration and bleeding. Symptoms can be resolved by conservative treatment in 2–3 weeks. Chronic radiation enteritis may occur after 3 months or 6 years. Chronic intestinal complications are usually due to obliterative vasculitis, which can lead to mucosal ulceration. In chronic radiation colitis, vascular telangiectasia and unhealed mucosal ulceration can lead to severe recurrent bleeding. Coagulation can be performed in colonoscopic focal bleeding telangiectasias. This bleeding control may require several sessions [64–66].

Colonoscopy in Bleeding Due to Idiopathic Ileocolonic Varices

Colonic varices are usually observed in cirrhosis or portal hypertension. A small number of varices are idiopathic, and they are considered to be congenital vascular anomalies. Idiopathic ileocolonic varices can cause massive lower gastrointestinal system bleeding. The mechanism that initiates the bleeding may be the trauma of the hardened feces passage. Surgery may be required if the medical treatment is inadequate [67–69].

Colonoscopy in Lower Gastrointestinal Bleeding Due to Trauma

In penetrating abdominal traumas, the colon may also be injured. Colonoscopy is contraindicated in colon perforations. Hematoma may occur in the colon wall or meso after blunt abdominal trauma. This can cause abdominal pain and hematochezia. Colonoscopic examination can detect hemorrhage and its localization. However,

if blunt abdominal trauma is severe, it may also cause colonic perforation. In this situation colon perforation should be investigated by other imaging methods before colonoscopy [70, 71].

Colonoscopy in Lower Gastrointestinal Bleeding After Polypectomy

Bleeding after polypectomy may develop immediately or may occur even after 1 month. Bleeding usually stops spontaneously. If the bleeding does not stop spontaneously, endoscopic treatments such as thermal therapy, colonoscopic clipping, and epinephrine injection are among the treatment options [28].

Colonoscopy in Lower Gastrointestinal Bleeding Due to Hematological Diseases

Gastrointestinal system bleedings can occur due to bleeding disorders. Bleeding may also occur in other parts of the body than the gastrointestinal tract. Low platelet counts or dysfunction may lead to bleeding. Factor deficiencies (hemophilia A, B), factor inhibitors, hereditary hemorrhagic telangiectasia, vasculitis, leukemia, disseminated intravascular coagulation, and vitamin K deficiencies are among the factors that cause gastrointestinal bleeding. Treatments are applied according to the etiology. Colonoscopy without treatment of coagulation disorders may cause complications [72–74].

Colonoscopy Preparation for Lower Gastrointestinal Bleeding

Colonoscopy can be performed for both diagnosis and treatment of lower gastrointestinal bleeding. An immediate colonoscopy can be performed with rectal washout. Delayed urgent colonoscopy can be performed with bowel preparation. For example, if there is no blood in the right colon on immediate colonoscopy, this indicates that the bleeding is caused by the left side of the colon. In some cases, the location of the bleeding may not be diagnosed [28, 75].

Indications for surgical treatment are hemodynamic instability persisting despite an aggressive resuscitation, persistent bleeding after more than 6 units of blood transfusion or severe bleeding [64].

Colonoscopy in Lower Abdominal Symptoms

Lower abdominal symptoms are abdominal pain, abdominal distension, anal pain, anal secretion, rectal discomfort, anal lesions, anal fistula, chronic constipation, change in bowel habits, diarrhea, and constipation periods [76, 77].

Colon neoplasms may be responsible for unexplained weight loss. The primary focus of metastatic lesions may be colon cancer. In such cases, colonoscopy can be performed to investigate the etiology.

Hemorrhoids

There are enlarged varicose veins in hemorrhoids. They can cause acute bleeding attacks and even massive bleeding. They usually cause chronic blood loss and cause iron deficiency anemia. Hemorrhoids can be divided into two groups as external and internal hemorrhoids. The external hemorrhoids are located distal to the dentate line whereas internal hemorrhoids are located proximal to the dentate line. Internal hemorrhoids can be classified according to the degree of the disease:

- Type 1: These hemorrhoids are located at the proximal part of the dentate line, and they do not prolapse out of the anal canal on straining.
- Type 2: These hemorrhoids are located at the proximal part of the dentate line, and they prolapse on straining but they reduce into the anal canal spontaneously.
- Type 3: These hemorrhoids are located at the proximal part of the dentate line, and they prolapse out of the anal canal on straining but they need to be reduced manually.
- Type 4: These hemorrhoids are continuously prolapsed out of the anal canal and cannot be reduced [78, 79].

Medical treatment is applied in the treatment. Apart from medical therapy, band ligation can be applied to internal hemorrhoids. But band ligation is not preferred for the external hemorrhoids due to being a painful procedure. Laser can also be applied in treatment. If medical treatment is insufficient, surgical treatment may be required. Rectal hemorrhage due to hemorrhoids may occur together with malignancy hemorrhage. It should be considered that patients with hemorrhoids may have a rectal malignancy, therefore, endoscopic examination should be performed [80–82].

Anal Fistula

Anal fistula is a tract that occurs between the anorectal lumen and the skin, and the lumen of the tract is epithelialized. Etiology may include previous abscess, hemorrhoidectomy, perforation due to foreign bodies, inflammatory bowel disease (Crohn's disease), tuberculosis, and actinomycosis. Prolonged chronic draining wounds are predisposing for cancer development. This cancer may develop inside the fistula tract lumen and therefore may not be diagnosed preoperatively. Lower gastrointestinal system endoscopy should be performed for etiologic differential diagnosis. Laser or surgery can be applied in treatment [83–87].

Chronic Constipation

The incidence of colorectal cancer and benign colorectal neoplasm is higher in patients with chronic constipation [88, 89].

Chronic constipation may be primary (idiopathic) or secondary. Secondary causes are known as organic (cancer, extraintestinal mass), endocrine or metabolic (diabetes, hypothyroidism), neurologic (parkinson, paraplegia), myogenic (scleroderma), anorectal (anal fissure, proctitis), drugs, diet, and immobilization [90]. Colonoscopy is important in diagnosis.

Is Colonoscopy Necessary Before Closing Temporary Ileostomy?

Temporary ileostomy can be performed for the safety of anastomosis after resection according to oncological principles in colorectal cancers. After a period, this ileostomy can be closed. The question is, is colonoscopy necessary to check the anastomosis line before closing the ileostomy?

There is no definite consensus on this issue in the literature. There are studies that recommend a control colonoscopy before closing the temporary ileostomy while other studies suggesting that routine colonoscopy are not necessary [91].

In our case, anastomosis after colon resection and a protective ileostomy was performed. The control colonoscopy before the ileostomy closure showed that the anastomosis line was too narrow to allow the passage of the colonoscope (Fig. 3.1).

Although there are different opinions in the literature, our opinion on this issue is to prove that the presence of normal physiological and anatomical structure from the temporary ostomy to the anus before any ostomy closure. If the distal gastrointestinal tract is anatomically compatible with physiological functions, we close the ostomy. If it is not, we go for correcting surgery. The picture shows the stenosis in the anastomosis in our case (Fig. 3.1).

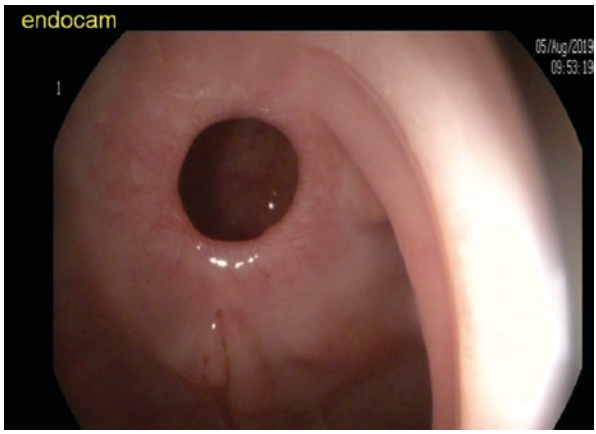

Fig. 3.1 Narrow colonic anastomosis

Change in Bowel Habits

Symptoms of colorectal carcinoma may present as changes in bowel habits. Patients with colon cancer may have constipation, diarrhea, and abdominal pain. We should consider colorectal cancer in the presence of these complaints [92–96].

Uncomplicated Diarrhea

According to the World Health Organization (WHO), diarrhea is defined as soft or watery defecation more than three times a day, or defecation that is much more than normal defecation habits [97].

The cancer types associated with diarrhea are carcinoid syndrome, colon cancer, lymphoma, medullary thyroid cancer, pancreatic cancer (especially islet cell tumors), and pheochromocytoma. Other causes of diarrhea include chemotherapy, radiotherapy, bone marrow depression, drug side effects, inflammatory bowel diseases, infectious causes (may be caused by viruses, bacteria, or parasitic diseases), and hyperthyroidism. In differential diagnosis, colonoscopy can be performed if there is no contraindication [98, 99].

Colorectal Cancer Screening in Patients Diagnosed with Inflammatory Bowel Disease

Patients with ulcerative colitis have an increased risk of developing colon cancer. The duration of the disease and the extent of involvement of the colon are proportional to the risk [100].

The pathological changes observed in the colon epithelium may change from nondysplastic changes to dysplasia, low-grade dysplasia, high-grade dysplasia, and cancer [101]. The risk of colorectal cancer is significantly increased in Crohn's disease. Cancer development was observed in the ileocolic area, colon segment, and also in the fistula [102].

The British Society of Gastroenterology recommends screening colonoscopy in all patients with ulcerative colitis and Crohn's disease 10 years after the onset of symptoms. Surveillance colonoscopy should be performed when the disease is in remission. The risk of cancer is directly proportional to the duration of the inflammatory bowel disease and the extent of the disease, and additional risk factors are primary sclerosing cholangitis and the family history of colon cancer. Screening intervals are recommended in these cases. Surveillance colonoscopy is recommended every year in the high-risk group, every 3 years in the middle-risk group, and every 5 years in the lower-risk group [103].

According to the recommendation of the American College of Physicians, colonoscopy is recommended every 1 or 2 years for inflammatory bowel disease 7 years after the onset of pancolitis or 12–15 years after the onset of left-sided colitis [104]. Colon cancer can be missed if the colonoscopy is performed at the active colitis [105].

For Follow-Up After Polypectomy

Colon polyps can be classified histologically as neoplastic and nonneoplastic (hyperplastic, hamartomatous, and inflammatory) polyps. Neoplastic polyps are adenomatous polyps and have a tendency to develop into malignancy. Adenomas can also be classified as tubular, villose, tubulovillosis, and serrated adenomas. Polyps can be grouped as flat and pedunculated according to their colonoscopic appearance [106, 107].

Complete colonoscopy is required for colonoscopic follow-up after polypectomy. For a complete colonoscopy a complete bowel preparation is required. Entire colonic mucosa should be visualized with the colonoscopy from anal canal to the cecum. If these steps cannot be done, colonoscopy should be performed at short intervals and complete colonoscopic examination should be completed. The presence of small hyperplastic polyp is considered as normal colonoscopy and subsequent control colonoscopic examination can be performed after 10 years. Hyperplastic polyposis syndrome has an increased risk of colorectal cancer. These patients have phenotypically large, multiple, and proximal hyperplastic polyps. Removing all of the polyps is recommended in these patients. If polyps cannot be removed endoscopically, then surgical resection should be considered. Optimal treatment and surveillance protocol in such patients are unknown; therefore, more intensive follow-up should be performed in these patients [108–110].

In patients with low grade adenoma with one or two small (<1 cm) tubular adenomas, colonoscopic screening can be performed with intervals of 5 years. These patients are accepted in the low-risk group. There are studies suggesting that control colonoscopy should be performed within 3 years in patients with high-grade dysplasia, villous adenoma, 3–10 small adenomas, and larger than 1 cm adenomas. However some authors classify those with 3–4 small adenomas or with more than 1 cm adenomas as intermediate risk and recommend these patients colonoscopy 3 years later. Patients with five or more small adenomas or at least three adenomas larger than 1 cm are considered as high risk and recommend colonoscopic examination 1 year later. Adenomas must be removed completely. Piecemeal removal is not a complete extraction. If partial removal is performed, complete removal of this adenoma should be ensured. If there are more than ten small adenomas, colonoscopic follow-up should be performed with shorter periods. If piecemeal extraction was performed, close follow-up (2–6 months) and complete removal should be provided. If there is a family history, follow-up should be done at shorter intervals [108, 111].

Colonoscopy for follow-up after colorectal cancer surgery will be described in other sections.

Colorectal Cancer Screening

Colorectal cancer is the third most common cancer [112, 113]. Incidence and mortality rates of colorectal cancer increase with age and 90% of new cases are over

50 years old. Colorectal cancer is commonly seen in the rectosigmoid region. Screening colonoscopy for colorectal cancer is performed in the United States and some European countries [114–116].

The American Cancer Society (ACS) recommends a regular screening program beginning at the age of 45 for individuals with an average risk of developing colorectal cancer. These screening tests can be stool-based tests or colonoscopy. Screening tests are recommended to continue until the age of 75 in patients with a life expectancy of more than 10 years. Between the ages of 76–85 years, patients' consent for colonoscopy, life expectancy, general health status, and the status of previous screening tests are effective in deciding to perform colonoscopy screening. Screening is not recommended for people over 85 years of age. Colonoscopy can be performed for diagnosis and treatment according to the general conditions of the patients over 85 years in the presence of complaints [114].

There are several options for colorectal cancer screening:

Stool-based screening tests: Highly sensitive fecal immunochemical test (FIT) or highly sensitive guaiac-based fecal occult blood test (gFOBT) is recommended every year, Multi-targeted stool DNA test (MT-sDNA) is recommended every 3 years.

Colonoscopy is recommended every 10 years, and CT colonography (virtual colonoscopy) is recommended every 5 years. It is recommended that colorectal cancer screening program should be started before the age of 45 and more frequently in people with high risk in colorectal cancer.

In an article published by Levin et al., colonoscopy is recommended in cases of familial adenomatous polyposis at the age of 10–12 years. In patients diagnosed by clinically and genetically as hereditary nonpolipozis colon cancer (HNPCC), colonoscopy is recommended 10 years before the youngest case in the immediate family or at the age of 20–25 [103, 115, 117].

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Intraabdominal Masses

Intraabdominal masses may be noticed by the patient or by the doctor at the examination. These masses can be found incidentally on intra-abdominal imagings (ultrasound, CT, etc.). Colonoscopy can be performed to determine whether these masses originate from the colon. Ultrasound-guided percutaneous biopsy, diagnostic laparoscopy, and laparoscopic biopsy are among the methods that can be applied according to the patient's condition in the histopathological diagnosis of intraabdominal mass [118–121].

Other Indications for Colonoscopy

Colonoscopy can also be performed for the detection of congenital anomalies, detorsion of sigmoid volvulus, and colorectal stenting in colonic obstructions [122].

Colonoscopy can be performed for unexplained weight loss and exploration of primary tumor site for metastatic cancer [123, 124].

We would like to examine the colonoscopy contraindications in detail as subtitles.

Contraindications in Colonoscopy

Absolute Contraindications

Colon Perforation

Colon perforations may develop as a result of penetrating or blunt abdominal trauma. As a result a transition zone occurs between the colon lumen and the peritoneal cavity. Colon perforations can be either alone or in combination with adjacent organ injuries, and perforations may develop as a complication of diseases other than trauma. For example there is a risk of perforation in sigmoid diverticulitis and also there is a risk of perforation of the terminal ileum in typhoid. In ischemic colitis colon perforation can occur as a result of toxic megacolon. Such diseases lead to perforation of the colon by leading the passage of colon contents into the peritoneal cavity. Colon content is the most pathogenic part of the gastrointestinal tract in terms of bacterial load. With perforation, bacteria can enter the peritoneal cavity and cause intraabdominal sepsis. Therefore colonoscopic examination is contraindicated in colon perforation [71, 125–128].

Acute Peritonitis

Acute peritonitis is an inflammatory reaction of the peritoneal cavity. Peritonitis may occur due to microbial causes or non-microbial causes (such as FMF and primary peritonitis). If the etiology of peritonitis belongs to the colon, the colon wall can be inflamed and the colonoscopy can directly lead to perforation. Colonic wall can become inflamed due to these inflammatory changes in peritoneal cavity. Therefore colonoscopic examination will increase the risk of perforation in the colon as the colon wall will be involved in the intraabdominal inflammatory event [129, 130].

Complete or High-Grade Intestinal Obstruction

Mechanical obstruction of the gastrointestinal tract may develop at any level of the gastrointestinal tract. This obstruction may occur in the stomach, duodenum, small intestine, or colon. Obstruction may be complete or partial. There is no gas or stool passage in complete obstruction. In incomplete obstruction, some passage may be possible. Obstruction may be caused by intra-luminal (tumors, bezoars, gallstones, etc.) or extraluminal (tumoral masses, cystic structures, etc.) pathologies. Symptoms vary according to the localization of the obstruction. In gastric complete obstruction, there is no bile seen in the vomit, whereas in the intestinal obstruction intestinal

content can come from nasogastric tube. Imaging methods (ultrasound tomography and magnetic resonance imaging) can be used for diagnosis [131–133].

In the sigmoid volvulus, the sigmoid colon rotates around its mesentery (Fig. 3.2) and forms a closed loop. It can be recognized by its unique image of the sigmoid volvulus on a standing abdominal direct radiograph. Colonoscopy is recommended for the reduction of sigmoid volvulus. If it is not successful, then early operation is recommended.

If laxative drugs are given orally before colonoscopic examination in patients with obstruction, it may increase the pressure in the proximal of the obstruction and may cause perforation. Therefore, oral laxatives should not be given to patients who are thought to have obstruction. Rectum and sigmoid colon can be cleaned with rectal enemas. If the obstruction is in the rectum or sigmoid colon segment, recto-sigmoidoscopy can be performed to find out the etiology after clearing the distal part of the obstruction with enemas applied rectally.

Patient's Refusal to the Procedure

Legally colonoscopy cannot be performed in the patient if the patient does not accept the procedure. The patient should be given detailed information about the procedure to be performed. It should be explained to the patient in a way that the patient can understand. The results of this should be clearly explained to the patient if the patient does not accept the procedure, and consent of the patient should be obtained.

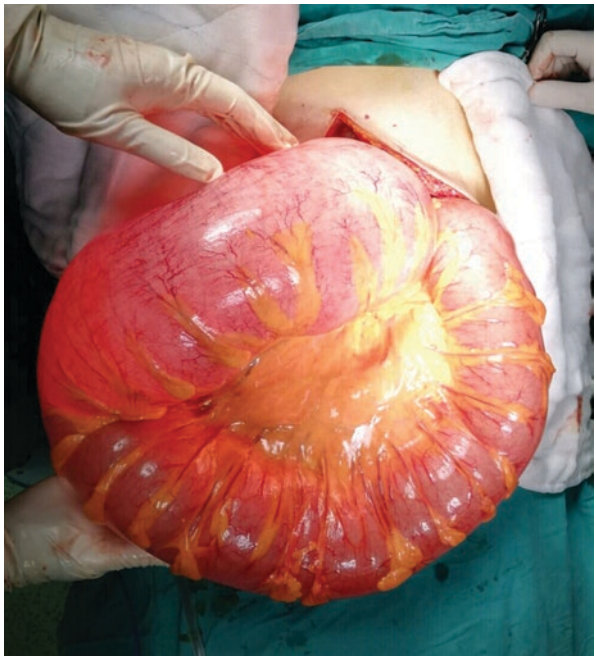

Fig. 3.2 Sigmoid volvulus

Toxic Megacolon

Etiological factors include inflammatory factors (ulcerative colitis, Crohn, Behcet disease) infectious factors (*C. difficile*, *Salmonella*, *Shigella*…), ischemia, and others (collagenous colitis, chemotherapy). Colon dilatation (>6 cm), submucosal edema, loss of colonic haustration, air-fluid levels, wall thickening, perforation, and septic thromboses in the portal system can be seen in this clinical situation. Total colonoscopy is contraindicated in the acute period of toxic megacolon, as it carries a risk of perforation. Flexible sigmoidoscopy can be performed carefully with minimal air insufflations. Etiological factors such as cytomegalovirus or pseudomembranous colitis can be investigated with sigmoidoscopy, and it should be considered that diagnostic flexible sigmoidoscopy also has a high risk of perforation. In a clinical study, three patients with toxic megacolon were diagnosed with flexible sigmoidoscopy, and one of these patients had colon perforation [128, 134–136].

Fulminant Colitis

In fulminant colitis disease, severe acute inflammation of the colon and systemic toxicity symptoms coexist. It is also called acute severe colitis and colonic dilation is usually detected in this disease. It can also be seen in inflammatory bowel diseases. In addition, it can be seen in infectious, amebic, and ischemic colitis. Colonoscopy is accepted as contraindicated. However, there are very few colonoscopy studies performed by experienced endoscopists; it has a high risk of perforation [137, 138].

Patients Who Have Consent for Colonoscopy and Cannot Cooperate or Cannot Be Sedated Adequately

The patient can give consent for colonoscopy, but if the patient is not cooperated and cannot be sedated adequately for colonoscopy, colonoscopy can lead to unwanted complications.

Relative Contraindications

Bleeding Disorders, Thrombocytopenia, Platelet Dysfunction

Colonoscopy is a minimally invasive diagnosis and treatment method. Mucosal laceration, erosion, and ulcerations can develop as complications during colonoscopy. Polypectomy or biopsy can be performed during colonoscopy. In order to avoid bleeding after all these procedures, the patient's hemostasis system should control properly and be able to prevent a possible bleeding.

Neutropenia

Neutrophil count <1500 cells/mm^3 is called absolute neutrophil count. Neutrophils are involved in body defense against bacterial and fungal infections. Neutrophil counts are accepted as 1000–1500 cells/mm^3 in mild neutropenia, 500–1000 cells/mm^3 in moderate neutropenia, and <500 cells/m^3 in severe neutropenia [139, 140].

The presence of neutropenia is a relative contraindication for colonoscopy. In colonoscopy, the incidence of bacteremia ranges from 2% to 4%. Antibiotic prophylaxis is recommended for colonoscopy in neutropenic cases [141, 142].

Previous Bowel Surgery

The mechanical strength of anastomoses after colon resection is 45% of normal tissue on the 14th day [143]. For this reason, the strength of the anastomoses is weak at first days and colonoscopy may lead to perforation in these anastomoses. There is a relative contraindication for colonoscopy in the early period.

Patients at Risk of Intestinal Perforation (Ehler Danlos Syndrome, Marfan Syndrome)

Ehler Danlos Syndrome (EDS)

It is an inherited connective tissue disease characterized by articular hypermobility, dermal extensibility, and cutaneous scarring. Hypermobility in the joints, hyperelasticity of the skin, tissue fragility, and late healing of wounds are among the symptoms of the disease. Colonoscopy is relatively contraindicated in Ehler Danlos syndrome due to the high risk of colon perforation [144, 145].

Marfan Syndrome

It has an autosomal dominant transition. It frequently affects the cardiovascular system and presents with aortic dissection and aortic dilatation [146, 147]. Major symptoms include eye, skeletal, and cardiovascular system symptoms [148, 149].

Colonoscopy is relatively contraindicated in Marfan syndrome. Case reports of spontaneous aortic rupture that may rarely develop after colonoscopy are available in the literature [150].

Acute Diverticulitis

Acute diverticulitis is an infectious disease of the diverticula in the colon. Bacterial infection presents in acute diverticulitis. The infection may remain local or transmural and may create edema, erythema, and fragility in the colon wall. Laboratory tests and

imaging methods (ultrasound, tomography, MR) can be used in diagnosis. Treatment is medical treatment in patients who does not develop complications. If complications develop, surgical intervention may be required. Colonoscopy is contraindicated as there is a tendency to colon perforation in acute diverticulitis. As a complication, if perforation has developed, then colonoscopy is absolutely contraindicated [151].

Previous Cardiac Infarction and Pulmonary Embolism

Previous cardiac infarction and pulmonary embolism are also contraindications.

Presence of Recent Surgeries

Since air is given into the colon in colonoscopy, the colon distends and intraabdominal pressure increases. This can lead to stretching the abdominal incisions. In addition, performing colonoscopy during the recovery period in patients that operated newly may lead to discomfort. Therefore colonoscopy is relatively contraindicated in newly operated individuals.

Very Large Abdominal Aortic Aneurysm

Aneurysm is a focal permanent dilatation of the artery diameter more than 1.5 times from the normal. Normally the infrarenal aortic diameter in patients older than 50 years old is 1.5 cm in women and 1.7 cm in men. If the infrarenal aorta is 3 cm or more in diameter, it is considered as aneurysmal [152, 153].

Imaging methods such as ultrasonography, computed tomography, and magnetic resonance can be used in diagnosis [154].

There are studies in the literature reporting that coexistence of abdominal aortic aneurysm (AAA), and colorectal cancer may be increasing in frequency. In the article of Veraldi et al. the association of abdominal aortic aneurysm and colorectal cancer is mentioned in 14 patients [155].

Colonoscopy has a relative contraindication in the abdominal aortic aneurysm. During a colonoscopy, blood pressure may increase and a rupture may occur in the abdominal aortic aneurysm.

Pregnancy (Second or Third Trimester)

It will be examined in detail in following chapters.

Hemodynamic Instability

There is a relative contraindication in patients with *hemodynamic instability*.

Colonoscopy Instruments and Colonoscopy Room Descriptions

Features of the Colonoscopy Unit

The endoscopy unit is a center for endoscopic diagnosis and treatment. An endoscopy unit must have a reception, registration, and waiting room. There should be a room for changing clothes near the waiting room. The room where the endoscopic procedure is performed should be in 200–300 square feet size. During endoscopic procedures, the patient should be monitored and sedated by the anesthesiologist. In the recovery room, patients can rest after endoscopy and satisfy their toilet needs. A secretary and a medical staff that assist to the endoscopist must be found in the colonoscopy unit. Equipment that should be found in the unit is toilet, sink, examination table, intravenous equipment and solutions, aspirator for oropharyngeal suction, medical drugs (analgesics, sedatives, anticholinergics, narcotic and benzodiazepine antagonists, and emergency cardiac drugs), and resuscitation devices (laryngoscope, ambulatory bag, endotracheal airway, cardiac monitor, defibrillator, resuscitative medications, endoscope and endoscopy set, electrocautery, and endoscopic accessories). During the colonoscopy procedure, complications can be developed and urgent surgery may be required. Therefore, the doors in the endoscopy unit should be wide enough to allow the passage of the stretcher. Care should be taken to ensure that the transport path is short and suitable for transportation in patient transport from the endoscopy unit to the operating room [156–158].

Colonoscopy Technique: Position Maneuvers, Colonoscopy Technique

Colonoscopy begins with the inspection of the anal canal. The presence of perianal fistula, anal fissure (chronic or acute anal fissure), and hemorrhoids can be investigated in anal inspections. Hemorrhoids can be classified as internal and external hemorrhoids. Internal hemorrhoids are located proximal to the dentate line, and external hemorrhoids are located distal part of the dentate line. It should be considered that hemorrhoids may develop as a result of collateral circulation due to portal hypertension [159].

Digital examination of the anal canal and distal rectum is performed after anal area inspection. If direct colonoscope is inserted into the anus without anal digital examination, complications may develop in the presence of masses obstructing the lumen.

The rectum extends between the anal canal and the promontorium, approximately 12–16 cm long. There is no haustra seen in the rectum. There are three valves formed by mucosal folds on the inner surface of the rectum, and they are called Houston valves. The upper and lower valves are placed on the left and the middle valve is placed on the right side. The middle valve (known as Kohlrausch's

plica) is accepted to be at the level of anterior peritoneal reflection. Since valves consist of only mucosa, biopsy can be taken easily and the risk of perforation is very low. One-third upper rectum is anteriorly and laterally coated by peritoneum. The 1/3 middle rectum is covered with a peritoneum only on the anterior face, and 1/3 lower rectum is completely placed extraperitoneally [160–162].

After the rectum, we can reach sigmoid colon border following the sacral promontorium. The sigmoid colon is approximately 35–40 cm and has haustras. However, in the distal part of the sigmoid colon, the haustras are completely erased and there is known as the narrowest part of the sigmoid colon with approximately 2.5 cm diameter [162–165].

The descending colon is adhered to the retroperitoneal tissue; therefore, when the patient lies on the left side during colonoscopy, the air-liquid levels are seen in the left colon lumen with the effect of gravity. The transverse colon (Fig. 3.3) is approximately 45 cm, and its lumen is visible in the triangular configuration. There is hepatic flexura (Fig. 3.4) between transverse colon and right colon. Right colon is approximate 25 cm long. The cecum (Fig. 3.5) is the widest part of the colon and is located in the right iliac fossa. Tri-radiate fold ('Mercedes Benz' sign, Crow's foot) which occurs with ending of three tenia colis at the base of the appendix can be seen inside of the cecum endoscopically. Ileocecal valve has upper and lower lips that are called Bauhin valve. From Bauhin valve you can enter terminal ileum [1, 162, 166, 167].

There are basic rules that should be followed during colonoscopy. If the colonic lumen is not clearly visible and there is any resistance, the colonoscope should not be pushed toward in the colonic lumen. Colonoscopy should be done with a minimum amount of air required and the excess air should not be given into the colon. Due attention should be paid to the patient's pain reaction [1].

Taking video records of the colon segments is recommended during colonoscopy. If it is not possible, photographs of the colon segments should be taken. When you reach the cecum, you must photograph the cecum for medico-legal reasons [167–170].

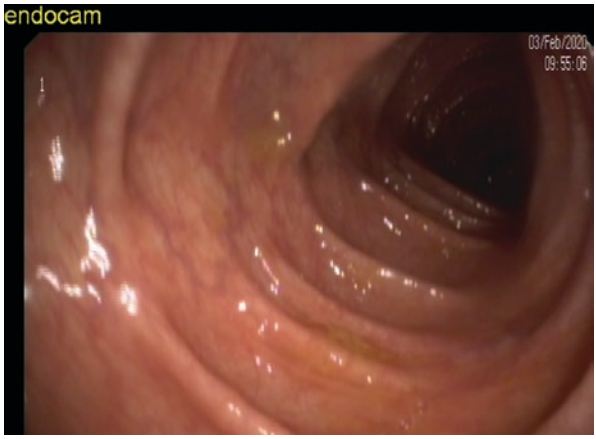

Fig. 3.3 Transverse colon

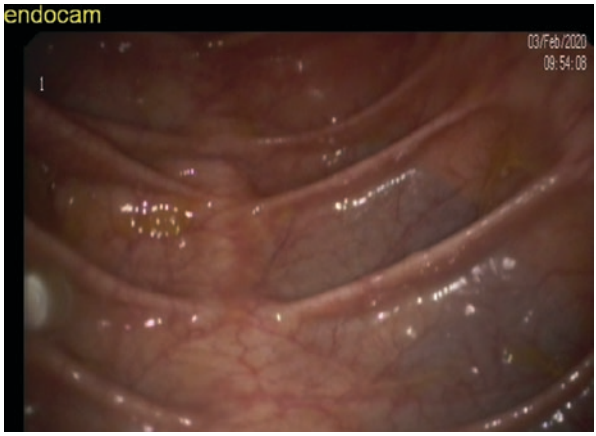

Fig. 3.4 Hepatic flexura

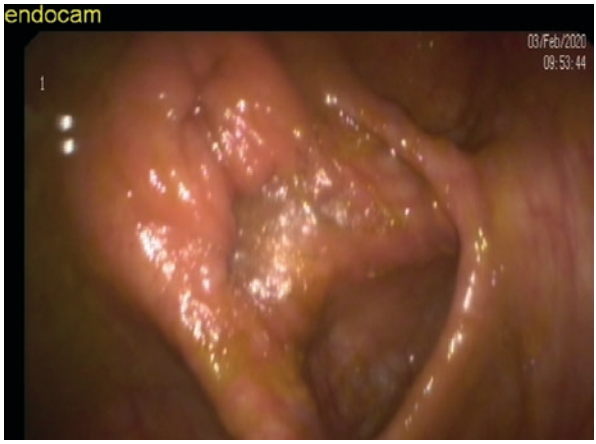

Fig. 3.5 Cecum and ileocecal valve

After the colonoscopy process is completed, the colonoscope should be drawn back. Meanwhile, you can examine the inside of the colon in detail. Aspirating the colon gas while removing the colonoscope causes a positive contribution to the comfort of the patient. When we reach to the rectum, retroflexion should be performed to the colonoscope for observing the inner surface of the rectum.

Robotic Colonoscopy

Robot-assisted colonoscopy is a new method. It can be made by giving less air into the colon lumen. It is reported that the patient's complaints after this procedure are low. Although it is reported that the complication rate after this procedure is lower than conventional flexible colonoscopy, it is also necessary to remember that the robotic colonoscopy is a new procedure. It is also reported that the scopes used in this process are disposable [171–173].

Colonoscopy Complications

These complications may be directly related to colonoscopic procedure or may be due to the other systems in our body (hypertension, cardiac problems, etc.). Complications such as perforation related to colonoscopy procedure, splenic trauma, bacteraemia, severing abdominal distension, bleeding, missed adenoma, incomplete removal of neoplasia, complications can be seen after this procedure [174, 175].

We would like to explain these complications in some detail.

Perforation

Some segments of the colon are intraperitoneal and some segments are extraperitoneal. Clinical symptoms and clinical signs differ depending on whether the perforated colon surface is intraperitoneal or extraperitoneal. In both retroperitoneal and intraperitoneal perforation, the treatment is same. We should stop oral feeding and start parenteral nutrition combined with broad spectrum antibiotic therapy. The perforated area must be closed by endoscopically or surgically [176, 177].

If the perforation site is easily accessible from the lower rectum and the anal canal, the perforation site can be sutured from the anal canal. If perforation requires surgical treatment, this surgery can be performed as laparoscopic or open surgery.

Splenic Trauma

It may occur when crossing the splenic flexura with a colonoscope. Splenic flexura is adjacent to the spleen. If the colonoscopy is tried to be forced through without seeing the lumen, the colonoscope tip may press the splenic tissue and cause an injury on the spleen. Patients can have pain in the upper left quadrant. Defense and rebound are faint as blood is not an irritant for the peritoneum. Orthostatic hypotension or prominent hypotension may develop according to the severity of bleeding. Diagnosis can be made by using imaging methods. In imaging, it is very important to demonstrate the integrity of the spleen parenchyma in ultrasonography. Also, the presence of fluid in the perisplenic area is an indirect finding of bleeding and computed tomography can also be used for diagnosis. In cases where medical treatment is insufficient, surgical treatment option can be evaluated [178, 179].

Bacteremia

Bacteremia after colonoscopy can be seen in 4.4% of cases [180].

In a study of Chun et al., colorectal stents were placed to 64 patients. Blood cultures were taken from these patients after stent placement. Positive blood culture was obtained in 6.3% of cases [181].

Prophylaxis should be performed against infective endocarditis in patients with heart valve disease and those with prosthetic heart valves [182].

Exitus

Deaths within 30 days following colonoscopy are reported as colonoscopy complications. It is seen in 0–83.3 cases in 10,000 colonoscopy. Most deaths are not directly related to the colonoscopy itself. It is mostly related to underlying comorbid conditions (such as congestive heart failure, advanced age, coronary artery disease, cirrhosis, pneumonia, atrial fibrillation, stroke) [183].

Acute Diverticulitis

Another complication of colonoscopy is acute diverticulitis that develops after colonoscopy. It was reported that it developed in 0.8–8.4 cases in 10,000 colonoscopy [183].

Severe Abdominal Distention

Excessive gas insufflation into the colon can lead to abdominal distension. Distension of the colon wall can cause pain. After the colonoscopy, patients can remove their gas and regress these complaints. However, if there is intestinal motility disorder, it is difficult for patients to remove the gas especially if spasmolytics are used in large amounts during colonoscopy. To prevent these complaints, a low-pressure colonoscopy should be performed and the air that insufflated into the colon should be aspirated while the colonoscopy process is completed.

Bleeding

During the polypectomy, severe bleeding may occur from the vessels that feed the polyp. Risk factors in bleeding occurrence include drug use affecting hemostasis such as aspirin coumadin, coagulation factor deficiencies, platelet count deficiency, and platelet function disorders [184].

Missed Adenoma

It is possible to overlook the polyps hidden between the colonic haustras. Virtual colonoscopy or second look colonoscopy can help for detecting missed adenomas. Insufficient cleaning of the colon leads to missed adenoma. The development of

colon cancer after colonoscopy is called interval cancer and missed adenomas may be the cause of most interval cancers [185–187].

Incomplete Removal of Neoplasia

Neoplastic polyps can be resected incompletely. Incomplete resection can lead to the development of colon cancer (interval cancers) after the colonoscopy [188, 189].

Other Complications

Gas explosion is rare and can be life threatening. Explosive gases such as hydrogen and methane can be formed as a result of the fermentation of nonabsorbable carbohydrates by the colonic flora. Explosion may develop during the use of electrocautery. When performing polypectomy, the electrocautery can cause a full-thickness burn on the colon wall, which can cause peritonitis with perforation.

Various complications have been reported within the first 30 days after colonoscopy. These complications which may be linked to a temporary use of anticoagulant agents and antiplatelet medications include cerebrovascular accident, transient ischemic attack, and pulmonary embolism [183, 190–192].

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Colon Polyps, Colonoscopy, and Colorectal Cancer in Pregnancy

4

Ibrahim Uyar

Backgrounds

Colon cancer is the most common type of cancer seen in women after lung and breast cancer. The incidence is higher above 50 years of age. In the United States, CRC (colorectal cancer) has been reported to decrease by 3–4% annually due to gastrointestinal cancer screening programs [1]. Especially in obese, young, and middle-aged women, the incidence of early onset CRC is increased [2]. The incidence of cancer is 1 per 1000 pregnancies, and among the cancer types seen during pregnancy, colorectal cancers are on the seventh line [3]. In a population-based study, it was reported that the incidence of cancer increased during pregnancy, and the incidence increased from 13.2% to 23.6% after 35 years of age [4]. The increased maternal age explains the increased incidence of CRC in pregnancy. In particular, changing dietary habits, increasing obesity rates, smoking, and excessive consumption of red meat are among the main risk factors. While a negative relationship was reported between parity number and CRC, another study reported that increased parity number increased CRC risk [5]. Physiological changes during pregnancy and changes in bowel habits may suppress CRC symptoms.

These symptoms are thought to be due to pregnancy since nausea, and vomiting are commonly expected in the first months. Abdominal pain, weight loss, enlargement of the fetus, and uterus in the following months, prolongation of the transit time of the gastrointestinal contents by the effect of progesterone hormone, and bleeding from time to time due to hemorrhoid problems are also often-seen facts of pregnancy (Table 4.1). Therefore, the diagnosis of CRC in pregnancy may be delayed [6, 7]. The age of having children has increased in recent years [8]. As the risk of malignancy increases with age, the probability of encountering malignancy

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Table 4.1 Signs and symptoms masked during pregnancy

Sign and symptoms	Pregnancy	CRC
Nausea and vomiting	1st trimester	Obstruction
Changing bowel habits	Progesteron	Long transition time
Abdominal distention and pain	Advanced gestational age	Parsiel or complete obstruction
Rectal bleeding	Hemorrhoids, fissure	Tumoral lesions and ulceration
Anemia	Dilutional anemia	Intestinal bleeding, chronic disease
Weight loss	Hyperemesis gravidarum	Advanced disease

CRC colorectal cancer

in pregnancy increases with each passing day. The general approach to the diagnosis of gastrointestinal malignancies in pregnancy is similar to that of non-pregnant women. Diagnostic arguments include physical examination, endoscopic evaluation and biopsy, CEA level (carcinoembryonic antigen), abdominal MRI, and CT imaging.

However, endoscopic evaluation and surgical treatment are inevitable in cases such as the condition of the mother and fetus, gestational week, strong malignancy suspicion, and severe GIS bleeding that may put the mother's life at risk. In this case, a multidisciplinary approach is required, and the team should include an obstetrician, a surgeon, a gastroenterologist, and a pediatrician.

Risk Factors and Prevention

Nutritional status, genetic, and environmental factors play an essential role in the etiology of CRC. Sometimes it occurs sporadically. Genetic factors range from 15% to 30%. In the pathogenesis of CRC, gastrointestinal adenomatous polyps become dysplastic and turn into cancer. Some are acquired, and some are hereditary. Adenomatous polyps exhibit a high degree of dysplastic properties, whereas they are distinguished from other nonadenomatous polyps by the mucosal invasion. Patients with a family history of hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome are under risk for colon cancer, ovarian, uterine, or kidney cancer. In this probable cancer patient population, colon cancer screenings and colonoscopy are initiated at the age of 20–30 years. Colonoscopy is performed every year after the age of 30. The most reliable method in the follow-up of these patients is the colonoscopy. In familial adenomatous polyposis (FAP), there is a mutation in the adenomatous polyposis coli (APC) gene, which is located on chromosome 5. These people have numerous polyps in the bowel, and the risk of bowel cancer increases with age. There is also an increased risk in Gardner's syndrome and Peutz-Jeghers syndrome [9, 10].

Adenomatous polyps can become malignant in 5–20 years. Especially those with severe dysplasia, those with villous morphology, and patients whose polyps are larger than 1 cm in size are at risk for malignancy. The late diagnosis of CRC in pregnancy and its advanced stages at the time of diagnosis and poor prognosis are attributed to two reasons [11–13].

The first is the masking ability of the symptoms occurring during pregnancy, such as nausea, vomiting, constipation, and hemorrhoids, and the second is that elevated estrogen and progesterone hormones, increased placental growth hormones, and angiogenic factors, and immunosuppression in pregnancy may play a role in tumor progression. It is also reported that abnormalities in cyclooxygenase enzyme (COX2) levels and P53 tumor suppressor protein increase cancer development. Environmental factors such as eating habits, being overweight, red meat–rich, and fiber-poor nutrition, and smoking also play a role in the long-term progression of cancer [14]. Pregnancy-specific protein (PSG) was found to be important in CRC progression and tumor angiogenesis and was also associated with poor prognosis [15].

Genetic tests can be used to identify the patients with familial risk factors such as FAP and Lynch syndrome, and those patients can be put under colonoscopy screening programs at an early age. Effective screening programs in the United States have reduced CRC rates in recent years [1]. Familial and genetic diseases can be diagnosed with PGD (preimplantation genetic diagnosis).

Colorectal Cancer Diagnosis in Pregnancy

The primary evaluation of CRC diagnosis consists of physical examination, laboratory findings, endoscopic examination and biopsy, abdominal CT, MRI, and ultrasonography. CRC is extremely rare in pregnancy and is usually in advanced stages when diagnosed [16]. Sometimes CRC may not reveal any symptoms. On physical examination, cachectic and anemic appearance, left supraclavicular lymphadenopathy (Virshow's nodule), abdominal distention, abdominal mass due to obstruction, irregularities, and enlargement of the liver in metastatic disease, presence of fixed mass and bleeding in the rectal examination are the findings of advanced disease [17].

Laboratory findings may not be specified in the early period. In advanced-stage patients, anemia and elevated liver functions due to metastatic disease can be present. Serum CEA (carcinoembryonic antigen) levels may show a slight increase in pregnancy but are usually normal. While those values are important in both the diagnosis and follow-up of the prognosis in pregnant women, sensitivity in this sense is low in pregnancy [18].

Low Gastrointestinal Endoscopy During Pregnancy

Colonoscopy, sigmoidoscopy, and rectoscopy are used for lower GIS endoscopic evaluation. Pathological confirmation of CRC, direct visualization, tissue sampling, and the diagnosis of synchronous lesions are the gold standard [19]. The drugs used for sedation during colonoscopy at the time of pregnancy and medications used in colon preparation are relatively contraindicated due to mechanical damage to the placenta and fetus during the procedure and hypoxia and hypotension of the mother. If diagnostic delays are likely to cause further harm to the patient, the outweigh of

benefits and risks should be considered while deciding on colonoscopy [20]. Sigmoidoscopy and rectoscopy are safe in pregnancy.

Pre-endoscopic Evaluation

Endoscopic evaluation and biopsy is the gold standard for the diagnosis of premalignant and malignant tumoral lesions of the gastrointestinal tract. However, strong indications are needed to perform an endoscopic evaluation during pregnancy. Endoscopic evaluation is necessary in cases of suspicion of malignancy, uncontrollable gastrointestinal bleeding, persistent nausea and vomiting, and obstruction that may avoid the regular passage of intestine [21].

Endoscopic evaluation, if possible, should be postponed to the end of delivery if patients' situation allows. If the postponement delays the treatment of the current disease, endoscopic evaluation should at least be postponed to the second trimester. Since the organogenesis of the fetus continues in the first trimester, the medications to be used in this period may have potential teratogenic effects. For bowel cleansing, drugs in category A or B groups should be preferred during pregnancy. Anesthesia and sedation should be applied with minimum dose concentration and shortest duration [22].

Invasive procedures such as endoscopic mucosal resection, polypectomy, and biopsy should be postponed until postpartum; if necessary, bipolar cautery should be preferred. Since the amniotic fluid conducts the electrical current, the earthing pad and the electrocautery should be located far from the uterus.

What Should the Obstetrician Do Before Endoscopic Evaluation During Pregnancy?

In the first evaluation of the patient who was consulted to an obstetrician, the week of pregnancy should be determined first at the initial evaluation. Serum β-hCG testing should be performed if the patient is receiving treatment for infertility and has a menstrual delay. Pregnancy should be questioned and evaluated in this respect in reproductive patients. The gynecologist should question the patient about the presence of pregnancy and the gestational age in terms of family history and genetic diseases, and the information should be noted. The history of medical diseases, diabetes, and heart diseases, the presence of severe anemia (due to malignancy and GIS bleeding) should be corrected before the procedure. The most important issue is to inform the patient in detail about the procedure and to obtain consent. Possible side effects for the mother and the baby, depending on the week of pregnancy, should be explained. The possible effects of colonoscopy on preterm membrane rupture, intrauterine growth restriction, and preterm labor on the second trimester and third trimester and the possibility of performing an urgent cesarean section should be explained. In this respect, it is vital to perform the procedure in a hospital with a perinatology clinic and neonatal care unit [23].

Precautions During Endoscopy in Pregnant Patient

While the evaluation of fetal cardiac activities of patients in the first trimester before and after the procedure are sufficient, it is recommended to perform fetal monitoring during the procedure in viable pregnancies of 24 weeks or more. The placental circulation of the growing uterus may be disrupted by the pressure of the vena cava and aorta. For this reason, the mother can be positioned on the left lateral side while lying down in order to prevent the hypotension, thus preventing the fetus from being affected by the hypoxic condition. Endoscopy time should be kept to a minimum [23]. However, the procedure might be challenging due to the enlargement of the uterus in later weeks. During this time, manipulation of the uterus may be necessary, and mechanical stress should be avoided as much as possible. Upper GIS endoscopy is considered safe to perform in pregnancy, while data on colonoscopy is limited. After the procedure, preterm labor, stillbirth, preterm membrane rupture possibilities should be closely monitored. Elective therapeutic interventions should be performed after birth. Epinephrine is generally used in cases of GIS hemorrhage, but the use of epinephrine during pregnancy can decrease uterine blood flow, and the pregnancy category of the drug is C [24]. Instead, beta-blockers are considered safer to use.

In a Swedish population-based national study, it was reported that patients who underwent endoscopy during pregnancy had an increased risk for preterm birth and small for gestational age, but the intervention was not associated with congenital anomalies. These findings are also reported to be independent of the trimester. Also, it was emphasized that the side effects of the underlying GIS disease might be more than the effects of endoscopy [25].

Colorectal Cancer Treatment During Pregnancy

CRC's standard treatment procedure is surgery, radiotherapy, and chemotherapy. There is no consensus on the standard treatment for CRC in pregnancy. A multidisciplinary approach is used to decide the optimal treatment in CRC, such as gestational age, tumor stage, emergency surgery requirement, and the need for adjuvant chemotherapy. Since CRC can be detected in any period of pregnancy, waiting for the labor to begin treatment reduces the patient's surveillance since the duration of pregnancy is 9 months. Therefore, in the gestational weeks, when the fetus gains viability, delivery can be performed after fetal lung maturation is provided. The type of delivery is decided according to obstetric indications. If the tumor obstructs the rectum and birth canal, then the cesarean section should be preferred [3]. If the gestational age is far from the viability limit, if the stage of the tumor is advanced, treatment should be initiated without considering pregnancy [11, 26].

If the gestational week is within the first 20 weeks, the continuation of the pregnancy is not considered, and surgery is performed. If treatment is postponed, it may cause tumor progression, and the mother's life would be negatively affected. Surgical treatment involves low anterior resection or abdominoperineal resection. If

tumor resection is possible, the pregnant uterus can be left in place, curative treatment is performed, and the pregnancy is allowed to continue. Hysterectomy is usually not required. However, if the tumor has spread and prevents access to the colon and rectum, or spread to the uterus and ovaries, the continuation of the pregnancy is not considered. Ovarian metastasis is higher in pregnant women (25%) than non-pregnant women [27, 28]. Therefore, ovaries should be evaluated carefully. When prophylactic oophorectomy is performed, especially in the first trimester, the risk of abortion may increase [18]. Unfortunately, it is challenging to diagnose CRC before 20 weeks because of the existing symptoms coincide with the symptoms of pregnancy.

If the diagnosis of CRC is established after 20 weeks of pregnancy, surgery may be postponed until after delivery. Delivery is performed after fetal lung maturation is achieved. The possibilities of tumor progression until delivery, the prematurity of the fetus, and the possible accompanying problems associated with prematurity should be explained in detail, and informed consent should be obtained from the patient. In general, CRC worsens pregnancy and vice versa. In a retrospective study of the clinical and molecular characteristics of patients with CRC in the peripartum period, all five patients were identified as stage IV [29].

Adjuvant chemotherapy is recommended in stages II and above [11]. Because of the teratogenic effect of chemotherapeutic agents, it is not recommended during the first trimester due to organogenesis, but chemotherapy can be performed in the second and third trimesters. However, intrauterine growth restriction and prematurity incidence have been reported to increase [30, 31]. The use of platinum-based chemotherapeutic agents is not recommended. Chemotherapy is contraindicated during lactation. Chemotherapeutic agents can pass into the milk and thus to infant and cause adverse effects.

Radiotherapy (RT) cannot be applied to the pelvic region during pregnancy and is contraindicated [3, 32]. It may cause spontaneous abortion, restriction of fetal development, and permanent damage to gonadal functions. RT is postponed until after delivery. Despite all these treatments, CRC prognosis during pregnancy is poor.

In conclusion, lower GIS endoscopy for elective and screening purposes during pregnancy is not recommended; it is postponed to after pregnancy. Women in the reproductive period should be tested for β-hCG before endoscopy. It should be performed by taking the necessary precautions with a multidisciplinary approach for the emergencies that might develop a risk for the mother's life. In the first trimester, considering the organogenesis, bowel preparation, and sedation drugs should be selected carefully according to the drugs' category. Pregnancy category A or B drugs should be selected. The second trimester is the most suitable period for invasive procedures during pregnancy. When performing endoscopy in the second and third trimesters, the patient should be positioned on her left lateral while lying down to prevent hypoxia and hypotension, and the procedure should be completed in a short time. In particular, mechanical stress and trauma to the uterus should be avoided. Fetal monitoring should be performed during and after the procedure. Patients who underwent an endoscopy and had benign results should also be closely monitored for preterm labor, stillbirth, and fetal growth restriction. The treatment of

patients with malignant results is decided according to the week of pregnancy, tumor stage, and histological type. In the future, more effective diagnosis and treatment will be provided by the use of noninvasive screening tests and widespread use of artificial intelligence in colonoscopy.

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Colonoscopy and Infectious Diseases

5

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Endoscopically Induced Infection: Risk factors [1]

Contamination of microorganisms: endogenous bacteremia/infection, contaminated endoscope (exogenous bacteremia/infection).

Type of transaction: simple endoscopy, tissue or fluid sampling, polypectomy, injection, spark plug or balloon dilatation, stent, prosthesis insertion.

Patient: heart valve disorder, prosthetic heart valve, venous catheter/port insertion, immunosuppression, hematologic disease, HIV infection, advanced liver and kidney disease.

The colonoscopy examines the part of the lower gastrointestinal tract which constitutes the large intestine from outside to the inside (anus, rectum, sigmoid colon, descending colon, transverse colon, and ascending colon) and, if necessary, the last part of the small intestine (terminal ileum). Bacteremia and post-procedure infections can occur as a complication of colonoscopy.

Feces is a mixture of digested food residues and various secretions and waste materials attached to the digestive system and contains abundant microorganisms. The digestive system contains a bacterial flora that occurs in a short time from birth. Although the amount of bacteria is 10^2–10^3/mL in the part of duodenum and 10^6–10^7/mL in the last part of the ileum, the amount of bacteria in the colon is approximately 10^{11}–10^{12}/g. Ninety-six percent to 99% of normal adult intestinal flora is anaerobic (especially *Bacteroides fragilis*, *Bifidobacterium*, *Lactobacillus*, *Clostridium perfiringens*, *Clostridium difficile* and other *Clostridiums*, peptostreptococci, etc.) and 1–4% of aerobic and facultative anaerobic organisms (coliform bacterias, *Enterococcus*, *Proteus*, *Pseudomonas*, aerob lactobacilli, *Candida*, etc.) [2].

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Normal enteric flora is a very important host defense mechanism. Loss of normal flora or frequent replacement of microorganisms such as *Pseudomonas*, *Klebsiella*, *Clostridium*, and *Candida* with normal flora due to the use of antibiotics causes serious infections, as in hospital infections.

Infections Related to Endoscopic Intervention

The incidence of bacteremia after colonoscopy ranges from 0% to 25% with or without biopsy and polypectomy. Bacteremia developing during or after colonoscopy in immunocompetent patients is generally temporary and asymptomatic [3–8]. The incidence of temporary bacteremia ranges from 0% to 1% in flexible endoscopes [9, 10].

The development of infections associated with endoscopic procedures:

1. Spread of microorganisms in the gastrointestinal tract via blood circulation to sensitive organs or prostheses during an endoscopic procedure and directly to the tissues adjacent to the treated area (endogenous infection)
2. The spread of microorganism with patient-to-patient contaminated endoscope and accessories of endoscope (exogenous infections)
3. The transitions of microorganisms from the healthcare personnel operating during the endoscopic procedure to the patient or from the patient to the healthcare personnel [11].

Endogenous infections caused by the patient's microbial flora are associated with mucosal trauma and tissue sensitivity caused by the procedure. It develops as a result of the spread of endogenous flora elements through the bloodstream and cannot be prevented by applying well-controlled disinfection procedures. Diagnostic esophagogastroduodenoscopy (4% and 4.4%) and colonoscopy (2–4% and 4.4%) have low bacteremia rates, while higher bacteremia risk was reported in esophagus varicose sclerotherapy (10–50% and 14.6%) and esophagus dilatation (34–54%) [12]. *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., and other types of enterococcus are isolated in endogenous infections associated with endoscopic procedures [12–14].

Frequently *Pseudomonas aeruginosa* and *samonella* spp. in exogenous infections where the species are isolated; the transmission of microorganisms takes place through the endoscope and/or accessories which were contaminated after use with the previous patient. Such infections can be prevented by correct and controlled disinfection procedures.

Microorganisms Commonly Infected by Endoscopes

Salmonella spp. is the most frequently isolated microorganism in infections associated with gastrointestinal system endoscopic procedures [15, 16]. Acute gastroenteritis, peritoneal abscess, and bacteremia/sepsis have been reported in 1–9 days after an endoscopic procedure [17, 18]. Infections are associated with the use of medium- and low-level disinfectants rather than high-level in endoscope disinfection. *Pseudomonas aeruginosa* Gram (−) is an opportunistic pathogen. *P. aeruginosa*

reduces the effectiveness of antibiotics and disinfectants with the biofilm layer it forms and makes it difficult to remove from the surfaces it is located on. Serious infections can develop in the form of sepsis, liver abscess, cholangitis, bloodstream infections, and pneumonia. Many *P. aeruginosa* infections that develop after endoscopic procedures in the gastrointestinal system are mostly detected after ERCP. This situation were associated with inadequate cleaning of the endoscope, the use of low-level disinfectants, contamination of automated washing/disinfection systems or endoscope rinsing water with *P.aeruginosa*, and most importantly, not washing with 70% ethyl alcohol after disinfection and insufficiency in the compressed air drying procedure [19–21].

Helicobacter pylori infections due to inadequate disinfection of the endoscope and biopsy forceps have been reported. In the patient infected with *H. pylori*, the endoscope is contaminated by 61% after the endoscopic procedure [22], but bacteria are eliminated with effective washing and disinfection in 2% Glutaraldehyde for 5–10 min [23, 24]. *Clostridium difficile* spores are inactivated in 2% glutaraldehyde in 5–20 min, and there are no reports of endoscopic procedure -–related *C. difficile* infection after effective disinfection [25].

Hepatitis-B and hepatitis-C: Diagnosis of chronic viral infections after endoscopic procedure is quite difficult, as it shows a long incubation period and patients can have asymptomatic or minimal symptoms. Although hepatitis-B and Hepatitis-C infection–related cases are reported after inadequate disinfection, the transition is very rare [26–28]. Bronowicki et al. reported that HCV positivity after coloscopy showed that the path of HCV transmission may be due to the use of contaminated syringes and multi-dose drugs [29].

HIV: There are no reports of HIV infection associated with the gastrointestinal tract endoscopic procedure. HIV is inactivated in 2% glutaraldehyde in 2 min [30].

Prions: Creutzfeldt-Jakob disease (CJD) is a neurological disease caused by prions. Theoretically, CJD does not occur after the endoscopic procedure, since the endoscope and its accessories do not contact with prion-infected tissues. Unlike variant CJD (vCJD), mutant prion protein can be found in various lymphoid tissues (tonsils, intestines) in the body and are resistant to routine conventional disinfectant/sterilizers. ESGE (The European Society of Gastrointestinal Endoscopy) recommends avoiding endoscopy in these patients. If this is not possible, the equipment used should be discarded after the procedure [31].

Fungal infections: Especially in immunocompromised patients, there may be a risk of cross fungal infections associated with endoscopic procedures. In a study, fungus was isolated from gastric aspirate, it was suspected that the equipment was contaminated, and fungal elements were seen in direct examination. The source, on the other hand, was identified as an immunocompromised patient in which the endoscope was previously used [32, 33].

Disinfection of Endoscope

Colonoscopes are flexible, semi-critical instruments, and disinfection processes should be done with high-level disinfectants (HLD). Different accessories such as forceps, sphincterotomy, polypectomy snares, sclerotherapy needles, and cytology

brushes used in endoscopic interventions should be sterilized. Besides, the water bottle used in washing should be disinfected or sterilized and attention should be paid to the use of sterile water [34].

The most important step to prevent the contamination of microorganisms from patient to patient through the endoscope is the disinfection procedures compatible with the current and effective guides in the cleaning and disinfection of the endoscope. *Mycobacterium tuberculosis* [35], HBV [36], HCV [37], and HIV [38] are inactivated by washing and subsequent suitable liquid chemical germicides.

High-level disinfectants (HLD) such as 2% glutaraldehyde, 0.35% peracetic acid, and chlorine dioxide (concentration containing 1100 ppm chlorine) are used in endoscope disinfection. Endoscopy unit should be disinfected with 2% glutaraldehyde for 10 min at the beginning of the day and between cases, for 5 min with chlorine dioxide containing 0.35% peracetic acid and 1100 ppm chlorine. Disinfection for 20 min with 2% glutaraldehyde, 5 min with chlorine dioxide containing 0.35% Peracetic acid, and 1100 ppm chlorine (it is recommended to have 10 min for sporicidal activity); it provides the desired efficacy at the end of the day and before ERCP, in high-risk situations such as before use in the immunocompromised patient and after use in the patient with pulmonary tuberculosis. Endoscopes used in the patients who are known to be infected with *M. avium intracellulare* and other high-resistant microorganisms should be treated with 2% glutaraldehyde for 60–120 min, with chlorine dioxide containing 0.35% peracetic acid, and 1100 ppm chlorine for 10 min [39].

Disinfection Procedures

Pre-cleaning process: Before disinfection with HLD, the endoscope outer surface, microorganism load, and organic material can be reduced by 4 logs or 99.99% with proper pre-cleaning in lumens and channels. It is the process of removing blood, mucus, and organic wastes on the endoscope and its ducts with a suitable brush, detergent-enzyme solvent, and pressurized water. The biofilm layer should not be formed immediately after use to prevent organic residues and liquids from drying out.

Rinsing: It is based on the removal of detergent or enzyme solvent chemicals used in pretreatment with intense water.

Disinfection: HLD is the process that eliminates all vegetative microorganisms and the majority of bacterial spores. Minimizing the biological load with sufficient pre-cleaning creates an effect equivalent to HLD sterilization in the absence of a large number of bacterial spores.

Last rinse: This should be done with 0.2 μm (bacteria, carbon, UV) filtered, large volume, running water. If it cannot be done with filtered water, it is recommended to pass 70% alcohol through the endoscope channels.

Drying: It is the necessary process step to minimize microorganisms that may exist in rinsing water and to prevent the microorganisms from colonizing and multiplying during storage.

Storage: Control valves, caps, and tips should be stored upright and in contact with one another without attachment. Reprocessing is not necessary if used in 5–7 days in properly treated, dried, and stored endoscopes [40, 41]. The point to remember: the effectiveness of HLD and manual washing depends on the staff operating and it is necessary to ensure continuity of training.

Antibiotic Prophylaxis in Gastrointestinal Endoscopy

Antibiotic prophylaxis during gastrointestinal endoscopic procedures is recommended for cases where there is a significant risk of developing endogenous infections. Regardless of whether polypectomy is performed or not, the rate of temporary bacteremia development after colonoscopy is around 4.4%, but it is short-lived (<30 min) and subsequently infectious complications do not develop [42]. However, microorganisms as a result of bacteremia cause infection in prosthetic or damaged valves in those with cardiac defects.

European Cardiology Association (ESC):

- Patients with cardiac problems at high risk of developing IE (patients with prosthetic valves or prosthetic materials used in heart valve repair, patients who have previously had IE, patients with congenital heart disease).
- Up to 6 months after the intervention in patients with congenital heart disease who underwent full surgical repair using prosthetic material or with a percutaneous technique.
- Antibiotic prophylaxis should be considered in cases where residual defect persists in areas where prosthetic materials or devices are placed with cardiac surgery or percutaneous technique (Evidence IIa, Recommendation C).
- Prophylaxis is not recommended for other vascular or congenital heart diseases (Evidence III, Recommendation C) [42, 43].

IE Prophylaxis According to the Type of Risky Intervention in Patients with the Highest Risk

Prophylaxis is not recommended for gastroscopy, colonoscopy, cystoscopy, and transesophageal echocardiography (Evidence III, Recommendation C). If there is a proven infection in patients at the highest risk or if antibiotic therapy is indicated to prevent a wound infection or sepsis associated with the intervention, the choice of an active antibiotic (Ampicillin, Amoxicillin, or Vancomycin) against enterococci will be rational. Vancomycin should only be given to patients who cannot tolerate β-lactams. If the infection is known to be caused by resistant enterococcal strains, or suspected, it is recommended to seek advice from an infectious diseases specialist [43].

The British Society of Gastroenterology (BSG) first evaluated the rationale in its recommendations regarding antibiotic prophylaxis in the gastrointestinal tract endoscopic procedures for the prevention of infective endocarditis (IE).

Reasons for prophylaxis against IE:

- IE usually occurs following bacteremia.
- The formation of bacteremia during certain procedures facilitates the development of infective endocarditis.
- Such bacteria are generally sensitive to antibiotics.
- Antibiotics should be given to those with heart disease that previously predisposes to IE, before any procedures that can create bacteremia.

Antibiotic prophylaxis recommendations of BSG before gastrointestinal endoscopy:

1. Antibiotic prophylaxis is recommended for preventing infective endocarditis (IE) before diagnostic or therapeutic endoscopic procedures in patients with high cardiac risk factors (Evidence III, Recommendation B).
2. IE should be considered in patients who have symptoms and signs and have known cardiac risk factors in the weeks after endoscopy (Evidence IV, Recommendation C).
3. Appropriate antimicrobial therapy should be planned in patients with signs of cholangitis (Evidence Ia, Recommendation A).
4. Additional doses of antibiotics were not required for prophylaxis before ERCP administration in patients under treatment for cholangitis (Evidence IV, Recommendation C).
5. Routine prophylactic antibiotherapy is advised for ERCP, whereas if biliary decompression is not achieved, therapeutic antibiotherapy is recommended (Evidence III, Recommendation B).
6. Prophylaxis is routine in certain circumstances in ERCP (Evidence III, Recommendation B).
   (a) Biliary diseases such as sclerosing cholangitis or hilar cholangiocarcinoma, in patients who are not likely to have or have bile drainage
   (b) Patients undergoing liver transplantation
   (c) Patients with a pancreatic pseudocyst
   (d) Patients with severe neutropenia ($<0.5 \times 10^9$/L) and hematological malignancy
7. Oral Ciprofloxacin or parenteral Gentamicin is recommended for prophylaxis of ERCP (Evidence IIa, Recommendation B).
8. In percutaneous endoscopic gastrostomy (PEG) or percutaneous endoscopic jejunostomy (PEJ), a single dose of parenteral Co-Amoxiclav should be administered 1 h before the procedure. Cefuroxime (incidence of infection with *C. difficile* or if the frequency of infection with microorganisms producing ESBL) may be an alternative option (Evidence Ia, Recommendation A).

9. In patients suspected of variceal bleeding, parenteral antibiotic therapy should already be arranged before endoscopy (Evidence Ia, Recommendation A).
10. Prophylaxis should be applied in cases of fine-needle aspiration and transgastric or trans-enteric pancreatic pseudocyst drainage from cystic lesions or adjacent structures (Evidence IIa, Recommendation B).
11. In patients with severe neutropenia ($<0.5 \times 10^9$/L) and with deep immune deficiency, antibiotic prophylaxis should be applied in attempts at high risk of bacteremia (Evidence IV, Recommendation C).
12. Positive culture results should be considered when deciding on antibiotic prophylaxis regimens. If necessary, microbiology specialists should be consulted (Evidence IV, Recommendation C) [10, 43].

Infection Control in Endoscopy Units

1. Hand Hygiene: Hand hygiene should be performed before invasive procedures, before contact with the patient, before wearing gloves, before leaving the patient care area, after contact with the patient, after contact with blood and body fluids or contaminated surfaces, and after removal of gloves. Although hand hygiene water and soap are sufficient, hand hygiene should be carried out using alcohol-based hand antiseptics after procedures in patients with known or suspected infectious diarrhea, such as *C. difficile* diarrhea.

   Personnel protective equipment (PPE): Each unit should have written policies/procedures on PPE use. Most of the infections are in the form of needle sting, blood splashing into the conjunctiva, inhalation of the microorganism, or transfer after direct hand contact. According to the direct contact with the patient and blood/body fluids, the use of protective equipment can be classified into two ways as low and high risk.

   At low risk, there is no direct contact with the contaminated endoscope, device, or body fluids. The low risk includes situations where access to the processing area is short-term and there is no direct patient care. Although PPE use is not required in the case of low risk, the exposure may change during the procedure.

   In high-risk situations, there is a direct contact with contaminated endoscope, device or blood/body fluids or situations where direct patient care services are provided. In high-risk situations, gloves and waterproof aprons, mask and face/eye protective glasses should be used as blood and body fluids are likely to splash on the face.
2. Management of safe drug: Studies have proven that conditions such as improper use of multiple doses of drugs and reuse of injectors may be a source for the transmission of pathogens to the patient.
   (a) Drug preparation procedures should be carried out in a drug preparation area outside the patient care area or endoscopic treatment room.
   (b) Drugs, serum, and serum sets should be prepared just before use and labelled to show that they are in use for a single patient.
   (c) In case of reuse of previously used vials, diaphragms should be wiped with 70% alcohol.

(d) In case of multiple-dose vials, vials should not be in the endoscopic processing room, opening and expiry dates must be recorded.
(e) When using a common injector, it is essential to change the needles.

3. Safety of potentially contaminated equipment or surfaces: Chemicals to be used for cleaning and disinfection should be environmentally protective, and their proper use should be ensured. The lethal activity of disinfectants should be monitored and recorded within the desired contact time, and alcohols should not be used for environmental/surface cleaning.
4. Terminal cleaning suggestions: It is the process of cleaning organic waste and biofilm layer on terminal cleaning surfaces. Cleaning and disinfection should be done with chemical agents (effective for bacterial spores) at the end of the day in the endoscopic treatment room. Continuity of personnel training should be ensured for terminal cleaning.

   It is recommended that the personnel working in the endoscopy unit be vaccinated against Hepatitis-B [44, 45].

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Information on Colon Polyps in Terms of Gastroenterology

6

Gozde Dervis Hakim

Colon Polyps

Mucosal formations that protrude toward the lumen in the gastrointestinal tract are called polyps. Colonic polyps are generally asymptomatic and can lead to symptoms such as obstruction, ulceration, and bleeding if they are too large. They can be two types: neoplastic (adenoma and carcinomas) or non-neoplastic type (Table 6.1).

Syndromes in the gastrointestinal tract, which often show a hereditary transition and have an increased risk of cancer, are called gastrointestinal polyposis syndromes (Table 6.2).

The common characteristic indicator of adenoma and carcinomas is "cellular dysplasia." However, according to microscopic details, they differ from each other. Serrated polyps are intermediate forms that carry malignant potential but can still enter the class of non-neoplastic polyps with hyperplastic polyps' classification. Submucosal lesions are not real polyps. They are polypoid-looking lesions covered with normal mucosa. Adenomas greater than 1 cm or having villous structure or containing high-grade dysplasia or containing any of these are called adenoma with advanced pathology (AAP) [1].

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Table 6.1 Classification in colon polyps

Neoplastic mucosal polyps	**Submucosal lesions**
Benign (adenoma)	Colitis cystica profunda
Tubular adenoma	Pneumatosis cystoides coli
Tubulovillous adenoma	Lymphoid polyps (benign and malign)
Villous adenoma	Lipoma
Malign (carcinoma)	Carcinoid
Noninvasive carcinoma	Metastatic neoplasms
Carcinoma in situ	Other rare lesions
Intramucosal carcinoma	**By their shape**
Invasive carcinoma (up to muscularis mucosa)	Sessile polyp
Serrated polyps	Pedinculated polyp
Sessile serrated polyp/adenoma	Flat polyp
Traditional serrated adenoma	
Non-neoplastic mucosal polyps	
Hyperplastic polyp	
Juvenile polyp	
Peutz jeghers polyp	
Inflammatory polyp	
Mucosal polyp (existence of normal mucosa in polypoid structure)	

Neoplastic Polyps

Adenomatoid Polyps

Epidemiology and Risk Factors

They make up about two-thirds of all colon polyps. If there is a polyp in the colon, 30–50% of the time, the probability of the existence of synchronous polyps in the remaining colon should be considered [2].

Among the risk factors are:

1. Age
2. Increased body mass index
3. Sex
4. Race
5. Genetic
6. Environmental factors

As the age increases, frequency, number, size, and dysplasia severity increase in adenoma [3, 4]. In the autopsy series, while colon polyps were found with a rate of 50% in cases around the age of 70, they were found in only 1/4 of these cases in the 20s and 30s [5, 6]. In the studies of people over the age of 50, approximately

Table 6.2 Classification of gastrointestinal polyposis syndromes

Inherited polyposis syndromes
Adenomatous polyposis syndromes
Familial adenomatous polyposis
Familial adenomatous polyposis variants
Gardner syndrome
Turcot's syndrome
Attenue adenomatous polyposis coli
Familial tooth agenesis syndrome
Bloom's syndrome
MUTHY polyposis (MYH polyposis)
Hamartamatous polyposis syndromes
Peutz jeghers syndrome
Juvenile polyposis
PTEN hamartoma tumor syndromes
Cowden's disease
Bannayan-Ruvalcaba-Riley syndrome
Rare hamartamatous polyposis syndromes
Hereditery mixed polyposis syndrome
Intestinal ganglioneromatosis and neurofibromatosis
Devon family syndrome
Basal cell nevus syndrome
Noninherited polyposis syndromes
Cronkhite-canada syndrome
Serrated polyposis syndrome
Lenfamatous polyposis
Noduler lenfoid hyperplasia

MUTHY mut Y homolog (*E. coli*), *PTEN* phosphatase and tensin homolog

27–32% adenoma and 6–10% adenoma with advanced pathology (AAP) were detected [7–10]. Advanced age is also a risk factor for right colon polyps [11].

Increased body mass index (BMI) is associated with increased colorectal adenoma risk. Increased abdominal visceral adipose tissue volume may be a better predictor than BMI [12]. *Lack of physical activity* is also a risk factor in the development of adenomatous polyp [13].

In men, compared to women of the same age, in the series of colonoscopy, an increased risk of 1.5 times was detected [14, 15]. In addition, in men, the relative risk of adenoma with advanced pathology increased by about 1.5 times [16].

Race: While the incidence of adenoma and proximal adenoma is higher in African-Americans and Hispanics compared to the Caucasians, large adenoma is more common in African-Americans [17]. Another database study found no difference between Hispanics and Caucasians in terms of the incidence of polyps greater than 10 mm [18].

Genetics: Syndromic conditions such as familial adenomatous polyposis and Lynch syndrome are associated with genetic predisposition. However, genetic predisposition can also be seen in those with sporadic adenoma who do not have

these syndromes, along with 95% Mendelian inheritance pattern. In epidemiologic studies, in cases whose first-degree relatives have colon cancer or adenoma, the risk of colon cancer or adenoma has been found to increase by 2–3 times [19].

Environmental factors: Increased fat consumption, excessive alcohol intake, obesity, smoking, low-calcium diet were associated with increased incidence of colorectal adenoma [20].

Cases Associated with Adenomatous Polyps

Uretherosigmoidostomy

In the cases where urinary diversion procedure is applied and the ureter is implanted into the sigmoid colon, the risk of developing neoplastic lesion on the side of uretherosigmoidostomy is high. After this procedure, at least 29% of cases were found to develop colonic neoplasm near stoma [21]. Juvenile polyps or inflammatory polyps have also seen to develop near stoma.

Acromegaly

In patients with acromegaly, the risk of developing colonic neoplasm increased by 5–25% and the risk of developing colon adenomas increased by 14–35% [22, 23]. In young patients, the risk increased in those with colon Cancer history in the family, multiple skin tags (acrochordons), or previously colorectal adenoma [22, 24, 25]. Although the link between acromegaly and the risk of developing colonic neoplasm is not clear, it is thought that this may be associated with an increase in growth hormone and/or insulin-like growth factor-1 (IGF-1). In patients with acromegaly, increased serum IGF-1 levels were found to be correlated with increased epithelial cell proliferation and increase in colorectal adenoma recurrence rate [25, 26].

Streptococcus bovis Bacteremia and JC (John Cunningham) Virus

Streptococcal bovis–induced bacteremia and endocarditis was found to be correlated with colorectal cancer and adenomatous polyps and FAP (familial adenomatous polyposis) [27, 28].

JC virus inhibits oncogenic polyomavirus tumor suppressor genes and has been found to be correlated with colonic adenomas and carcinomas [29].

Cholecystectomy

Due to the lack of gallbladder, there is increased bile acid exposure to the colon. This results in a shift from primary bile acids to secondary bile acids. This leads to increased proliferation activity of the colonic mucosa [30].

Anatomic Distribution

In the autopsy series, large adenomas show distal predominance.

Clinical and Natural Course

Adenomas are often asymptomatic. They are detected incidentally during colonoscopy examination carried out for colon cancer screening. The most common symptom in colon polyps is occult or overt bleeding. Small adenomas do not usually bleed.

According to histopathological data, bleeding was found due to erosion on the surface of colon polyps [31]. Bleeding is intermittent and positivity can usually develop in the secret blood test in the gaita. Other symptoms that can be seen in colonic polyps are constipation, diarrhea, and flatulence.

As a result of large volume lesions, constipation or reduction in fecal caliber is seen. Large polyps can cause intermittent intuseptions and cause abdominal pain in sub-quadrants caused by occasional cramps. In patients with villous adenoma, secretive diarrhea that can lead to life-threatening water and electrolyte depletion and hypovolemia may develop [32]. The tumor that can cause this syndrome is typically 3–4 cm and above and is usually localized to the rectosigmoid region. Secretive villous adenomas secrete uninterrupted water and sodium and excessive potassium. Very large-scale polyps can cause obstruction in the bowel, albeit rarely. Although the growth rate of each adenoma is variable, usually, small polyps grow by an average of 0.5 mm per year [33]. Over 7–10 years only a small portion of adenoma (5% or less) advances to cancer. In advanced adenomas (high-degree dysplasia, >10 mm size, or villus component content), the risk is higher [4].

Pathology

Endoscopic and Histological Properties

Adenomatous polyps are benign neoplastic epithelial tumors. The vast majority of adenomas detected in endoscopy (60–75%) are less than 1 cm [34].

According to their appearance, adenomas are classified as:

Sessile
Pedunculated
Flat
Depressed
Excavated

Sessile polyp: The base and upper part of the polyp are of the same diameter.

Pedunculated polyp: The base is thinner. Mucosal stem is located between the bowel wall and the polyp.

Flat polyp: According to "the Japanese Society for Cancer of the Colon and Rectum," they are the polyps with the height that is less than half of the diameter of the polyp. Approximately 27–36% of polyps are made up of flat polyps [35–38]. Flat adenomas can be macroscopically, completely flat or slightly raised and can carry a trace of depression in the middle. In a study comparing polypoid lesions, flat polyps were found to be at greater and higher risk of grade dysplasia and to carry early-stage cancer [35, 36, 39] However, the National Polyp Study Group found in their study that the risk of high degrees of dysplasia did not increase in flat polyps [37].

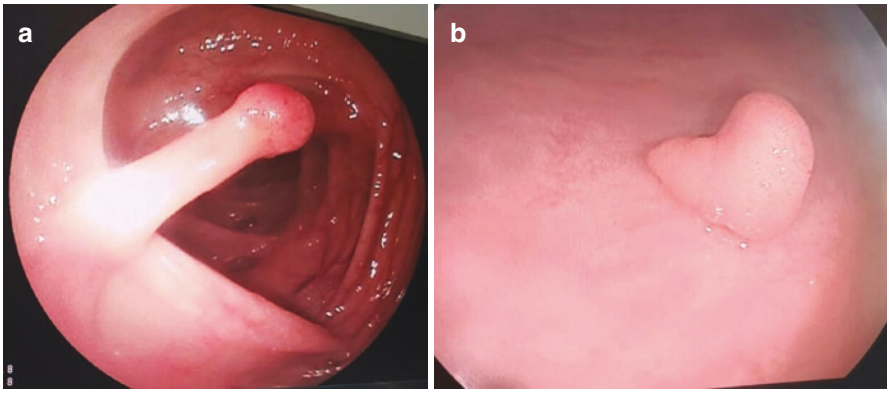


Fig. 6.1 (**a**) Polyp with stalk (**b**) sessile polyp

Depressed polyp: The thickness of the lesion mucosa is less than the neighboring mucosa. These lesions are more likely to accommodate high-grade dysplasia or malignancy even if they are small [40–45]. It is about 1% depressive [38, 40].

In gastrointestinal tract superficial neoplastic lesions, Paris classification helps classify adenomas in the form of polypoid (Fig. 6.1a, b)–nonpolypoid lesion [46].

Histological Appearance

The neoplastic nature can be determined by the histological detection of glandular structures of adenomas. All adenomatous polyps in the colon are dysplastic. Adenomatous epithelium is characterized by hypercellularity in colon crypts with abnormal cellular differentiation and regeneration. Tubular adenoma is the most common subgroup. It is seen in 80–86% of the adenomas in the colon [3, 34]. It is characterized by a branched adenomatous epithelial network. In order to be classified in the form of tubular adenoma, more than 75% must have tubular components. Tubular adenomas usually have small and mild dysplasia.

Villous adenoma has an appearance characterized by long finger-shaped projections directed from the polyp stroma toward the surface without extra branching structure. It contains more than 75% villus structures. They make up 3–16% of adenomas [3, 34]. Villous adenomas often have greater and more serious dysplasia.

Tubulovillous adenomas contain histological structure in the form of a combination of both types. It contains a villous component of 25–75%. They make up 8–16% of colon adenomas [3, 34].

All of the adenomas in the colon are dysplastic. Dysplasia in colorectal adenomas is divided into low-grade dysplasia and high-grade dysplasia. Low-grade dysplasia includes light–medium dysplasia while high-grade displasia includes severe dysplasia and carcinoma in situ [1].

Advanced cell proliferation in the crypts leads to the accumulation of the cells. Polarity loss develops and excessive glands are formed. This irregular cribriform appearance is called carcinoma in situ. Carcinoma in situ is characterized by intracryptal cell proliferation. But the important thing is that the border of the

basement membrane around the glands have not been exceeded. If neoplastic cell foci extending beyond the basement membrane are seen and there is an extension of neoplastic cells toward the lamina propria layer of the mucosa, this lesion should now be defined as intramucosal carcinoma. Due to the lack of lymphatic vessels in the lamina propria, it can be said that lesions that do not exceed the lamina propria will not make metastasis [47, 48]. Therefore, both carcinoma in situ and intramucosal carcinoma are called noninvasive carcinoma to avoid unnecessary, more aggressive approaches [1]. If neoplastic cells have spread toward the muscularis mucosa layer, they carry a risk of lymphatic invasion and should now be called lesion invasive carcinoma. If an adenoma contains invasive carsinoma foci, it is called malignant polyp. According to the studies, in all adenomatous polyps, there exist 70–86% mild-grade dysplasia, 18–20% moderate dysplasia, 5–10% severe dysplasia (carcinoma in situ), and 5–7% invasive carcinoma [34, 49, 50]. Although high degree dysplasia is mostly seen in large and villous polyps, there is a possibility of observing invasive cancer foci in adenomas with severe dysplasia [3].

Classification of Adenomas According to the Size

Adenomatous polyps are divided according to their size as follows:

- Smaller than 1 cm
- 1–2 cm
- Larger than 2 cm

In addition, polyps smaller than 5 mm and are called *dimunitative polyps*. In countries with high prevalence of colon cancer, adenomas tend to be larger [51, 52]. While adenoma size is proportional to age, large adenomas are more commonly seen in distal colonic segments [3, 6, 49]. Diminutive polyps are usually detected incidentally during endoscopy, there is a 30–50% likelihood for them to be adenomatous; they can have a slight malignancy potential [53, 54]. For this reason, dimunitative polyps seen during colonoscopy should be removed.

The potential of malignancy of adenomatous polyps are determined according to the following:

Size.
Histological type.
Degree of dysplasia.
The potential for malignancy is directly increased polyps with large, villous histology and high-grade dysplasia.
Polyps with villous structure greater than 1 cm, or including high degree dysplasia or carcinoma are called ADENOMA WITH ADVANCED PATHOLOGY (AAP).

Pathogenesis

Adenomatous polyps occur with the development of errors in one or more of the steps during cell proliferation or cell death (apoptosis), a normal process.

Adenoma: Carcinoma Hypothesis

Generally, colon cancers are thought to be taken origin from previously benign adenomas. In the light of various studies, hypotheses have been established on the conversion of adenomas into cancer. Epidemiological, clinical, pathological, and molecular hypotheses are as follows.

Epidemiological Evidence

The prevalence of adenoma and the frequency of colon cancer in a society are parallel to each other geographically. In fact, in those migrating from low-risk to high-risk zone in terms of colon cancer, the prevalence of adenoma has been observed to have increased. In addition, the risk of adenoma and cancer is increasing with age. According to the age distribution curve, adenomas occur 5–10 years before cancer [55–58].

Clinicopathological Evidence

According to the National Polyp Study group, endoscopically removed adenomas have reduced the risk of estimated colorectal cancer [55]. Prospectively controlled studies have reported that sigmoidoscopies have decreased colorectal cancer incidence by 21–31% and mortality rate by 26–38% [56–58]. At the same time colon cancer and large adenomas were also found to be in the same localizations.

Molecular Genetic Evidence

During the progression of adenoma to carcinoma, it plays an important role that the oncogenes are active and the tumor suppressor genes are inactive. In studies with K-ras oncogene, it was seen that K-ras mutation plays a role of 9% in small polyps; 58% in adenomas larger than 1 cm, 47% in colon cancers. Therefore, it suggests that K-ras oncogene activation plays a role in the middle stages of tumorigenesis and it can be said that it has an effect on the growth patterns of polyps. However, the failure to detect K-ras oncogene in a large number of colon polyps and cancers has suggested that there may be other genetic factors. Tumor suppressor genes normally prevent tumor formation. Loss of function in tumor suppressor genes in 5q, 18q, 17p chromosomes plays a critical role in colorectal tumorigenesis. APC (adenomatous polyposis coli) gene is found in the long arm of Chromosome 5. It plays a ‘gatekeeper’ role in colon carcinogenesis. The APC protein plays an important role in colonic epithelial homeostasis. The mutated APC protein reacts with intracellular beta-catenin and thus translocks to the active beta-catenin nucleus and enables cell proliferation by realizing the transcriptional activation of c-myc, cyclin D1, and “peroxisome proliferator actenor receptor delta.” The increase in the level of beta-catenin brings with it an increase in proliferation and adenoma occurs as a result

[59]. While the APC mutation is monitored at similar frequency during tumor progression at all stages, allelic loss or loss of heterozygosity (LOH) increases as it progresses from early adenoma to invasive carcinoma. In addition, showing mutational APC even in adenomas with a size of 0–5 cm strengthens the idea that the adenocarcinoma sequence also covers the early stages [60]. APC gene mutation or loss plays a critical role in early stages in both sporadic adenomas and in patients with active adenomatous coli.

The DCC (deleted in colon cancer) tumor suppressor gene is localized in the 18q chromosome. Loss in the DCC gene plays a role in the adenoma progression, in late stages. The loss of 18q is seen in 10–30% of early adenomas, while in larger adenomas it occurs up to 60% [61].

The TP53 gene is localized in the short arm of 17 chromosomes. Colorectal carcinomas are usually the result of allelic loss in 17p. The high incidence of p53 gene mutations in human cancers is an indication that p53 has important functions in the sequence of important and critical events in tumor development. p53 performs these functions in cellular processes such as gene transcription control, DNA repair, cell cycle control, genomic instability, chromosome decomposition, angiogenesis, apoptosis, and tumor suppression. The p53 protein defined as "protector of the genome" with all these functions and especially its role as suppressor to tumor development is activated in various cases of genomic stress, such as DNA damage, hypoxia, nucleotide pool depletion, viral infections, and oncogene activation. However, the deterioration of the normal p53 function causes the deterioration of the functions of intracellular pathways that suppress cancer development, which contributes to the canceration process of cells [62]. Functional inactivity in p53 usually results in a "missense" (meaningless or changing meaning) mutation in DNA [63]. Studies showing the frequency of p53 mutations in colorectal tumors are mainly based on immunohistochemical expression, DNA sequence studies, and 17p allelic loss. The change in p53 was shown at 5–26% in adenomas, 53% in the invasive foci of adenomatous polyps, and 70% in adenocarcinomas. This data shows that p53 inactivation plays a role in the late stages of conversion from adenoma to carcinoma [61]. Oncogene and tumor suppressor genes initiate adenoma-carcinoma process by stimulating cell proliferation and inhibiting cell death, but stability genes, or "caretakers," normally keep genetic changes to a minimum. Therefore, as a result of their inactivation due to mutation or losses, mutation development is allowed in the digger target genes.

Diagnosis

Colorectal polyps do not usually give symptoms. They are usually detected incidentally in the examinations during unexplained iron deficiency anemia or colorectal cancer scans. Methods used for the diagnosis of colon polyps are:

1. Fecal occult blood test
2. CT (computarized tomography)
3. Sigmoidoscopy

4. Barium enema
5. Colonoscopy
6. CT colonography
7. Fecal DNA analysis

Fecal Immunochemical Test (FIT)

FIT is a method that directly measures the presence of hemoglobin in feces. It is a test that does not require a drug-special diet or any restrictions. Foods with peroxidase activity do not create false positivity. There is no need to discontinue aspirin or other nonsteroidal anti-inflammatory drugs. While for FIT it is enough to give fecal samples only one time, for fecal occult blood testing (gFOBT) it is required to give fecal samples three consecutive days after a special diet. FIT for colon lesions is much more sensitive than gFOBT [64, 65]. In addition, positive FIT is highly specific to lower GI bleeding. However, FIT positivity may also occur due to rapid transit after high amounts of upper GI bleeding. In a two meta-analysis review, the sensitivity of one-time FIT in capturing colorectal cancer in medium-risk population was determined as approximately 80% [66]. In advanced adenoma detection, the sensitivity and specificity of FIT are lower than the colorectal cancer detection rate, and the sensitivity was found to be approximately 25–56% and specificity 68–96% [66]. Compared to gFOBT, the detection of FIT colorectal carcinoma and advanced adenoma used for screening also showed high sensitivity and high patient compliance [66–69]. In a meta-analysis, FIT was found to be superior to colorectal cancer compared to gFOBT (RR 1.96, 95% CI 1.2–3.2) and advanced neoplasia (RR 2.28, 95% CI 1.68–3.10) [70].

Guaiac-Based Fecal Occult Blood Test (gFOBT)

The guaiac test defines the hemoglobin by turning the paper, which is impregnated with guaiac reagent, to blue as a result of peroxidase reaction. In randomized controlled studies that use different FOBT, in CRC detection, gFOBT sensitivity is 31–79% and specialty is 87–98% [66, 71]. gFOBT sensitivity is less in advanced adenomas compared to CRC.

Adenomatous polyps usually do not bleed, so tests with hemoglobin presence in the feces are very likely to skip polyps. In studies using FOBT of different types, in the detection of advanced adenoma or advanced neoplasia, there are sensitivity rates ranging from 7% to 20%, and specificity rates ranging from 92% to 99% [66]. The detection rate of gFOBT for right colon lesions is low compared to left colon lesions [72, 73]. Compared to FIT, the detection rate of gFOBTs for CRC and advanced adenoma is lower. Polyps smaller than 1 cm usually do not bleed. Adenomas greater than 1.5–2 cm have a higher risk of bleeding. Colonoscopy or sigmoidoscopy is also recommended besides FOBt, as small polyps rarely bleed.

Multitarget Stool DNA Tests with Fecal Immunochemical Testing

Tests of molecular experiments for the detection of multitarget stool DNA testing mutations (MT-sDNA, also known as FIT-DNA, called Cologuard in the United States), DNA (KRAS), are a group of tests consisting of a combination of

immunochemical tests (FIT) that can detect hemoglobin in the blood infected with feces from colorectal lesions and tests of gene amplification techniques involving methylation biomarkers associated with colorectal neoplasms. Evidence of effectivity of MT-sDNA has only been proven by comparative studies. There is no randomized controlled study in colorectal cancer screening yet. In a study in which MT-sDNA and a one-sided FIT test were compared in 9989 subjects, the sensitivity of MT-sDNA and FIT was found 92% and 74%, respectively, in colorectal cancer detection [10]. MT-sDNA sensitivity is not affected by colorectal cancer stage or localization. The specificity of MT-sDNA is less than FIT specificity (87% versus 95%).

Sigmoidoscopy

Sigmoidoscopy is a 60 cm fiber-optic device for the left colon, where the processes such as taking a biopsy or removing a polyp can be performed, as well as displaying the mucosa extending from the rectum to the splenic flexura and lesions that may be located in the colon. Flexible sigmoidoscopy can detect colon polyps around 10–15% [74]. As found in many retrospective studies, distal colorectal cancer has decreased by 60–75% to sigmoidoscopy [75].

Colonoscopy

It is a procedure performed with a fiber-optic flexible colonoscopy device, which provides visualization of some ileum together with the entire colon from the rectum to the terminal ileum. In a meta-analysis involving six studies, colonoscopy screening was found to reduce the risk of colorectal cancer incidence and death by 40–60% compared to screening with sigmoidoscopy [76].

Observational studies have shown that colonoscopy reduces the incidence of colorectal cancer. In a population-based study in which 94,959 individuals aged 55–64 participated, the participants were grouped as those with and without colonoscopy screening and the risk of colorectal cancer was investigated. In this randomized group, colonoscopy screening rate was 40%. In these screened population, colorectal cancer was detected in 50%, adenoma in 31%, and high-risk adenoma in 10% [77].

In a systematic review study, colonoscopy sensitivity was found to be 75–93% in detecting 6 mm or larger adenomatous polyps [67]. In a systematic review study involving 465 patients with previous tandem colonoscopies, miss rate of polyps in any size and adenomas ≥10 mm, 5–10 mm, and <5 mm was found as 22%, 2%, 13%, and 25%, respectively [78]. Colonoscopy can be considered the gold standard for colorectal cancer screening. However, in 10% of the cases, cecum cannot be reached. It usually requires sedation. It is more costly than FOBT, FIT, and sigmoidoscopy. The polyps or neoplasms behind the flexura or folds can be overlooked. These constitute some limitations of colonoscopy [79]. For high-quality colonoscopy, bowel should be cleansed sufficiently, examination should be done until cecum, and withdraw time should be 6 min or more.

Various imaging modalities have been added to capture small polyps by colonoscopy. However, according to many study results, chromo endoscopy (dye-spraying

the colonic mucosa) has been reported to have a small superiority in detecting adenoma compared to conventional colonoscopy. This procedure has not found widespread use as it needs more time than colonoscopy, it is more expensive, and it detects more likely non-neoplastic polyps. According to a meta-analysis involving randomized studies, the NBI high-resolution white light did not excel in detecting adenoma by the colonoscope [80]. Therefore, advanced imaging techniques are not recommended for the screening of the population with moderate risk.

Colon Capsule Endoscopy

Colon capsule endoscopy is recommended by US Food and Drug Administration (FDA) only in patients whose colonoscopy could not be performed. However, it is not a screening method [81–83].

Barium Enema

The probability of detecting polyp with barium enema depends on the size of the polyp. 5–10% false positivity rate due to inadequate colon cleansing, or 10% false negativity rate due to diverticula, redundant bowel, weak mucosal coating. Therefore, barium enema is not used as a routine screening test. According to the data of the National Polyp Study Group, the rate of detecting polyps less than 6 mm, 6–10 mm, and larger than 10 mm was 32%, 53%, and 48%, respectively [84].

Computed Tomography Colonography (CTC)

Computed tomography colonography (CTC) contains a large number of thin sections, CT data, using a computer to create images of two- and three-dimensional intestinal mucosa. After bowel preparation, intravenous glucagon application can be performed if necessary to provide relaxation in the bowels. Air or carbon dioxide is administered by a catheter placed in the rectum. Imaging sections are taken during a single 32 s breath-holding sequence. No sedation is required. There are no controlled studies on the effect of CTC on colorectal cancer incidence or mortality. Seven studies are based on the sensitivity and specificity rates of CTC for the detection of colorectal cancer and ≥10 mm adenomas. Accordingly, the sensitivity of CTC for the detection of colorectal cancer and ≥10 mm adenomas is 67–94%, and the specificity rate is 96–98% [67].

Polyp detection sensitivity rates in symptomatic patients from the societies with high prevalence were found to be 29–59% for small polyps, 47–82% for medium polyps, and 63–92% for large polyps [85]. According to the Multicenter Study, the sensitivity in detecting ≥10 mm adenomas was 90%, and the sensitivity in detecting 6–9 mm adenomas was 78% [86]. In the light of all these studies, the CTC detection rate of polyps less than 5 mm is quite low.

Treatment

Little is known about the natural course of adenomatous polyps left untreated. However, it has been observed that the size of the polyps affects the progression time to carcinoma. It has been shown that cancer developed from 1 cm polypoid

tumor of unknown histology within 2–5 years with barium enema follow-ups [87]. Following the polyp detection, the cumulative rates related to cancer development were calculated as 2.5%, 8%, and 24% for 5, 10, and 20 years, respectively [88].

According to another radiological study, the doubling time required for the development of cancer from polyp was determined to be 4–6 months [89]. According to a mathematical model applied to serial barium enema examinations, it takes 2–3 years for the diminutive polyp (<0.5 mm) to reach 1 cm [90]. In the light of the studies, it can be said that the growth rate of the polyp is 2–4 mm per year [91]. Although the growth rates of the polyp have been found to be slow, it is recommended to remove all the polyps detected during the endoscopy process. Some definitions must be known before proceeding to the removal processes of polyp.

The presence of two or more adenomas is called multiple adenomas, and the presence of up to 10–100 polyps is called multiple adenomatous polyposis syndrome. Simultaneous detection of adenoma or carcinoma as index colorectal neoplasm is called synchronous lesion, and detection of one at least 6 months after the other is called metacranous lesion. The probability of developing synchronous adenoma is 30–50% especially in the presence of one adenoma at advanced ages [49, 53, 92, 93]. Therefore, if polyp is detected during rectosigmoidoscopy, a full colonoscopy must be performed.

Similarly, if polyp is detected during barium X-ray, CT colonography, or capsule endoscopy, a full colonoscopy must be performed to remove the detected polyps. As a result of polypectomies, it has been determined that the risk of colorectal cancer is reduced [53]. If polyp is detected during colonoscopy, the polyp must be defined for polypectomy. The polypectomy method to be selected varies depending on the endoscopic appearance and size of the polyp. First of all, polyp feature can be determined with Paris classification and Kudo pit pattern; location and size should be taken into consideration (Tables 6.3 and 6.4) [42, 46].

Kudo Classification

When the colon surface mucosa is examined with scanning electron or stereomicroscope, angled images of the Lieberkühn crypts, each of which consists of 5–6 cells, are monitored. These are called pit patterns. In the diagnosis of colon polyp, pit pattern analysis, which is defined by chromo-magnified endoscopy, is used [42].

Table 6.3 Kudo classification

Type I: Normal colonic mucosa; round pit
Type II: Asteroid pit, generally hyperplastic polyps are in this type
Type III divided into 2 groups:
L (long): Tubular or round pit that is larger than the normal pit
S (small): Tubular or round pit that is smaller larger than the normal pit
Type IV: Dendritic- or gyrus-like pits
Type V divided into 2 groups:
Type Vir: Irregular arrangement and sizes of IIIL-, IIIs-, IV-type pit pattern
Type Vns: Non-structural: Loss or decrease of pits with an amorphous structure

Table 6.4 Paris classification

Ip	Pedunculated polyps
I ps	Semipedunculated polyps
Is	Sessile polyps (higher than the height of closed forceps (2.5 mm))
IIa	Flat elevation of the mucosa (below than the height of closed forceps (2.5 mm))
IIa/IIc	Flat elevation with the central depression
IIb	Completely flat mucosal change, not protruding above mucosal surface
IIc	Mucosal depression, slightly depressed, lower than 1.2 mm

The Paris classification was re-updated in 2005 but does not contain a new definition, lateral spreading tumor (LSTs). LSTs are flat or sessile and size of ≥10 mm polyps having the risk of invasive cancer; it is classified as granular (homogeneous or nodular-mix) and non-granular (eleve or pseudo depressed) according to surface morphology.

ESGE divides superficial colorectal neoplasia into sessile or flat and peduncle [94].

Sessile or flat polyp: *Classified as diminutive (<5 mm), small (6–9 mm), and ≥10 mm polyps.*

Peduncle polyp: *Classified into two as polyp with head <20 mm and stalk <10 mm and polyp with head ≥20 mm or stalk ≥10 mm.*

Sessile or Flat Polyps

1. ***For diminutive sessile or flat polyps***

   Cold snare polypectomy for en bloc resection

   For 1–3 mm polyps, polypectomy with cold forceps is recommended.

   Cold forceps polypectomy:

   The simplest method to remove polyp is removing the polyp with cold forceps. It should be preferred in polyps of 1–3 mm size [95]. Jumbo forceps can be used in polyps that are slightly larger than 1–3 mm and are too small to be caught with snare. Electrocautery-related risks are avoided and the risk of colonic perforation is negligible [96]. However, if the correct polyp size is not chosen, it includes minor bleeding and residual polyp risks during polypectomy [97]. Therefore, care should be taken.

   Hot forceps polypectomy:

   Hot forceps polypectomy is another option for small polyps. A similar procedure is applied with cold forceps polypectomy, but after taking the polyp into forceps in hot forceps polypectomy, it is gently pulled into the lumen and then cut with an electrocautery. With the electrocautery used in this technique, it was aimed to completely destroy the residual tissue behind [98]. The tissue remaining in the forceps should also be sent for histopathological examination. In studies conducted, the probability of residual polyps remaining with hot forceps was found to be 22–17% [99, 100].

   A 16% residual polyp was identified by cold forceps or snare polypectomy. Therefore, with the thought that the hot forceps method does not give any advantage, the frequency of the use of the hot forceps polypectomy technique has decreased considerably and has lost its popularity. Hot biopsy forceps polypectomy is not

recommended due to high incomplete resection rates, insufficient tissue sampling, and side effects (delayed bleeding, thermal injury) [94].

2. ***For small (6–9 mm) sessile or flat polyps***

   For en bloc resection, snare polypectomy is recommended.

   Snare polypectomy:

   Snare polypectomy is preferred for removing polyps of 1 cm and above [95]. Snare consists of a metal ring that can be opened and closed. It is passed over the polyp, closed, slightly pulled toward the scope; if electrocautery will be used, it should not be too close to protect the scope. Depending on the use of snare electrocautery, it is called hot or cold snare polypectomy. Although there are a wide variety of snare types, most often oval or hexagonal types can be used. Mini-snares can be used for cold-snaring small polyps or to remove tissue remaining after piecemeal polypectomy [101].

   Cold snare polypectomy:

   Cold snare polypectomy is superior to cold biopsy forceps in the total removal of diminutive polyps. In the study of 52 patients with 117 polyps (<5 mm), cold snare forceps was found to be superior to cold biopsy when histological eradication rates and polypectomy time were taken into account [102]. With cold snare polypectomy, side effects from thermal electrocautery are avoided. According to the study conducted by Pohl et al., a relatively low residual neoplastic tissue presence (6.8%) was shown by hot snare polypectomy [103]. In a randomized controlled study involving 70 patients with anticoagulants and polyps up to 10 mm in size, hot snare polypectomy and cold snare polypectomy techniques were compared and significantly higher rates were obtained in the intraprosedural and post-procedural bleeding compared to the cold snare polypectomy group. However, complete polyp removal rates were equal in both groups [104]. According to the studies conducted, cold snare polypectomy showed superiority compared to hot snare polypectomy with low delayed bleeding rate, low post-polypectomy syndrome rate and shorter processing time [105]. According to (the Recommendations for Follow-Up After Colonoscopy and Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer) American Gastroenterology Association (AGA) 2020 consensus about polypectomy, patient who has diminutive (≤5 mm) and small (6–9 mm) polyp(s) should be treated using cold snare polypectomy [106].

3. ***For sessile or flat polyps of ≥10 mm size***

   Advanced endoscopic imaging techniques should be used to evaluate submucosal invasion

   Chromo-endoscopy: Obtaining images by applying various dyes to the gastrointestinal mucosa.

   Magnification endoscopy: Hundred times the magnification of the image.

   NBI (Narrow band imaging): Identification of mucosal surface and mucosal vascularity by using narrower range and shorter wavelength light types instead of a wide range of white light.

   FICE (Fuji intelligent chromo-endoscopy) and I-SCAN techniques: Simultaneous presentation of the images obtained by changing the light wavelengths that create real images thanks to optical virtual filters using software technology.

NBI studies show high degree of invasion in Sano capillary pattern IIIB, Hiroshima C3, and NBI International Colorectal Endoscopic Classification (NICE) [107–110]. Kudo pit pattern Vn shows deep submucosal invasion according to the advanced chromo-endoscopy studies [111, 112].

According to advanced endoscopic imaging techniques

(a) ***By size for noninvasive lesions***

Medium (10–19 mm): hot snare polypectomy

Large (≥20 mm): If en bloc endoscopic mucosal resection (emr)/en bloc resection is not possible or safe with EMR, refer to the reference center if piecemeal resection/lesion is >40 mm or if the lesion is complex.

Patients with lateral spread and large (≥20 mm) sessile colorectal lesions (0-IIa, 0-Is, 0-Isp according to Paris classification) or polyps with inaccessibility (ileocecal valve, appendix orifice, anorectal junction, behind haustra folds) should be referred to a center with an EMR-ESD specialist. EMR includes submucosal injection procedure to separate mucosal lesions from the underlying muscularis propria. Then the lesion is resected with the help of snare. The target for EMR is to remove the lesion completely without leaving any recurrence or residual tissue. Ideally, en bloc resection with histologically clean borders should be performed. In flat and sessile colonic lesions, en bloc EMR is limited to lesions of ≤20 mm from proximal to splenic flexura, and ≤25 mm in sigmoid colon and rectum [113].

According to the Paris classification, if there is 0-IIa + c or 0-III, nongranular surface and advanced surface pattern, if the lesion is larger than 20 mm, it is possible to perform accurate pathological classification and provide high curative treatment by removing the lesion by en bloc ESD [114]. Nongranular or granular or mixed lateral spreading tumors (>20–30 mm) in the rectum should be evaluated for ESD.

(b) ***If submucosal invasion is suspected***

If submucosal invasion is suspected, colonic tattoo application should be performed 3 cm distal to the lesion, and be referred to an upper center for EMR or endoscopic submucosal resection (ESD) or operation. In case of deep mucosal invasion, colonic tattoo should be applied 3 cm distal to the lesion and referred to the upper center for operation.

Sano IIIA and kudo pit pattern VI are predictive for superficial submucosal invasive carcinoma, and these patients benefit from en bloc resection. The presence of ulceration, excavation, deep demarked depression, IIc and II a + c, non-granulation, mucosal friability, fold convergence, kudo pit pattern V in polyp morphology is associated with submucosal invasive carcinoma. Surgical treatment should be chosen instead of endoscopic treatment [115–118].

India ink, methylene blue, indigo carmine, indocyanine green can be used for endoscopic tattooing. ESGE guideline suggested choosing sterile carbon particle suspension. The colonic submucosa is divided into three layers as SM1 < 1000 μm, SM2 < 2000 μm, and SM3 > 2000 μm; and SM3 lesions are defined as deeply invasive lesions that cannot be removed after submucosal injection. Kikuchi et al. have re-adapted the classification of SM1, SM2, and SM3 to the submucosal depth for non-polypoid lesions in the form of upper-middle and lower, and the most used classification

Table 6.5 Treatment recommendations for the flat polyps

Paris classification × Tumor size	<10 mm	10–20 mm	20–30 mm	>30 mm
0-IIa, IIc, IIa + IIC Lateral spreading tumor (LST), non-granular type	EMR	EMR	ESD	ESD
0-Is + IIa LST, granular type	EMR	EMR	EMR	POSSIBLE ESD
0-Is villous	EMR	EMR	EMR	POSSIBLE ESD
	<10 mm	*10–20 mm*	*20–30 mm*	*>30 mm*
Intramucosal tumor with non-lifting sign	EMR	EMR/ESD	ESD	ESD
Rectal carsinoid tumor	EMR	ESD/ SURGERY	SURGERY	SURGERY

system for flat or sessile lesions is the KIKUCHI classification system [119, 120] (Table 6.5).

Kikuchi et al. determined lymph node metastasis as 0–3% for sm1 lesions, 8–10% for sm2 and 23–25% for sm3 lesions [120]. If there is sub-mucosal invasion histopathologically, submucosal invasion depth, presence of lymphovascular extension, measurement and cleaning of the vertical, lateral and horizontal margins of the lesion should be specified.

Peduncle Polyps

1. ***For polyps with head <20 mm and stalk <10 mm: hot snare polypectomy.***
2. ***For polyps with head ≥20 mm or stalk ≥10 mm: Hot snare polypectomy and prophylactic mechanical hemostasis should be performed after inflating the polyp base with 1/10,000 adrenaline.***

In the histopathological classification of pedunculated polyps, the Haggitt classification is used.

According to the Haggitt Classification, the polyp is divided into five zones.

Level 0: Noninvasive disease, muscularis not exceeding mucosa
Level 1: Limited at the head
Level 2: Into the neck
Level 3: Into the stalk
Level 4: Crossing stalk, reaching submucosa

The risk of lymphonodular metastases is quite low when level 1–2–3 is resected endoscopically [121, 122]. However, Matsuda et al. found the risk of lymph node metastases as 6.2–8% for level 3 in their retrospective multicenter study [123].

According to the AGA, the recommendation for the patient who has pedunculated polyp(s) is prophylactic mechanical ligation of the stalk with a detachable loop or clips on pedunculated polyps with head ≥20 mm or with stalk thickness ≥5 mm to reduce immediate and delayed post-polypectomy bleeding [106].

Post-polypectomy Management

Although there is no clear information about the optimum time of post-ESD endoscopic surveillance after the colonic ESD procedure, as suggested in the ESGE guideline, many authors recommend performing the resection within the next 3–6 months. If complete resection is achieved and it is proved that there is no endoscopic and pathological recurrence in the control endoscopy performed after 3–6 months, it should be checked again after 1 year. In this control, if there is no recurrence or local recurrence or secondary primary tumor, standard surveillance intervals can be started [124].

Low-risk group patients according to ESGE: patients with 1–2 tubular adenomas <10 mm with low-grade dysplasia.

High-risk group patients according to ESGE: patients with adenomas with villous histology or high-grade dysplasia or ≥10 mm in size, or ≥3 adenomas [125].

In line with this grouping, ESGE and U.S. According to the Multi-Society Task Force on Colorectal Cancer and the American Cancer Society guideline, post-polypectomy surveillance consensus is indicated in Table 6.6 [106].

Serrated Polyps

Serrated polyps are the most common nonadenomatous polyps.

The World Health Organization classified serrated polyps into three groups:

1. Hyperplastic polyps (HP)
2. Sessile serrated adenomas (SSA/P)
3. Traditional serrated adenomas (TSA)

After better understanding of colorectal cancer pathways, it has been shown that the development of colorectal cancer is not from a single pathway and that colorectal cancer can develop from three different pathways with different frequency. These pathways:

1. Adenoma-carcinoma chromosomal instability pathway (50–70%)
2. Serrated pathway (30–35%)
3. Mutator lynch syndrome pathway (3–5%) [126, 127]

Table 6.6 Follow-up times for postpolypectomy

According to the endoscopical findings	Follow-up time (next colonoscopy) (year)
There is no polyp	10
If there is small (less than 10 mm) hyperplastic polyp in the rectum or sigmoid colon	7–10
One or two small (less than 10 mm) tubular adenomas	5–10
Three or ten tubular adenomas	3
One or one more tubular adenomas (more than 10 mm)	3
Villous or tubulovillous adenomas with or without high-grade dysplasia	3
Adenoma with high-grade dysplasia	1
More than ten adenomas	1

Phillip et al. described five molecular subtypes. Subtype 1, 2, and 3 are associated with the serrated pathway. Subtypes 1 and 2 have CpG island methylator phenotype (CIMP) and BRAF mutation, but KRAS is negative, either microsatellite instable (MSI) high or microsatellite stable (MSS)/MSI low cancer. The third subtype originates from Kras mutation but uses a different alternative pathway. Subtypes 2 and 3 are associated with high mortality [4]. Subtype 4 shows colorectal cancers originating from the traditional adenoma—carcinoma pathway and is MSS/MSIlow, CIMP, BRAF, and KRAS negative.

Subtype 5 is the type associated with lynch syndrome, MSIhigh, but CIMP, BRAF, and KRAS is negative and is associated with a high prevalence of familial colorectal cancer history [127]. SSAPs are less common than HP, making up 1% of all polyps [128].

The serrated pathway is still not well understood. One of the most important problems is the difficulty of recognizing these lesions. Unlike adenoma, all serrated lesions are not associated with colorectal cancer. TSA is easier to recognize thanks to its protuberant pine cone shape. While SSA/P is associated with colorectal cancer development, HP has no relationship. The endoscopic views of both SSA/P and HP are very similar, so it is difficult to distinguish both types with image-enhancing endoscopy (IEE) techniques. *Hyperplastic polyps* are the most common non-neoplastic polyps in the colon. According to autopsy data, its prevalence is 20–35% [6, 92]. They are typically located in a rectosigmoid and generally in the form of nodular, polypoid lesions less than 5 mm [54, 129]. Hyperplastic polyps are serrated polyps of normal structure and proliferative properties. They have a normal cellular structure and do not contain dysplasia, but have a characteristic saw-tooth pattern. Its epithelium consists of well-differentiated goblet cells and absorptive cells. They proliferate from the crypt basal [130].

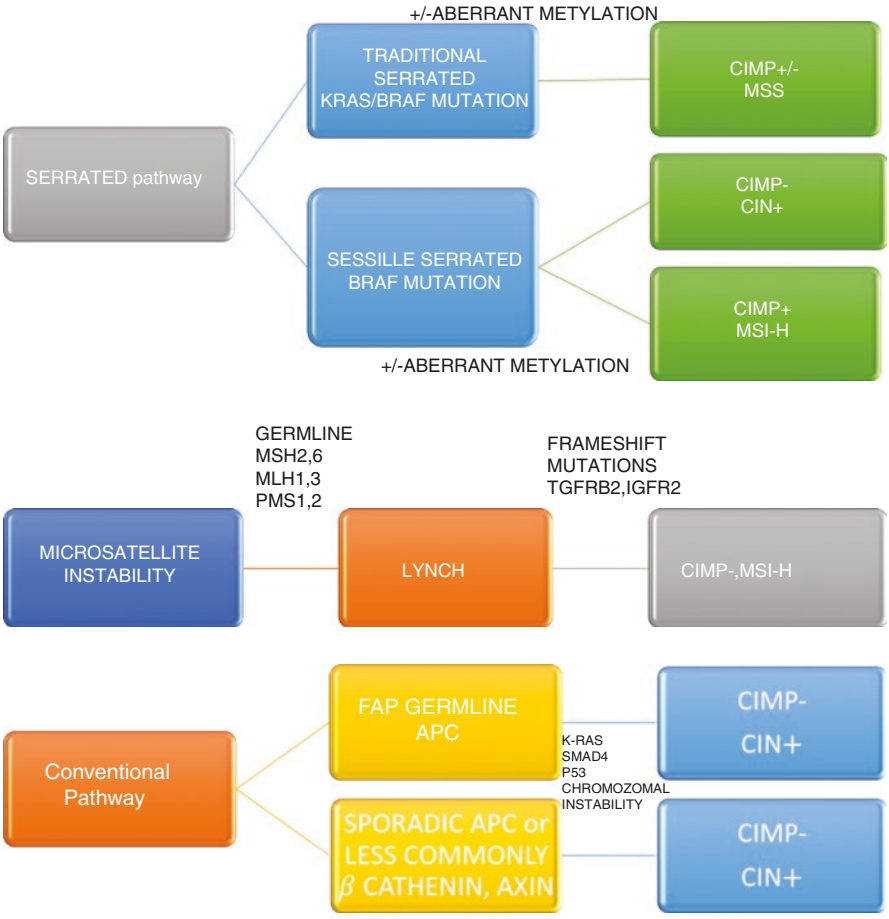
Sessile serrated polyp/adenomas: Typically covered with flat and mucus cap. It has irregular distribution in crypts. Dilatation, serration, and horizontal expansion are observed in the crypt base. There are crypts that tend to herniate into the muscularis mucosa, branched (L or T-shaped), and immature (irregularity in cellular maturation in crypts, thin nuclear enlargement, compression, pseudo-stratification and increased mitotic activity, scattered epithelial cells without goblet cell and mucus at the base of the crypt) [130–132].

- According to WHO, at least three crypts or at least two adjacent crypts must have one or more of the cryptic properties defined above for the diagnosis of serrated polyp/adenoma [131].
- According to the American Gastroenterology Association, only one crypt showing the above-mentioned properties is sufficient for the diagnosis of sessile serrated polyp/adenoma [132].

Genetic pathways of the colon polyps is shown in Table 6.7.

TSA is more similar to conventional adenoma in terms of appearance and behavior. It mostly has a peduncle. It shows adenomatous dysplasia with its crypt structure with branching, budding, and saw image.

Table 6.7 (a–c) Genetic pathway of the colon polyps



While sessile serrated polyps tend to locate in the proximal colon, TSA is mostly located in the distal colon.

Cancer Risk

Although the risk of cancer does not appear to increase in small rectosigmoid located hyperplastic polyps, it is unclear whether small distal hyperplastic polyps are associated with increased risk of proximal neoplasia [3, 133–137].

According to a systematic review involving 18 studies, the risk of proximal advanced or non-advanced neoplasia was found to be 1.3% in the presence of distal hyperplastic polyp [136]. SSA/P often shows dysplasia. The risk of colorectal cancer in proximal SSA is 1 in 17 patients. The prevalence of high-grade dysplasia and cancer in these lesions is 5–16% [128]. In a study of 110 SSAs, the rate of apparent dysplasia was 37%; the rate of high-grade dysplasia and intramucosal carcinoma

focus was found to be 11% [138]. Risk factors for simultaneous advanced adenoma in patients with SSA/P include SSA >10 mm, proximal colon localization, and dysplasia [130, 139, 140].

Management

All serrated polyps should be removed as soon as they are detected. Although hyperplastic polyps do not have a high risk of cancer, TSA and SSA cannot be easily distinguished and they have high risk of invasive carcinoma progression.

Serrated Polyposis Syndrome

Serrated polyposis syndrome consists of multiple serrated polyps in the colon. It was previously called hyperplastic polyposis syndrome.

WHO described the serrated polyposis syndrome in 2010 as follows [141]:

1. At least five histologically defined serrated polyp from proximal to sigmoid colon and at least two must be larger than 10 mm.
2. SPS in the first degree relative of the person with any number of serrated polyps from proximal to sigmoid colon.
3. More than 20 serrated polyps of any size in the entire colon.

*Serrated lesion refers to any combination of hyperplastic polyps and sessile serrated polyps.

The average age of SPS occurrence is 44–62. It shows an equal distribution in both genders. Surgery is recommended when colorectal cancer is identified or polyp number and size do not allow endoscopic follow-up (Table 6.8).

In general, surgical intervention is performed by preserving the rectum and removing the cancerous colon segment or the segment containing large polyps.

Non-neoplastic Polyps

Juvenile Polyps

Juvenile polyps are hamartomatous lesions. They are characterized by lamina propria and dilated cystic glands rather than increased numbers of epithelial cells. They are relatively more common in childhood but also they can be diagnosed at any age.

Table 6.8 Follow-up times for sessile serrated polyps

Serrated lesions	Next colonoscopy (year)
One or two sessile serrated polyps, less than 10 mm	5–10
Less than 10 mm, non-dysplastic, sessile serrated polyp or polyps	5
More than 10 mm sessile serrated polyp or polyps	3
Sessile serrated polyp or if the polyps pathology contains dysplasia	3
Traditional serrated adenoma	3
Serrated polyposis syndrome	1

Juvenile polyps are most common between 1 and 7 ages. They are mostly single, with a peduncle, between 3 mm to 2 cm sized. Isolated juvenile polyps are most common in the rectosigmoid colon, because of this localisation, these polyps can cause lower gastrointestinal bleeding or can prolapse through the rectum which can require polypectomy. Asymptomatic patients do not require treatment. Juvenile polyps are usually solitary and are not associated with an increased colorectal cancer risk [142].

Peutz-Jeghers Polyps

Peutz-Jeghers polyps are hamartomatous lesions which consist of glandular epithelium supported by smooth muscle cells that is contiguous with the muscularis mucosa. These polyps demonstrate a distinctive, arborizing pattern of smooth muscle derived from the underlying muscularis mucosa. They are usually benign but they can grow progressively and may exhibit malign transformation. Patients with PJS are at increased risk of both gastrointestinal (gastric, small bowel, colon, pancreas) and nongastrointestinal cancers including breast cancer [142–144].

Inflammatory Pseudopolyps

Inflammatory pseudopolyps are non-neoplastic polyps that are composed of a mixture of inflamed lamina propria and distorted colonic epithelium. They are the result of the mucosal ulceration and regeneration phases that occur in response to localized or diffuse inflammation (e.g., ulcerative colitis or Crohn disease, amebic colitis, ischemic colitis, dysanterria). They are usually solitaire, large, and may tend to bringing and scattered throughout the involved areas of the colon. Their images can mimic neoplastic polyps but they do not undergo neoplastic transformation. However, they may be associated with surrounding dysplasia in patients with inflammatory bowel disease [143, 144].

Large/giant or grouped pseudopolyps can cause colonic obstruction. Rarely, abdominal pain may also occur. If large pseudopolyps are found in the ileum, they may present with intussusception. Inflammatory pseudopolyps do not require excision unless they cause symptoms (e.g., bleeding, obstruction). Treatment is directed at the underlying cause of inflammation. Cap polyposis is a rare inflammatory pseudopolip, consisting of elonge crypts, mixed inflammatory infiltrate in lamina propria, and a hood covered with fibrinopurulent exude [145].

Mucosal Polyps

It is in the form of blisters consisting of normal mucosa. It is not clinically relevant. They are usually small.

Submucosal Lesions

Colitis cystica profunda: It is rare. It consists of dilated, mucus-filled glands in the submucosa. They can be solitary or multiple. They are usually smaller than 3 cm and are located in the rectum. Dysplasia is not seen.

Pneumatosis cystoides coli: It is characterized by the expansion of the colon or small intestine submucosa with multiple gas-filled cysts and the formation of a

polypoid image. There are air-filled cysts radiologically and pathologically. When the cyst is touched endoscopically with a biopsy forceps or sclerotherapy needle, the diagnosis can be made by the rupture of the cyst.

Other lesions: Benign lymphoid polyps are large or peduncle polyps that can cause bleeding or pain. Malignant lymphoma and chronic lymphocytic leukemia may present as multiple colonic polyps.

Lipomas: Soft, yellowish colored, usually asymptomatic submucosal lesions located incidentally, located near the ileocecal valve, or mostly in the right colon.

Carsinoids, fibromas, norofibromas, leiomyomas, granular cell tumours, hemangiomas, endometriosis are rare submucosal lesions [146].

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Role of Imaging in Colorectal Cancers

7

Dilek Oncel

General Consideration

Colorectal cancer (CRC) is a major health problem. It is the most common gastrointestinal cancer and the third most common cancer in general in most of the countries over the world. In terms of mortality, it is the second most common cause of cancer death for men and women only secondary to lung cancer [1–3].

Risk factors for CRC include dietary, hereditary, and environmental factors. In terms of etiology, colorectal cancer can be divided into two as genetic and non-genetic forms. The sporadic non-genetic form is the most common one with a percentage of 70–80. It is known to be caused by the malignant transformation of the adenomatous polyps. This transformation takes years and often is related to factors like improper diet low in fruit and vegetables and high in red meat and saturated fat, consumption of toxic products like alcohol and tobacco, and also obesity. Sedentary life style is also considered as a risk factor, as well as inflammatory bowel diseases (ulcerative colitis and Crohn's disease). Familial adenomatous polyposis and Lynch syndrome (the hereditary non-polyposis colorectal cancer) are examples of the genetic syndromes with increased risk of CRC [3–5].

The potential risk of developing CRC from colorectal adenomas is related to both size and histology. However, with imaging techniques, no histological distinction can be made between adenomas and hyperplastic polyps. Therefore, size is the most important criterion for estimating the risk of malignancy. Polyps with a size of 10 mm or larger are almost always adenomas and the risk of malignancy is substantial. Intermediatesized polyps (6–9 mm) can be adenomas or hyperplastic polyps. Therefore, there is still a risk of malignancy although it is relatively low. Polyps smaller than 6 mm are mostly hyperplastic with a very low risk of malignant transformation [3–6].

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In recent years, the mortality rate has significantly decreased and 5-year survival has improved due to successful screening and early detection techniques as well as optimization of surgical techniques, new neoadjuvant therapies, and developments in diagnostic imaging modalities [3–8].

As anatomy, lymphatic and vascular drainage are different, the therapeutic options of colon cancer also differ significantly from the rectal cancer. In rectal cancer, an exact locoregional staging is essential, whereas in colon cancer, ruling out a second cancer proximal to a stenosing tumor is more important. For both rectal and colon cancer, ruling out metastatic disease prior to a potentially curative surgical approach is mandatory [7–13].

Techniques Used for Early Detection

Early stages of colorectal cancer are associated with a relatively high 5-year survival rate, whereas late stages, characterized by nodal and distant metastasis, are associated with poor survival, despite the use of intensive and costly chemotherapeutic protocols. Therefore, the main concern for CTC should be directed toward prevention and early diagnosis. As more than 80% of CRC arise from benign lesions such as adenomas, early detection of adenomatous polyps may prevent the development of colorectal cancer and also allow treatment of cancer in its early phase [3, 14, 15].

Screening methods are classified into biological assays (for the detection of occult stool blood) and colorectal imaging techniques. The detection of occult blood in the stool is most widely used because of its accessibility, low-cost, and proven effectiveness in reducing the CRC incidence and mortality. The genetic syndromes with increased risk of CRC can be diagnosed with different genetic tests [3, 14–17].

Although fecal occult blood test screening has been shown to reduce colorectal cancer mortality, screening tests that delineate colorectal cancer directly, including both endoscopic and radiologic methods, would be expected to be more sensitive than the fecal test to detect early stage cancers, which may further help to decrease disease-specific mortality [15].

In patients suspected of having colon or rectal cancer, after a detailed clinical work-up such as physical examination, family history, measurement of carcinoembryonic antigen (CEA) levels, the first examination method to be used is optical colonoscopy (OC). In cases of incomplete colonoscopy, mainly due to failure to pass the stenotic segment where the lesion could not be reached by OC, computed tomography (CT) colonography (CTC) can be performed. Barium enema is considered as the last method of choice, if neither OC nor CTC is available to locate the tumor. Barium enema is not recommended for standard screening protocols [3, 14, 15, 17].

Considering the imaging tests, optical colonoscopy is the method of choice as a screening test. It can be repeated at different time intervals depending on the expected risk of CTC. Optical colonoscopy is the gold-standard method in the early detection of CRC, not only for its high diagnostic performance but also for the

possibility of biopsy or resection in the same session. Therefore, it allows both the definitive pathologic diagnosis and the therapeutic polypectomy. However, patients with tumoral obstruction, older patients, and patients with other comorbidities are more likely to have an incomplete or difficult OC [18].

If OC is not available, other imaging methods to be used are the double-contrast colonography (Barium enema) and the CT virtual colonoscopy (CT colonography). CTC is recommended to replace the Barium enema because of a lower discomfort and a better tolerance. Also CTC is more easily performed than barium enema [3, 17, 19].

CTC is a well-validated technique for the early detection of polyps with a high sensitivity comparable to OC and definitely higher than barium enema. CTC is well tolerated by patients, safe, and also cost effective and is therefore suitable for screening purposes. There are studies that are showing an increased sensitivity (96%) of the CT virtual colonoscopy, similar to the optical colonoscopy, but the values vary depending on the lesion size. Although CTC is the radiological method of choice for the detection of early colorectal neoplasia, it is not recommended as a primary screening tool. However, it can be still used on an individual basis for screening. Concerning it as a screening test for cancer, radiation exposure is a drawback with a potential risk of cancer induction. However, in this context benefit can be considered as outweighing the potential harm [19–21].

In the joint statement of European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) [22], there are basically five main recommendations:

1. ESGE/ESGAR recommend computed tomographic colonography (CTC) as the radiological examination of choice for the diagnosis of colorectal neoplasia. ESGE/ESGAR do not recommend barium enema in this setting.
2. ESGE/ESGAR recommend CTC, preferably the same or next day, if colonoscopy is incomplete. Delay of CTC should be considered following endoscopic resection. In the case of obstructing colorectal cancer, preoperative contrast-enhanced CTC may also allow location or staging of malignant lesions.
3. When endoscopy is contraindicated or not possible, ESGE/ESGAR recommend CTC as an acceptable and equally sensitive alternative for patients with symptoms suggestive of colorectal cancer.
4. ESGE/ESGAR recommend referral for endoscopic polypectomy in patients with at least one polyp 6 mm in diameter detected at CTC. CTC surveillance may be clinically considered if patients do not undergo polypectomy.
5. ESGE/ESGAR do not recommend CTC as a primary test for population screening or in individuals with a positive first-degree family history of colorectal cancer (CRC). However, it may be proposed as a CRC screening test on an individual basis providing the person is adequately informed about test characteristics, benefits, and risks.

Magnetic resonance (MR) colonography is a similar technique with a major advantage of no ionizing radiation which is a potential limitation of screening CT

colonography. But MR colonography has inferior performance when compared to CTC; therefore, it is not considered as the primary radiological technique. At this moment, MR colonography can be used as an alternative to CT colonography when the latter is contraindicated [23, 24].

Criteria to Be Included in the Screening Programs

With effective screening programs, both the incidence and mortality of CRC can be reduced significantly.

The population at an average risk of developing CRC are subjects older than 50 years old, without other associated risk factors. They can be followed up annually for the detection of occult stool blood and if needed with further imaging techniques.

The population with increased risk of developing CRC are subjects with personal or familial history of CRC or adenomatous polyps, those with genetic syndromes, or patients with chronic inflammatory diseases. Each of them can benefit from a customized screening program. The screening program must begin at the age of 40, and the optical colonoscopy is recommended as a screening method.

Screening for colorectal cancer is not recommended in adults over the age of 75 years or in adults with a life expectancy of less than 10 years [3, 14].

Imaging in Colorectal Cancer

Most of the times colon tumors are identified through colonoscopy, and imaging helps staging these tumors. If the tumor is located in the colon, the initial staging will be done through thoraco-abdomino-pelvic CT. In most cases, this will be sufficient for an accurate staging and the images will be later used as reference for the post-treatment examinations. When the detected lesions are considered as being indeterminate, with non-specific appearance, it will be necessary to complete with other imaging examinations or biopsy. The imaging techniques that can be used in this situation are magnetic resonance imaging (MRI) or positron emission tomography-computed tomography (PET-CT) [4–6, 25, 26].

There are situations in which colon tumor formations are detected incidentally in the course of imaging explorations performed for other purposes or for non-specific symptoms. In these cases, colonoscopy should be done for the confirmation of the existence of a tumoral process. The staging of the tumor will be made in the same manner as in the case of the tumors diagnosed through colonoscopy [25–27].

The rectal tumors will benefit from the high-resolution pelvic MRI or transrectal ultrasound for their initial local staging. For the detection of distant metastases, PET/CT can also be used along with CT and MR [4–6, 28, 29].

Once the diagnosis of colon or rectal cancer is ascertained, staging should be performed using the latest version of the American Joint Committee on Cancer (AJCC) tumor, node, and metastasis (TNM) classification [30] (Table 7.1).

Table 7.1 TNM staging of colon and rectal cancer

T stage
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor invades the submucosa
T2 Tumor invades the muscularis propria
T3 Tumor invades into pericolorectal tissues:
T3a Invasion ≤1 mm
T3b Invasion 1–5 mm
T3c Invasion ≥6–15 mm
T3d Invasion ≥15 mm
T4a Tumor penetrates the visceral peritoneum
T4b Tumor invades into adjacent organs
N stage
N0 No evidence of lymph node metastases
N1a Metastasis in one regional lymph node
N1b Metastases in 2–3 regional lymph nodes
N1c Tumor deposits in the subserosa or pericolic/perirectal tissues (not to be differentiated by imaging)
N2a Metastases in 4–6 regional lymph nodes
N2b Metastases in 7 or more regional lymph nodes
M stage
M0 No distant metastases
M1a Metastases confined to one organ
M1b Metastases in more than one organ
M1c Metastases to the peritoneum with or without other organ involvement

Therapeutic options of colon cancer differ significantly from rectal cancer. The treatment strategies differ depending on the staging of the disease and also for local/primary tumor management and management of distant metastatic disease.

The local treatment of *colon cancer* relies primarily on the location of the tumor. The standard surgical approach is radical resection. Usually the involved part of the colon is resected (right or left hemicolectomy) together with the removal of the associated mesentery and regional lymph nodes. If the pathologic specimen reveals lymph node positivity and extramural lymphovascular invasion, adjuvant chemotherapy is indicated. As neoadjuvant therapy has not been shown to significantly improve survival over surgery alone, the role of preoperative imaging for T and N staging is also questionable. Preoperative imaging of colon cancer is mostly beneficial and used for identifying distant metastases [31–33].

Surgical options for *rectal carcinoma* are more variable and depend on the relationship of tumor to the sphincter and circumferential resection margins and peritoneal reflection. In rectal cancer accurate preoperative staging is essential because undetected local mesorectal nodes may lead to high recurrence rates. Also, neoadjuvant chemo-radiotherapy in addition to primary resection has been shown to decrease local recurrence and improve survival in patients with high-risk rectal cancer which are determined radiologically before surgery. Therefore, preoperative imaging for local staging of rectal cancer is important for both determining the need for neoadjuvant therapy and the surgical strategy [31–33].

Metastatic Spread

In 25% of patients with colonic cancer and in 18% of patients with rectal cancer, metastases are present at the time of the first diagnosis. For initial staging of CRC, National Comprehensive Cancer Network guidelines suggest the use of chest/abdomen/pelvis CT or MRI. PET/CT is reserved for surveillance or problem solving [32–34].

Identifying nodal disease is still a diagnostic problem for the radiologist. Although lymph node size is not accurate for defining lymph node metastases, nodes of >8 mm are suspicious for nodal involvement on CT, MRI, and endorectal ultrasonography (ERUS). However, as size is not a good predictor for malignancy, morphological criteria should also be used for defining lymph nodes involvement. Morphological features such as the presence of a round shape, heterogeneity within the lymph node, and irregular borders due to capsular penetration by malignancy are far more reliable criteria [35].

MRI is the preferred examination for nodal staging in rectal cancers. PET/CT may provide additional information and could increase the accuracy of lymph node involvement significantly for local and distant lymph nodes. However, in the case of small lymph node metastases, PET also may not allow reliable results due to limited spatial resolution [35–37].

Concerning distant metastasis, early detection of liver metastases is of vital importance to control the disease because if the tumor spread is limited, cure can be achieved with appropriate resection. Ultrasound, CT, MRI, and PET/CT are all used to identify hepatic metastases. The goals of imaging are to identify the location of all metastatic tumours, determine the feasibility of local resection, exclude the presence of extrahepatic tumor sites, and evaluate the possibility of adjuvant therapy [38].

The sensitivity of ultrasound to detect liver metastases is low and variable due to limited contrast between liver lesions and the liver parenchyma. CT has a better diagnostic performance compared to US in the detection of CRC liver metastases. The effectiveness of CT is considered to be equal to MRI for the detection of metastasis over 1 cm. However, if the lesion is smaller the 1 cm, the sensitivity of CT is much lower and this is particularly important if a liver resection is planned. Also, liver steatosis which is a common a side effect of neoadjuvant chemotherapy may further decrease the sensitivity of CT especially for small metastasis, and in these circumstances, the performance of MRI is far better. Therefore, in all patients that are potential candidates for liver resection, MRI with hepatocyte-specific contrast agents and diffusion-weighted imaging (DWI) should be performed. Recently, DWI and the use of hepatobiliary contrast agents have further improved the sensitivity of MRI. With hepatobiliary contrast agents, the uptake of contrast within the hepatocytes results in peak parenchymal enhancement approximately 10–20 min after the administration, and this is referred to as the hepatobiliary phase. Lesions like metastases which do not contain hepatocytes are strongly hypointense compared to the surrounding enhanced parenchyma in this phase. MRI is considered superior to CT

and PET/CT for the detection and characterization of small liver lesions, particularly with the use of DWI-MR and hepatocyte-specific contrast agents [38–40].

If there is extensive metastatic disease, such as peritoneal disease, bone metastases, etc., a CT scan is sufficient to follow for treatment response on palliative chemotherapy. The use of PET/CT is still controversial in metastatic CRC [4–6].

Although CT of the chest is useful to assess for lung metastases and CT detects more pulmonary lesions compared to chest X-ray, a large number of these lesions are non-specific and differentiation of metastases from benign incidental lesions may not be possible. Therefore, for CRC patients without liver and lymph node metastasis on abdominal and pelvic CT, preoperative staging chest CT may not be beneficial for deciding the presence of metastatic disease [41, 42].

Restaging: Therapeutic Response Evaluation

Patients after primary tumor resection or chemoradiation therapy (CRT) for locally advanced CRC require a regular post-treatment evaluation. Within the first 5 years after curative therapy, there is an increased risk for a locoregional relapse, distant metastases, and metachronous secondary tumors. The introduction of preoperative adjuvant CRT has led to a reduction in local recurrence rates and has become standard of care for patients with locally advanced rectal cancer [1, 5, 10].

For restaging after CRT, neither MRI nor transrectal ultrasound or PET is sufficiently accurate for identifying the true complete response. T2-weighted MRI has been standardly used for local restaging and DWI MRI may be useful for the response evaluation after chemoradiation therapy. DWI has shown to be feasible as an early marker of treatment response because cell death and vascular alterations typically occur before size changes. It also has been proved that DWI in addition to standard MRI significantly improves the performance of the study to evaluate therapy response for local tumor. However nodal staging remained challenging. High b-value DWI is sensitive for detecting the location of lymph nodes, but characterization of nodes is not reliable. A transient decrease in the ADC (apparent diffusion coefficient) may occur early in treatment related to cellular swelling, reduction in the blood flow, or extravascular extracellular space; but it is not consistently seen; and increases in ADC value with therapy response may also occur within 3–7 days. Therefore the utilization of ADC values in the CRC evaluation needs further standardization and validation [43–46].

Follow-Up of Colorectal Cancer

Follow-up of patients plays a pivotal role in improving the survival rates. Appropriate follow-up protocols not only help to detect the primary tumor recurrences (local or distant) but also the development of a metachronous tumor. Also, late complications and outcome of the therapy can be monitored. The site of recurrence gives a strong clue for prognosis. If the patient has mesenteric/nodal and/or multiple sites of local

recurrence, the prognosis is worse. However, perianastomotic recurrences can be re-resected completely and much better outcomes with long-term survival can be achieved [4, 28, 47, 48].

In CRC, almost 80% of recurrences were found in the first 3 years after surgical resection of the primary tumor. As patients with a history of CRC have an increased risk of developing second cancers, particularly in the first 2 years following resection, surveillance colonoscopy should be performed once in the first 2 years to identify and remove metachronous polyps. Post-treatment PET/CT scan is not recommended for routine use, neither for surveillance of patients with resected early-stage CRC nor to detect metastatic disease in the absence of other evidence of such disease [4, 5, 11, 16].

The imaging monitoring of the patients treated for colonic tumors is made through computerized tomography every 6 months. For small liver metastases, MRI can be used. To evaluate the efficiency of the chemotherapy in non-operated patients with tumors in late stages, thoraco-abdomino-pelvic CT is recommended every 3 months [16].

The patients with operated rectal tumors, especially those who have received neoadjuvant radiotherapy, undergo the pelvic MRI periodically, complementary to the thoraco-abdomino-pelvic computed tomography. This is because MRI is more accurate, compared with the computed tomography, in the differentiation of the tumoral relapses in the pelvic area from the post-irradiation fibrosis [29, 37, 49].

Although there is a limited data about the correct interval and frequency of imaging studies in the follow-up of colon and rectal cancer, CT of the chest and abdomen, and pelvic MRI in patients with high risk for local recurrence is advised 3–6 monthly in the first 2–3 years. This interval increases to 6–12 monthly, up until 5 years. After 5 years, patients are further followed up on an individual basis [16, 28].

Imaging Modalities

Ultrasonography

The ultrasound examination of the digestive tract is challenging because of the high air content of the digestive tract and intestinal peristalsis leading to severe sonographic artifacts. Therefore, although highly depending on the experience and patience of the examiner, the ultrasound examination of the digestive tract is usually done for the exploration of parenchymal organs [4, 5, 15, 17, 50].

However, on many occasions ultrasonography is the first method of choice for patients with abdominal pain, bowel movements impairments, or other symptoms in the abdominal area [8]. It is a highly accessible method with low-cost and non-irradiating, repeatable, and comfortable for the patients Also, in many cases, it provides very useful information, allowing the exclusion or diagnosis of other diseases with similar symptoms to the CRC. Therefore the examining physician must be

familiar with the ultrasound appearance of colorectal cancer which is usually a parietal hypoechoic thickening of the bowel with the loss of normal stratification. The tumor formation can be eccentric or circumferential, and the lumen can be stenosed with an increased stiffness. If the pericolic fat is invaded by tumor, it reveals an "infiltrated" hyperechogenic appearance. Peritumoral adenopathies can also be detected as hypoechogenic and round [5, 17, 50].

Colorectal cancers may also lead to liver metastases. Computed tomography is the method of choice for the staging of the colon cancer. However, in clinical routine ultrasound is still the first imaging technique that is currently used and therefore has also an important role. Most of the hepatic metastases are seen as hypoechoic nodules in ultrasound but they can also be iso- or hypoechoic. Usually there is a hypoechoic halo surrounding the lesion. This hypoechoic halo is a strong predictor for a focal liver lesion to be malignant [5, 17, 50].

The assessment of the retroperitoneum should not be missed during abdominal ultrasound in patients with colon cancer. Metastases can be located between inferior vena cava and aorta, which is a difficult localization to examine due to gas-distended bowel loops and also in obese patients. When ascites is present in a patient with colon cancer, peritoneal carcinamatosis is the first thing to be considered. In this case, interhepatophrenic area, peritoneal recesses, and rectovesical space should be examined for the peritoneal nodules [5, 6, 17].

Transrectal Ultrasonography (Endorectal Ultrasound)

This is a staging procedure which is widely used in rectal cancers. It helps the visualization of the five parietal layers and the surrounding organs in the pelvis. A transducer with the frequency between 5 and 10 MHz is preferred. Doppler ultrasonography, contrast-enhanced ultrasonography (CEUS), and sonoelastography may provide additional information about the tumor [51–53].

Tumor extension to the rectal wall and adjacent organs can be visualized with transrectal ultrasound. In the case of infiltrative tumors, there is either focal or circumferential thickening of the wall along with the loss of parietal stratification. Proliferative tumors are seen as hypoechoic masses with endoluminal protrusion. The disorganized vasculature of tumors can be assessed with Doppler examination and they are found to be rigid at sonoelastography [51–53].

Because of the reduced field of view, only local staging (T and N) can be done with transrectal ultrasound. The transrectal ultrasound allows differentiation of rectal walls and the diagnostic performance is higher in early stages owing to the high spatial resolution (T1 and T2 tumors). However, for advanced stages, MRI provides better visualization of the mesorectal fascia, the peritoneum, and the surrounding organs and is the method of choice [51–53].

Because of the reduced field of view, the assessment of the mesorectal fascia and lymph nodes are not feasible with the transrectal ultrasound. Tumoral stenosis is another problem which may not allow the transducer to pass and the tumor

cannot be properly assessed. Other limitations are related to post-surgery and post-radiation changes of the rectal wall. Differentiating the post-surgery/radiation appearance from a possible tumor residue, or a relapse, and the differentiation of stage T2 from stage T3 can be difficult because of local inflammatory or fibrotic changes [51–53].

Computed Tomography

Abdominal CT and CT virtual colonoscopy can be used in detection, characterization, and staging of colon tumors. With computed tomography both abdominal and thoracic cavities can be assessed along with the lungs and bones. The site of the tumor, presence of lymphadenopathy, ascites, peritoneal implants, and involvement of adjacent organs can all be delineated. Therefore, for staging of colon cancer, the preferred imaging technique is computed tomography [4, 6, 27, 54–56].

For CT examination, luminal distension, with oral contrast, water or air, and intravenous administration of the iodinated contrast agents are recommended. IV contrast should be used for CT and can be performed as a single post-contrast portal venous phase of the chest, abdomen, and pelvis. However, a multiphase protocol of the liver consisting of arterial, portal venous, and delayed phases may improve diagnostic characterization of focal liver lesions. Thin slices with coronal and sagittal reformats may also improve the staging accuracy of CT [4, 6, 27, 54, 55].

A typical CT appearance of a colorectal tumor is a polypoid mass (Fig. 7.1). Tumor can also be seen as an irregular focal or circumferential parietal thickening, associated with endoluminal narrowing or colon stenosis. The local extracolonic invasion is assessed by the infiltration of the pericolonic fat (Fig. 7.2). After the

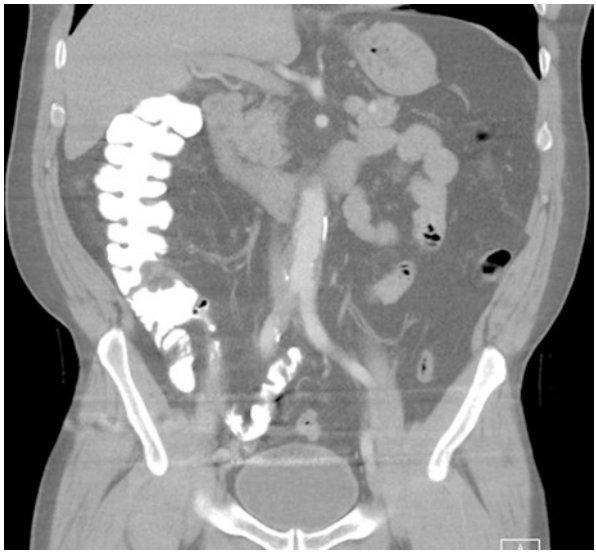

Fig. 7.1 A 62-year-old female with biopsy-proven tubulovillous adenoma of the cecum. Iv and oral contrast-enhanced CT image with coronal reformation showing a polypoid mass arising from the medial wall of the cecum. The wall is regular and pericolonic fat is clear with no stranding

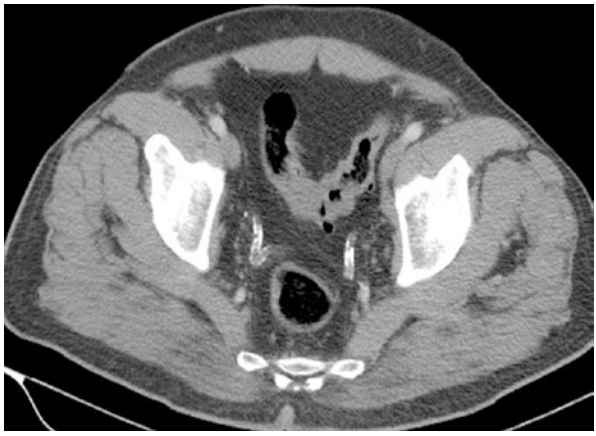

Fig. 7.2 A 48-year-old male with biopsy-proven adenocarcinoma of the sigmoid colon. Axial iv contrast-enhanced CT image demonstrates circumferential wall thickening of the sigmoid colon, with minimal stranding in the pericolonic fat. The local T staging of the tumor is relevant to T3a with less than 1 mm pericolonic invasion

administration of the iodinated contrast agent, both the adenomatous polyps and the adenocarcinomas show enhancement. In the case of a tumoral occlusion, the colon appears dilated proximal to the stenosis and the transition zone is easily viewed using multiplanar reconstructions. The tumoral perforation is more common in the cecum area, and it is detected by the presence of pneumoperitoneum and the infiltration of pericolonic fat [4, 6, 27, 54, 55].

Local staging (T staging) of the CRC with CT is difficult because of the impossibility of differentiating its early stages. Loss of fatty cleavage plane between the colon and the surrounding structures (retroperitoneum, anterior abdominal wall, liver, spleen, pancreas, or stomach) suggests tumoral invasion and tumor is graded as stage T4 [27, 30, 54, 55] (Fig. 7.3).

CT provides tumoral staging by identifying the local invasion, the lymph nodes, and parenchymal metastases, mainly in the liver, but also peritoneal, in the lungs and bones. The size of the lymph nodes is not a good indicator of malignancy because even small lymph nodes may contain tumor foci. However, the presence of an irregular border, a central necrosis, calcifications, or a tendency to conglomerate may be suggestive of tumoral lymph node invasion [27, 54, 55].

The most commonly affected organ for distant metastasis is the liver. Liver metastases >1 cm can be identified with high accuracy with CT. The CT appearance of CRC liver metastases is hypodense and hypovascular liver masses compared with the liver parenchyma. Sometimes the hepatic metastases reveal the peripheral ring enhancement during the arterial phase. They may also have a cystic or calcified character in the case of mucinous colon cancer. CT examination cannot differentiate small liver metastases from benign focal liver lesions. The association of the hepatic steatosis (often seen after chemotherapy) also hinders the diagnosis of liver metastases. In general, the abdominal CT with intravenous iodinated contrast, during portal phase, represents the imaging technique of choice for the detection of liver metastases, with high diagnostic accuracy (95%) However, small liver metastases

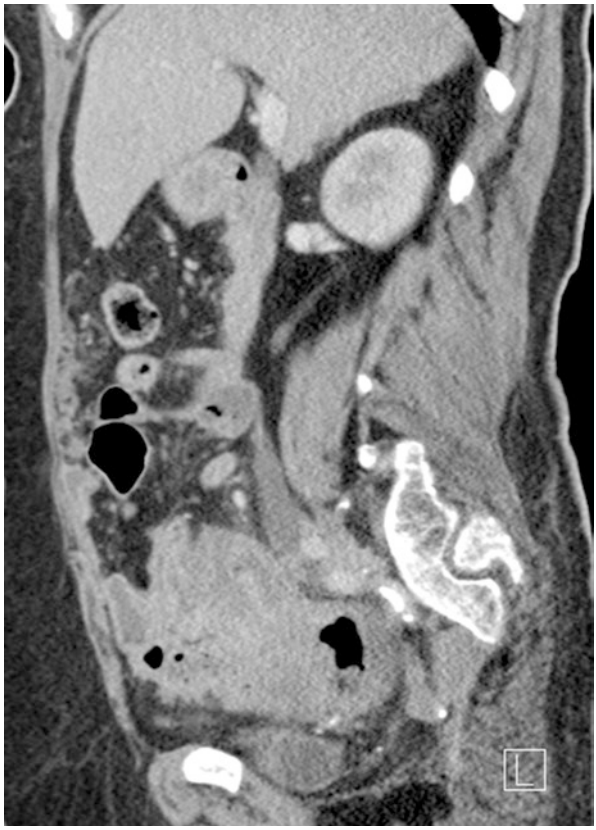

Fig. 7.3 A 44-year-old female with biopsy-proven adenocarcinoma of the cecum. Iv contrast-enhanced CT image with sagittal reformation demonstrates a bulky mass in the cecum with diffuse invasion to pericecal fat and small intestine. Also along the anterior abdominal wall, multiple peritoneal deposits can be seen denoting peritoneal dissemination. There are also multiple regional and distant metastatic lymph nodes (not shown in the image). TNM staging of the tumor corresponds to T4bN2a M1c

and indeterminate focal lesions may need further examination with MRI [32, 34, 38].

Lung metastases can also be identified with high accuracy (Fig. 7.4). The chest CT can detect lung metastases that have a unique nodular appearance, sometimes cavitary or calcified. Lymphangitic carcinomatosis associated with pleural effusion is another form of pulmonary metastasis [34, 42].

Peritoneal dissemination is identifiable by the presence of peritoneal thickening and tumoral deposits in the omentum, associated with intra-abdominal fluid collections. Small peritoneal deposits may require an abdominal MRI or PET-CT [34].

Bone metastases are rare, and they have a lytic or mixed appearance (lytic and sclerotic). They can feasibly be detected with CT [34].

Brain metastases from colorectal cancer do not have a specific CT appearance by means of primary tumor. They are seen as hypodense focal masses with surrounding edema and usually show peripheral ring-like enhancement. Small metastasis are better seen in contrast-enhanced brain MRI [34] (Fig. 7.5).

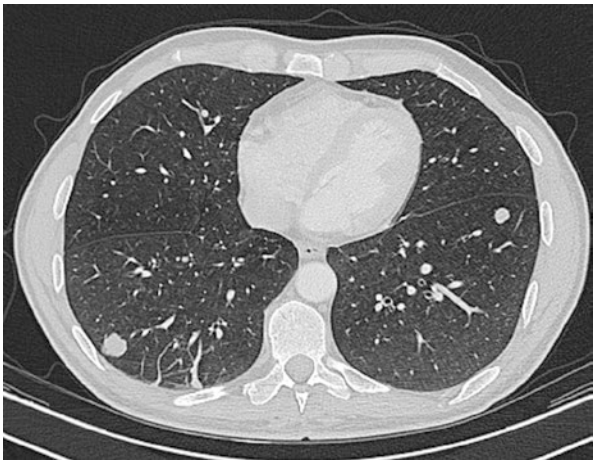

Fig. 7.4 A 57-year-old male with biopsy-proven adenocarcinoma of the rectum. Axial CT image of the lung demonstrates multiple pulmonary nodular lesions in right and left lower lobes. The masses are round with distinct margins with slight lobulation but no spiculations. No other distant metastases are detected. The primary rectal tumor was staged as T3c but the lung metastases correspond to M1a and the patient undergoes systemic chemotherapy instead of neoadjuvant chemoradiotherapy

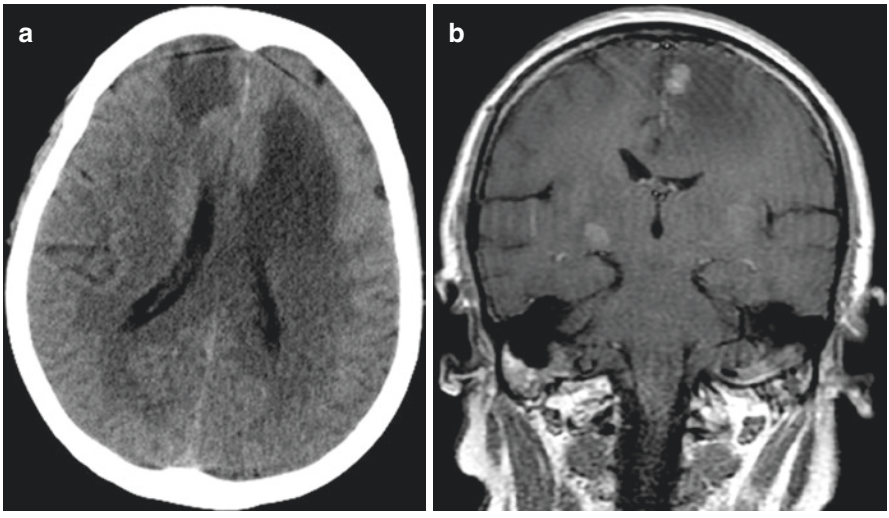

Fig. 7.5 A 47-year-old male with biopsy-proven adenocarcinoma of the rectum. (**a**) Axial non-contrast CT image of the brain demonstrates hypodensities in bilateral frontal lobes corresponding to substantial edema. (**b**) Post-contrast T1W coronal MR image demonstrates multiple metastatic masses with surrounding edema and nodular enhancement. Although the patterns are non-specific, the multiplicity of lesions together with subcortical locations and substantial perilesional edema is convenient with multiple brain metastases

CT Colonography (CTC)

Standard abdominal CT does not have an optimal performance to detect small intracolonic lesions. CTC may be regarded as a potential alternative to endoscopy. This method is applied in patients with known CRC and incomplete OC, for both complete assessment of the colon and for oncological staging [18–22].

CTC is a minimally invasive imaging technique with high values of sensitivity for the detection of polyps with sizes over 10 mm (95%). Virtual colonoscopy, CT colonoscopy, or more technically correct CT colonography are all interchangeably used for defining the technique. CTC is useful in elderly subjects with comorbidities, in case of an incomplete optical colonoscopy. Another indication is the evaluation of the entire colon for the exclusion of a synchronous cancer. It is necessary to prepare the colon 24 h before the examination [19–21, 56].

CTC provides high-intrinsic-contrast between the air contained in the colonic lumen and the large bowel walls based on the X-ray attenuation. If CT colonoscopy is used for screening purposes, low-radiation-dose CT acquisition protocols are preferred. But if CT colonoscopy is a part of the CT examination aiming to cover all abdominal organs, regular dose CT protocols should be used [18, 21, 57, 58].

Luminal distension by air or by carbon dioxide, through a rectal tube, is also crucial in performing a virtual colonoscopy. For adequate colonic distention, air or carbon dioxide is usually given with a thin rectal catheter prior to CT colonoscopy. 1–1.5 L of air or 3–4 L of carbon dioxide is usually sufficient. Despite the larger volumes, carbon dioxide is more comfortable for the patient, as it is gradually absorbed by the colonic walls. No sedation or IV medications were administered as part of the CTC examination [18, 21, 57–60].

The CT acquisition is acquired in both supine and prone positions. This is to optimize the distention of the various colonic segments and to distinguish polyps from fluid or from residual fecal deposits. Colonic distention is also favored by parenteral administration of spasmolytic agents, such as glucagon or hyoscine-*N*-butyl bromide, which inhibit peristalsis. By administering positive contrast material orally like barium or iodine, fecal and fluid tagging can be performed, helping to distinguish fecal/fluid residues from polyps. Dedicated software can be used for removing the tagged residual fluid and accurate quantification of polyp volume can be done to be used in follow-up studies [18, 21, 57–60].

The interpretation is done by analyzing the 2D and 3D images, along with virtual endoluminal navigation. 2D and 3D reconstructions of the dataset are performed, allowing for standard interpretation of the abdominal CT scan as well as endoluminal "fly through" images, namely, virtual colonoscopy. There is also software (computer-aided detection—CAD) that automatically detects the lesions in the colon. Lesion characterization and classification is possible using the reporting system according to the model "CT Colonography Reporting and Data System (C-RADS)." This system allows the location, the morphological (sessile, flat, or pedicle tumor), and dimensional analysis of the detected lesion. C0 suggests an inadequate examination and C1 represents normal appearance of the colon. C2 lesions are indeterminate and refer to identification of less than three polyps with

the diameter between 6 and 9 mm. C3 lesions denote either a polyp over 10 mm or more than three polyps ranging in size from 6 to 9 mm. C4 lesions describe the presence of a colonic tumor mass, with luminal narrowing or the invasion of adjacent organs [18, 21, 57–60].

The main disadvantages of CTC are irradiation and the impossibility to perform biopsy or to treat the detected lesions. Also image interpretation greatly depends on the examiner and shows substantial variability because of different levels of experience [21, 59, 60].

Several studies have shown that the sensitivity for CTC to detect colon cancer is comparable to OC. For the detection of adenomatous polyps ≥10 mm, the sensitivity is also considered to be equal. For the detection of adenomatous polyps 6–10 mm, the sensitivity is also considered to be equal or comparable. However, for lesions smaller than 6 mm, OC reveals better results when compared to CT. Suboptimal examination technique and interpretative errors can impair the performance of CTC. [61, 62].

Preoperative visualization of the entire colon and rectum is needed for the identification of synchronous colorectal neoplasia. CTC is recommended as the method of choice in patients with incomplete colonoscopy or with contraindications to colonoscopy. It is an effective and safe diagnostic option to complete colorectal visualization, if an obstructing CRC prevents complete colonoscopic assessment. CTC may further allow accurate segmental tumor location [56, 58].

An alternative method to CTC can be MRI colonography. It has no risk of radiation exposure but no sufficient data is available to recommend this method as a screening modality [23, 24].

Magnetic Resonance Imaging

The preferred imaging technique for the staging of colon tumors is computed tomography. However, although rare, in certain situations abdominal MRI is used for staging an initial colon cancer or a colon tumor may be incidentally detected in MRI scans of the abdomen for other purposes. The MRI appearance of the colon tumor is non-specific. Generally, there is a thickening of the colonic wall, with the loss of stratification and a slight hypersignal on T2 sequence with fat suppression. The pericolic fat infiltration and the presence of perilesional adenopathies are important additional signs [63].

For the evaluation of the colon, MR colonography can be considered as a different imaging modality. MR colonography is similar to CT colonography in many aspects. Bowel preparation is similar to that for CT colonography. Dual positioning, both prone and supine, is recommended. As with CT colonography, sedation and analgesia are unnecessary but adequate colonic distention is essential. There are two main approaches to MR colonography: bright-lumen and dark-lumen techniques. Bright-lumen MR colonography involves the administration of enema containing gadolinium chelate, whereas the dark-lumen approach involves the administration of water, carbon dioxide, or room air [23, 24, 63].

With similar bowel preparation and colon distension, MR colonography may be comparable to CT colonography and colonoscopy. Advances in MR technology over the last decade allow reduced acquisition times and reduced motion artifacts (peristalsis and respiration), resulting in MR colonography to be much more on the stage. Compared to CT, MR colonography has the advantages of high soft tissue contrast and no ionizing radiation. It is also noninvasive like CT colonography and provides the similar advantage of extracolonic assessment. On the other hand, acquisition methods show a wide range of variation among centers, the costs are higher, and availability is limited. Because of these factors, the use of MR colonography remains questionable [23, 24, 63].

The primary diagnosis of rectal cancer is often possible with rectoscopy following a digital rectal examination. For defining the treatment strategy, the accurate diagnosis of local tumor location, T stage of the tumor, and tumor extension such as mesorectal fascial involvement and extramural or venous invasion are crucial. The tumor node metastasis classification of the American Joint Committee on Cancer is the internationally accepted standard for the staging [30].

The modality of choice for locoregional staging in rectal cancer is MRI. Transrectal US can also be helpful in specific cases. Similar to colon cancer, all patients should receive a full OC to rule out second colon cancers and a CT of the abdomen and thorax, in order to detect or rule out metastatic disease. Similarly, there is no indication for the routine use of PET/CT in the primary staging of rectal cancer [11, 12, 37].

MRI is the recommended modality for initial staging due to its high accuracy for the definition of localization, determining the total extension and the relationship of the tumor to the peritoneal reflection. MRI is also accurate in measuring the distance between the anorectal junction and the distal part of the tumor and for determining the length of the tumor. The relation of the tumor to mesorectal fascia should also be noted on primary staging MRI [36, 37] (Fig. 7.6).

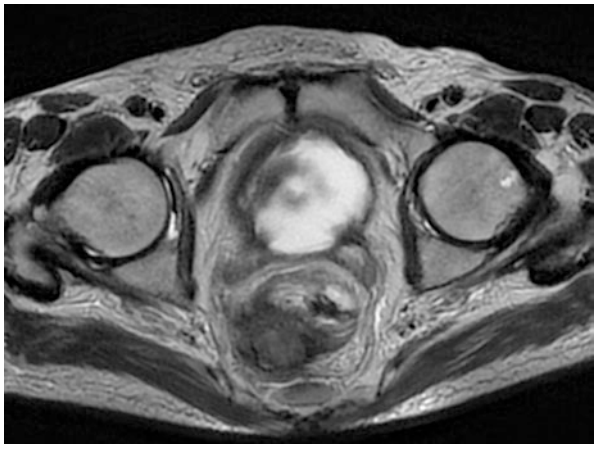

Fig. 7.6 A 69-year-old male patient with adenocarcinoma of the rectum. Axial T2-weighted MRI image showing a T3c tumor that invades the mesorectal fascia posteriorly at the 7 o'clock position. This patient is of high risk for local recurrence and suitable for neoadjuvant chemoradiotherapy

Most staging failures with MRI occur in the differentiation of T2 stage and borderline T3 stage, and overstaging is often caused by desmoplastic reactions. It is difficult to differentiate the spiculation in the perirectal fat caused by fibrosis alone (stage pT2) from spiculation caused by fibrosis that contains tumor cells in stage pT3d. Therefore accurate staging may be difficult in this concern [36, 37].

Endorectal ultrasound is the most accurate method to perform T staging in early T1 and T2 rectal tumors. Endorectal ultrasound is an established modality for the evaluation of the integrity of the rectal wall layers. Especially to identify early T1 tumors of 1–3 mm in size, EUS is the sole method as MRI's local resolution is too low to allow this differentiation. Also, the accuracy to differentiate between T1 and T2 tumors in MRI is not high enough. Therefore, the role of MRI to stage very early tumors is limited. The main limitation for EUS, especially for high-located and stenosing tumors, is the the limited field of view. Also with EUS, complete visualization of the mesorectal fascia (MRF) and detection of pathological lymph nodes outside the mesorectum are usually not possible [52].

According to the 2016 ESGAR guidelines for imaging rectal cancer, MRI should be performed in all patients with rectal cancer. MR imaging should be performed with a scanner of at least 1.5 T field strength using an external phased-array coil. The use of an endorectal coil is no longer recommended. Using spasmolytics or cleansing enema needed prior to the examination is controversial. The MRI protocol should include high-resolution T2-weighted sequences performed in three planes. The slice thickness should be at least 3 mm. Diffusion-weighted sequences are especially required in restaging of rectal cancer after chemoradiotherapy (CRT) because it can differentiate primary rectal cancer or remnant tumor after CRT. There is no general consensus about the use of IV contrast agents [36, 37].

On the T2W sequences, a rectal tumor appears slightly hyperintense compared to muscles and hypointense compared to perirectal fat. Fat suppression is not

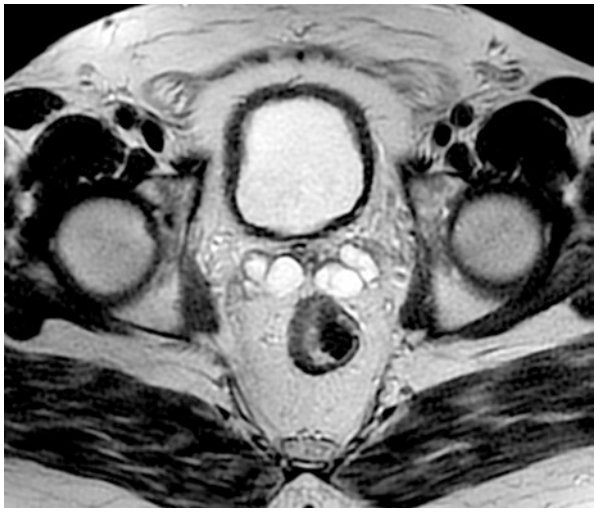

Fig. 7.7 A 57-year-old male patient with biopsy-proven adenocarcinoma of the rectum

recommended because of the existing contrast between the tumor and the perirectal fat. In tumoral stages T1 and T2, tumor growth is limited to the rectal wall. In tumoral stage T1, the tumoral growth does not exceed the submucosa, and in stage T2 it does not exceed the muscularis layer (Fig. 7.7). The MRI examination is not accurate in differentiating tumor stages T1 and T2, but it is very good in determining the tumoral invasion of the perirectal fat. MRI has a great accuracy in determining the depth of the perirectal invasion. Because the depth of the perirectal invasion is an important independent prognostic factor, the layering of T3 stage according to the depth of the invasion is necessary. Thus it is considered that a depth of the perirectal invasion higher than 5 mm will lead to a dramatic decrease in the survival expectancy at 5 years. The invasion of adjacent organs or structures (bladder, prostate, or seminal vesicles, uterus or ovaries, vagina, peritoneum recesses, the levator ani muscles or the pelvic wall) is considered T4 stage [30, 36, 64] (Fig. 7.8).

Axial T2-weighted image demonstrates an asymmetric wall thickening of the rectum at the right side. The thin hypointense line representing the muscular layer is intact, and the perirectal fat is homogeneous indicating a T2 stage tumor.

MRI can deliver anatomic information about the tumor location, the distance to the anal verge, and sphincter complex. For low-lying tumors, the involvement of the internal sphincter, the intersphincteric fat plane, and/or the external sphincter should

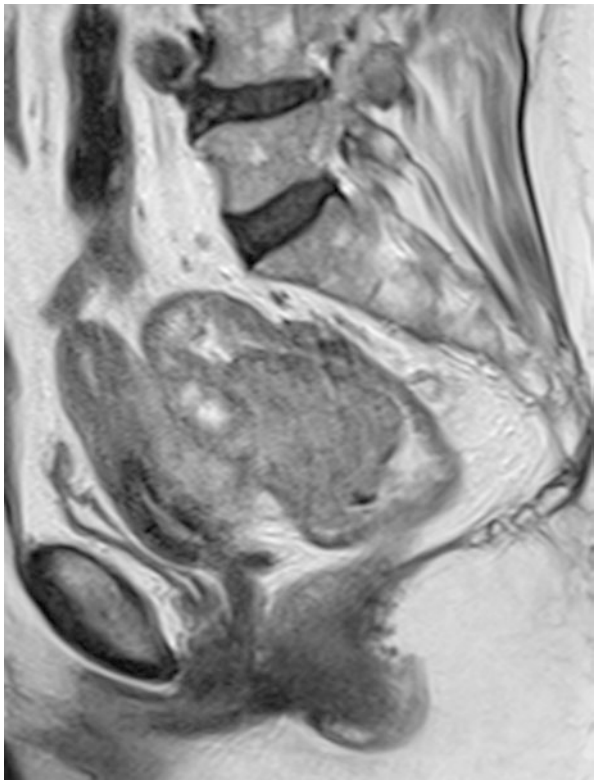

Fig. 7.8 A 67-year-old female with adenocarcinoma of the rectum. T2W sagittal MR image demonstrates T4b rectum cancer invading the uterus. The intervening fat plane between the tumor and the uterus is obliterated, indicating the tumor infiltration

be differentiated, due to different surgical approaches. For higher tumors in the upper third, the relation to the peritoneal reflection has to be taken into account [64–66].

T staging of the tumor is one of the most important stratification criteria on how primary rectal cancer should be treated. Early tumors (T1/sm1), which can potentially be treated by local excisional therapies, need additional staging with endorectal ultrasound, as MRI cannot differentiate whether a tumor reaches the submucosa or not. MRI is also limited to discriminate between T3a and T2 tumors, mostly due to desmoplastic reaction in the mesorectal tissue adjacent to the tumor [64, 66].

Apart from local staging, the MRI examination also provides information related to the relationship between the tumor and certain surrounding structures. One of these structures is the mesorectal fascia (MRF). MRI is the gold standard to assess MRF invasion. A mesorectal fascia without tumoral invasion will allow the total excision of the mesorectum, as this surgical procedure decreases the risk of tumor recurrence. If the tumor exceeds or less than 1 mm away from the fascia, mesorectal fascia is considered as invaded. If the MRF is involved on MRI (distance of nearest tumor or lymph node ≤1 mm), the likelihood of a possible circumferential resection margin after total meserectal excision (TME) is high. In general, the penetration depth into the mesorectum measured by MRI is considered equivalent to pathology and should, therefore, be mentioned in the MRI report [48]. CT has a role in assessing a negative MRF in patients that cannot receive MRI, but it is only reliable in mid- and upper third tumors [64–66].

The peritoneal reflection on the upper side of the urinary bladder and on the anterior wall of the upper rectum should also be examined for invasion. Tumors that invade the peritoneum are staged as T4a. The potential to assess the mesorectal fascia and peritoneal involvement are important advantages of magnetic resonance imaging as compared with transrectal ultrasound. Additionally, the involvement of the anal sphincter should be assessed before surgery because it has great significance in the preoperative planning [64–66].

In *nodal staging* of a rectal tumors, lymph nodes are grouped as mesorectal, superior rectal, inferior mesenteric, internal and external iliac, retroperitoneal, and inguinal nodes. The most commonly affected lymph nodes are the ones located at mesorectal level, inside the mesorectal fascia. However, it is also important to mention if we consider that lymph nodes located outside the mesorectal fascia are affected by tumoral metastases—they will have to be surgically excised to avoid relapse, or the preoperative radiation therapy should be done on a broader field. Pelvic side wall lymph nodes or lymph nodes in the obturator fossa should be carefully addressed because these lymph nodes are outside the TME resection plane and the standard radiation field, so they can be left untreated [36, 64–67].

When compared to transrectal ultrasound, MRI is certainly superior especially in detecting lymph nodes outside the mesorectal fascia. However, MRI is still limited in revealing the malignant or benign character of the detected lymph nodes because size criterion using a limit of 5 mm is not very reliable because up to 50% of metastatic lymph nodes are 5 mm or less. The additional assessment of shape, border, and signal heterogeneity can help in the assessment; an irregular outline of lymph

nodes associated with non-homogeneous signal is a much stronger predictor of malignancy [64, 67].

Extramural vascular invasion is an additional risk factor. This feature is present when tumor signal is seen within a vessel that expands the vessel or leads to an irregular vascular contour. This can be observed especially in patients with liver metastases. Also, these patients have increased risk to develop distant metastases in the follow-up. Therefore, the presence or absence of extramural vascular invasion should be reported at the primary staging and at restaging [68, 69].

Restaging of the high-risk patients and assessment of the response to neoadjuvant chemoradiotherapy are also crucial. MRI also plays an important role in the follow-up of patients who underwent organ-sparing local excision [46, 70–72].

Restaging with MRI should be performed before a surgical procedure, after 6–8 weeks of the end of the treatment, allowing for the possibility of a prolonged effect of radiation. The surgical approach might be different in the case of a good response, and organ-sparing resections might be an option. Apart from an assessment with MRI, patients may also need a clinical and endoscopic reassessment.

The conventional T2-weighted sequences are insufficient to assess for residual tumors; therefore, other techniques, like diffusion-weighted imaging, have to be applied to improve the sensitivity. Diffusion-weighted (DW)-MRI helps to evaluate biological and functional effects of treatment. In DW-MRI, differences in the random movement ("diffusion") of water protons provide the contrast and this is mainly dependent on cellular density. In tissues with low cellularity, as water protons can move relatively freely in the extracellular tissue space, DW-MRI signal is low. However, in tissues with high cellularity such as tumors, extracellular space is smaller which results in a restricted proton diffusion and a high DW-MRI signal. The degree of proton diffusion can be quantified via the "apparent diffusion coefficient" (ADC), which indirectly reflects the cellular tissue structure. Usually, the change in lesion size is observed much later than treatment-induced cellular death and vascular changes; therefore, DW-MRI might be a used as a biomarker of treatment outcome [73, 74].

Recurrent disease is more common in the rectum than the colon. Detection of recurrent disease is not always robust, because the distinction between tumor and scar tissue related to recent surgery or radiation may be challenging. In patients who show symptomatic disease and/or rising carcinoembryonic antigen (CEA) during surveillance after rectal cancer surgery, PET/CT imaging may help to improve the detection of a recurrence when the conventional methods are not decisive [9, 71].

Liver MRI is ideally performed with and without IV contrast, with multiphase dynamic post-contrast imaging as the standard acquisition. In most cases, metastases will be T1 hypointense and T2 hyperintense and will demonstrate peripheral enhancement (Fig. 7.9). Concerning the contrast agents, in addition to the traditional extracellular ones, hepatobiliary agents can also be preferred (Fig. 7.10). Hepatobiliary agents allow for both dynamic contrast images (arterial, portal venous) and hepatobiliary phase images. The hepatobiliary phase images are acquired at a delayed time point which differs slightly according to the type of agent used but mainly correspond to greatest liver parenchymal enhancement due to uptake of the contrast agent

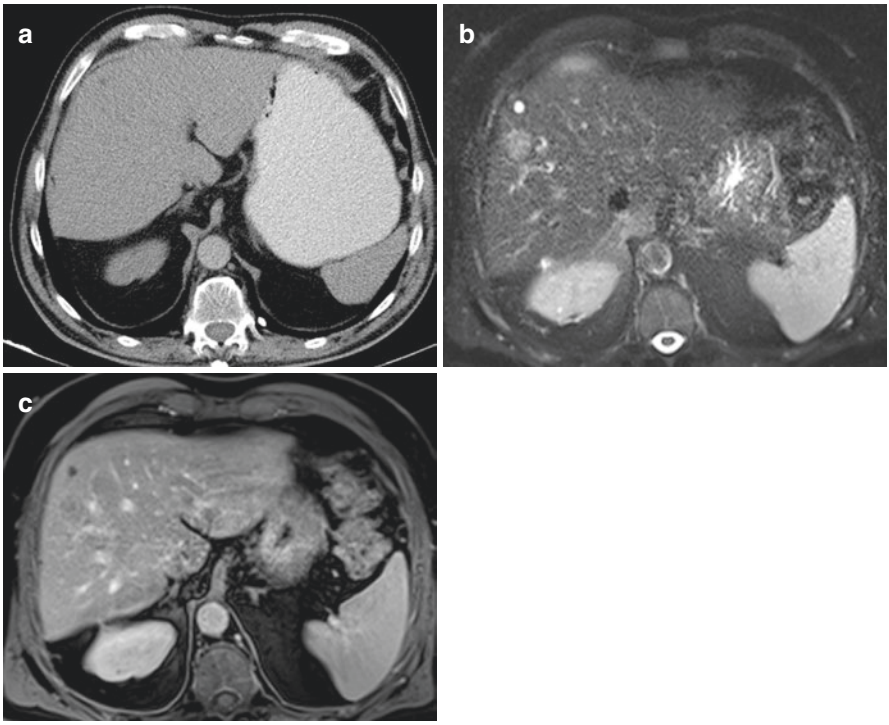

Fig. 7.9 A 69-year-old male with biopsy-proven adenocarcinoma of the rectum. (**a**) Axial iv contrast-enhanced CT image demonstrates a non-specific millimetric hypodense lesion in the segment 8 of the right lobe of the liver. (**b**) Axial fat-saturated T2W MRI image demonstrates two adjacent hyperintense focal lesions in the segment 8 of the right lobe of the liver. The anteriorly located smaller lesion has a high T2 signal with distinct margins and the posteriorly located lesion is relatively faint. (**c**) Axial contrast-enhanced T1W image (portal venous phase) demonstrates no enhancement in the small lesion which is a simple cyst, whereas the other lesion shows slight peripheral enhancement and considered as metastasis

by hepatocytes. The hepatobiliary phase increases the conspicuity of metastatic liver lesions as they appear dark against a bright liver parenchyme. More accurate delineation of metastasis by means of size, number, and location may play an important role both in treatment and follow-up. Similarly, MRI with diffusion-weighted imaging also produces greater diagnostic accuracy, especially when combined with hepatobiliary phase imaging. Liver metastases are more conspicious in DWI, having higher signal on high-b-value images and low ADC values [39, 40, 75].

Although the use of iv contrast agents should be preferred, iodinated contrast agents used for CT are potentially nephrotoxic and should be avoided in patients with compromised renal function. Gadolinium-based IV contrast agents used in MRI are not nephrotoxic and may be a better option for patients with mild renal insufficiency. However, gadolinium agents should also be avoided in severe renal dysfunction due to the risk of nephrogenic systemic fibrosis. Therefore, in patients

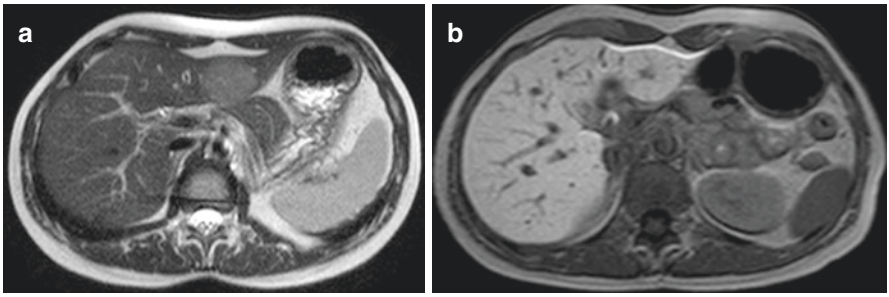

Fig. 7.10 A 37-year-old female with biopsy-proven adenocarcinoma of the sigmoid colon. (**a**) Axial T2W MR image demonstrates a hyperintense focal lesions in the segment 2 of the left lobe of the liver which is hardly visible on CT. MRI is used for further characterization. (**b**) A late T1W axial image after the administration of hepatocyte-specific contrast agent (gadoxetic acid disodium-Primovist) reveals that the lesion is enhanced in the same manner as the liver parenchyma, therefore containing hepatocytes. It is diagnosed as focal nodular hyperplasia

who cannot receive an IV contrast agent due to severe allergy or renal failure, MRI without an IV contrast agent may be an option that provides better anatomic detail than CT without contrast [75].

Positron Emission Tomography (PET-CT)

PET/CT is a unique combination of the cross-sectional anatomic information provided by CT and the quantitative metabolic information provided by fluorodeoxyglucose (FDG)-PET. The principle of positron emission tomography is based on the differential metabolic profile of tumors compared to normal tissue. Due to increased metabolic activity, and change in the tumor biology, tumors preferentially show an increased uptake which results in radiolabelling. Fluorodeoxyglucose (FDG) is the most common PET tracer used [26, 76].

Malignant cells have higher glucose metabolism; therefore, the glucose analogue 18F-FDG is differentially taken up by the tumor cells. FDG also accumulates in areas of infection, inflammation, in organs of increased metabolic activity such as brain, myocardium, liver, or kidneys leading to false-positive results. FDG uptake is also influenced by the presence of mucin. FDG-PET may yield false-negative results especially in mucinous tumors [76–78].

The metabolic response to chemotherapy assessed by FDG-PET/CT correlates well with clinical response, tumor biology, and disease-free survival metastatic CRC. If there is a lack of a metabolic response to treatment, it may indicate primary resistance to therapy. Additionally, if metabolic activity within a tumor site increases following a period of therapeutic response, this indicates secondary resistance. The sensitivity of tumor detection by FDG-PET/CT depends on the avidity of the tumor cells for FDG, which is strongly linked to tumor grade (aggressiveness) and cellularity. Metastatic CRC is generally highly avid, except mucinous tumours, which may not be detected by a FDG-PET/CT scan [79, 80].

It is considered that PET-CT does not bring additional information compared with thoracoabdomino-pelvic CT in the initial staging of colon cancer and also did not show any additional benefit in the local staging of rectal cancer and currently it is not used as a primary staging modality. FDG/PET is mainly useful in the assessment of local recurrence and metastatic disease when conventional imaging is not helpful. The more common clinical application of PET/CT is in identifying nodal and distant metastases (Fig. 7.11). However, particularly in those two situations PET-CT is recommended in patients with colorectal tumors: Firstly, in patients with rising carcinoembryonic antigen values during oncological monitoring and the conventional imaging cannot detect the location of the tumoral recurrence. And secondly, in patients with single liver metastasis who are candidates for liver resections. It is considered that, in these patients, performing PET-CT before surgery leads to a decrease in the number of useless laparotomies. It is believed that chemotherapy decreases the sensitivity of PET-CT for diagnosing the colorectal cancer metastases. For this reason, in patients which are potential candidates for liver metastasectomy, PET-CT examination should be performed before starting chemotherapy to detect other possible tumoral locations [26, 76].

Combining metabolic and anatomical imaging FDG-PET/CT has taken an important place in treatment response assessment. Metabolic changes in response to treatment occur before any structurally detectable change such as tumor shrinkage. In the patients receiving neoadjuvant therapies, serial FDG-PET/CT examinations may help to decide the appropriate length of neoadjuvant chemotherapy to maximize tumor response before surgical resection. Also, FDG-PET/CT may lead to changes in therapies for those patients with tumors that show no metabolic change [79, 80].

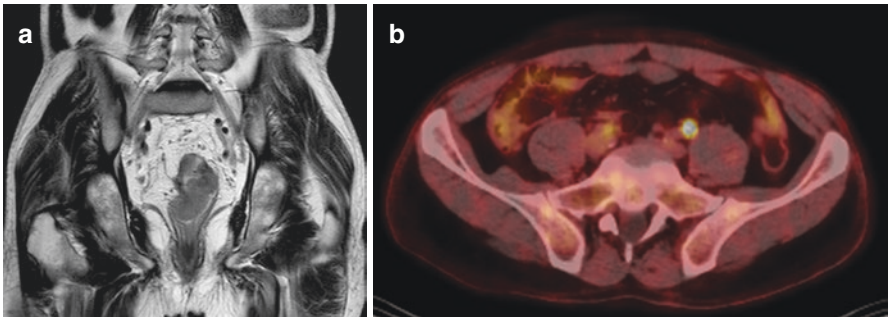

Fig. 7.11 A 48-year-old male patient with biopsy-proven adenocarcinoma of the rectum. (**a**) T2W coronal MR image demonstrates a polypoid mass in the rectum showing no mesorectal infiltration. The perirectal fat is homogenous and the hypointense line representing the muscular layer is intact corresponding to T2 stage. There are a few small lymph nodes inside the mesorectal fascia with no suspicious features of metastases. (**b**) FDG PET-CT demonstrates a high tracer uptake in the lymph node adjacent to the left iliopsoas muscle which is considered as metastatic. It is not obvious in CT or MR images. As this lymph node is outside the mesorectal fascia and circumferential resection margin, PET-CT plays an important role in the management of the patient because the lymph node should be resected and included in the radiation area to prevent recurrence

When radiation therapy is applied, due to radiation-related increased FDG uptake by rectal mucosa, FDG-PET may yield false-positive results; therefore, to monitor tumor response, FDG-PET should be performed after 4 weeks following the completion of CRT [76, 77].

Limitations of FDG-PET/CT are that the technique is cost- and time-consuming and is not widely available. It has a very limited benefit of CRC follow-up in early stage tumors; therefore, a regular follow-up is not indicated [77].

The role of FDG-PET in the evaluation of recurrent colon cancer is also controversial. This technique also has low sensitivity revealing mucinous adenocarcinomas in which metabolic activity is low. Incidental physiologic bowel FDG uptake or inflammation will produce increased tracer uptake, giving rise to false-positive findings that can mimic a tumor [76, 77, 81].

Imaging-Guided Therapeutic Procedures

Radiofrequency Ablation and Microwave Ablation

Radiofrequency ablation (RFA) and microwave ablation (MWA) are minimally invasive procedures which aim to destroy tumor cells in the liver by high-frequency or microwave current-induced heating. A probe is inserted transcutaneously into the tumor under CT guidance, and high-frequency or microwave heating is applied. This procedure is recommended for CRC patients in whom non-resectable liver metastases are present or in whom the general condition does not allow metastasis resection [82].

Transarterial Chemoembolization

Transarterial chemoembolization (TACE) is a minimally invasive procedure used for the treatment of liver metastases. High-dose chemotherapy or drug eluting beads (e.g., mitomycin C, irinotecan, and Tcisplatin) are locally infused to the feeding arteries of metastasis, and this may be accompanied by selective embolization [82].

Selective Internal Radiation Therapy

Selective internal radiation therapy (SIRT) represents a new minimally invasive technique for treating non-resectable liver tumors. As the blood supply of liver tumors are predominantly by hepatic artery, by single delivery of 90yttrium microspheres into the hepatic artery, a potential preferred uptake by the tumors is aimed. SIRT is only recommended for the treatment of disseminated liver metastases in those CRC patients lacking alternative therapeutic strategies and only within clinical studies [82].

Conclusion

Radiological imaging plays an important role in the screening, primary diagnosis, staging, management, evaluation of treatment response and follow-up of CRC. Significant advances have been made in imaging technologies over the last decades. Each modality has its inherent advantages and limitations.

Optical colonoscopy is considered as the most precise modality in the detection of primary CRC simultaneously allowing biopsy and therapeutic polypectomy. Virtual CT colonoscopy is a potential alternative to OC, showing a similar diagnostic performance. However, radiation exposure and the lack of therapeutic possibilities remain primary concerns. A similar imaging modality, MR colonoscopy although having the advantage of no ionizing radiation is not recommend as a screening tool due to lack of convincing data.

If the tumor is located in the colon, the initial staging will be done through thoraco-abdomino-pelvic CT. In most cases, this will be sufficient for an accurate staging and the images will be later used as reference for the post-treatment examinations. When CT is not sufficient, MRI or PET-CT can be used.

MRI and ERUS reveal the best results in the local staging of rectal carcinoma. MRI is the superior imaging modality for the evaluation of primary tumor location, extension and mesorectal fascia involvement and plays an important role in accurately defining patients to receive preoperative chemoradiation prior to surgery. ERUS, is currently the most accurate imaging modality in the assessment of T1 rectal tumor [2].

For the detection of distant metastases, CT is the most commonly used method. For detecting small liver metastasis, MRI may be necessary. The hepatobiliary MRI contrast agents and DWI improve the sensitivity of MRI. Similarly in treatment response monitoring, DWI also has a promising role as a reliable marker to improve MRI performance, Characterization of metastatic lymph nodes remains challenging for MRI. Although FDG-PET/CT may provide an increased accuracy in metastatic lymph node assessment, utilization of this modality is limited and cannot be applied broadly.

Periodic thoraco-abdomino-pelvic CT is recommended for follow-up in patients with treated colon cancers. The patients with operated rectal tumors, especially those who have received neoadjuvant radiotherapy, better undergo pelvic MRI in addition to the thoraco-abdomino-pelvic computed tomography. This is because MRI is more accurate, in the differentiation of the local tumoral relapses from the post-irradiation fibrosis.

When considered in combination with the progress in treatment options, improvements in imaging technology will play an important role in reducing the incidence and mortality of colorectal cancer as well as optimizing the patient management.

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Surgical Management of Colorectal Polyps

8

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Colorectal cancers are the third most common cancer in the world and also the second most common cause of cancer-related deaths. Although the incidence of colorectal cancer decreases with the growing popularity of endoscopic imaging and screening, the number of cases still increases in the patient group below 50 years of age [1]. Most colorectal cancer cases are sporadic and develop slowly for several years with the adenoma-carcinoma sequence [2, 3].

The development of cancer from adenomatous polyps (adenoma-carcinoma sequence) takes 8–10 years. In the past, all colorectal cancers were thought to originate from adenomatous polyps, but the development of Lynch Syndrome with gene repair damage, the presence of non-polyposis autosomal dominant colorectal cancers, and the presence of serrated adenomas have demonstrated cancer development mechanisms other than adenomatous polyps [4, 5].

In patients with adenoma, the risk of cancer development in 5 years is 4% and in 10 years it is 14% [6].

Colorectal Polyps

Polyp is a non-specific clinical term that defines any protrusion from the surface of the intestinal mucosa, irrespective of its histological structure. Colorectal polyps can be classified as neoplastic (tubular adenoma, villous adenoma, tubulovillous adenoma), hamartomatous (juvenile, Peutz-Jeghers, Cronkite Canada), inflammatory (pseudo polyp, benign lymphoid polyp) or hyperplastic [7].

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Polypectomies performed by colonoscopy evaluation are considered minimally invasive, easy to perform and highly effective to prevent colorectal cancer [8]. Colonoscopy polypectomy was introduced by Wolf and Shinya in the early 1970s. With the development of technology and increased number of experienced endoscopists, it is considered as a safe procedure with low complication rates. Bleeding is the most common polypectomy complication with the rates between 0.3% and 6.1%.

Large polyps, which are equal to or larger than 2 cm, are challenging for the endoscopists as they carry the risk of perforation (0–1.3%), haemorrhage (0–22.1%) and insufficient safety margin during the operation [9].

Polyps can be classified according to their appearance in endoscopy, they can be seen protruding, sessile and flat. There are three morphological growth patterns; polypoid, non-polypoid and depressive (surface, spread and invasive mucosa) [10].

In 2002, scientists from a group of Western and Japanese pathologists, surgeons and endoscopists came together to publish the Paris classification, which categorized these lesions according to their "superficial" morphology and histology to standardize terminology. This system, which classifies the morphology of all gastrointestinal system polyps endoscopically, has given the possibility of standard definition [11].

For polypoid lesions, protruded and pedunculated polyps are classified as 0-1p, protruded and sessile classified as 0-1s, nonpolypoid superficial and elevated lesions are classified as 0-2a, flat lesions are classified as 0-2b, superficial shallow and depressed lesions are classified as 0-2c and nonpolypoid and excavated lesions are classified as 0-3 [3, 12, 13].

The introduction of high-resolution endoscopes into clinical practice has improved the detection rates of neoplastic lesions compared to standard endoscopes. Endoscopes also allow critical evaluation of mucosal surface properties with or without topical dye application. State-of-the-art endoscopes and endoscopy systems include built-in digital chromoendoscopy techniques that can be activated at the push of a button. With these methods, mucosal and vascular features of the lesion are examined and Kudo classification defined in 1994 was created to define the microarchitecture of epithelial pits by chromoendoscopy. In this way, revealing the risk of malignancy and invasion of the polyp leads the experts to decide between endoscopic excision and surgical resection [14].

Kudo et al. first emphasized the applicability of "pit patterns" to differentiate neoplastic and non-neoplastic polyps with the use of magnification endoscopy. Kudo et al. classified colorectal polyps according to their appearance, structure and staining. Type I pits appear as round pits; Type II pits appear as stellar or papillary pits; Type III-s pits are small round, tubular pits (smaller than Type I) and Type III-L, roundish and tubular pits (larger than Type I); Type IV wells appear as branch-like or gyrus-like wells, and Type V pits appear as unstructured wells. Type I and II are in the category of changes that are benign (e.g. normal, hyperplastic, inflammatory polyps), while III–V pit pattern classes show the changes that are neoplastic and malignant [15, 16].

Cold Forceps Biopsy/Cold Snare Polypectomy

The gold standard in the treatment of lesions is the procedure that first starts with evaluation of polyps detected during colonoscopy followed by polypectomy performed during the same time. Polypectomy with biopsy forceps without cautery may be sufficient to remove polyps smaller than 3 mm. Biopsy forceps combined with chromoendoscopy has been reported to be sufficient in 90% of all small polyps (≤3 mm) and 100% of adenomatous polyps of 1–3 mm in size. However, it is necessary to ensure that no residual lesions remain by chromoendoscopy [17]. In a study of 146 patients with 231 diminutive polyps, it was reported that while cold forceps biopsy polypectomies confirmed by narrow band imagining endoscopy in 1–3 mm polyps were suitable for complete resection, cold snare polypectomy was found more successful in diminutive polyps larger than 3 mm [18]. In this case, the use of wide-mouth (Jumbo) forceps would be beneficial. In a limited number of patients (*n*: 143), it was reported that in diminutive polyps' residual lesions remained after polypectomy applied with cold biopsy forceps. Complete resection rate in diminutive polyps was 39% and 62% in adenomas [19].

Cold snare polypectomy was first reported in 1992 as a new technique for the excision of small colorectal polyps without electrocautery [20]. It is a frequently preferred method for polypectomy of polyps less than 10 mm with its low complication rate and rapid application. It is accepted as a safe method for small polyps, which have no extensive arterial vascularization and so bleeding risk [21].

Complete excision rate is quite high in polyps less than 7 mm and cold snare polypectomy may not be successful in polyps 8–10 mm in size [22]. Safety of the excision should be ensured by enclosing at least 2 mm border resection from the normal mucosa [22, 23]. Cold snare polypectomy by slightly elevating polyps from the submucosa by saline injection will decrease the chance of perforation.

Reducing the air in the colon slightly (without using a snare) will reduce the tension on the wall which will decrease the chance of perforation. The missing and broken-down polyps in the colon after polypectomy of small lesions is one of the most serious problems. Since most of the polyps detected in colonoscopy are smaller than 10 mm, cold snare polypectomy can be used safely. More successful polypectomies can be performed with thinner snare wire (compared to normal hot snare wire) and small lasso diameter (13–27 mm) [23, 24].

Hot Biopsy Forceps

Hot forceps biopsy may be an appropriate treatment option in the excision of small polyps. The polyps completely covered with forceps are carefully elevated from the surface of the colon, cut with electrocautery and finally polypectomy is completed with the created pseudo stalk. However, this method may also involve residual polyp tissue [25, 26]. It has been reported that jumbo forceps use gives better results and lower complication rates when compared to standard hot forceps biopsy [27].

Hot Snare Polypectomy (HSP)

Hot snare polypectomy is accepted as standard in polyps that are 10–19 mm in size. The elevation of the polyp by the injection of saline in the submucosal area may provide safer polypectomy. This provides complete resection and reduces the risk of perforation. Diluted adrenaline, epinephrine-containing hyaluronic acid, dextrose solutions, hydroxyethyl starch contents, succinylated gelatine and polidocanol-like substances can be used as an alternative to fast-absorbing serum physiologic [28].

The use of cold snare biopsy and hot snare biopsy has grown since they prevent residual lesions during polypectomies. Use of cold snare, which does not cause deep tissue heat damage, is found more useful and safer than hot snare in diminutive polyps (<5 mm) and small polyps (5–9 mm) [29].

The use of a high-frequency generator in hot snare polypectomies can minimize bleeding immediately after polypectomy by coagulation, but on the other hand it may also damage deep vessels with the risk of delayed bleeding or even perforation [30].

Most endoscopists perform hot snare polypectomy with low energy coagulation settings (25 W). Bleeding during the procedure, perforation and late postoperative bleeding can be considered as the main complications in both cold and hot snare biopsy. Repici et al. reported the emergency bleeding rate of cold snare polypectomy as 1.8%. It has been reported that the rate of emergency bleeding for hot snare polypectomy is 0–1.4% [31]. Bleeding in post-polypectomy period is higher in patients with hot snare polypectomy than cold snare polypectomy. In addition, perforation rate was higher in hot snare patients which was stated in the meta-analysis covering many studies [29].

Endoscopic Mucosal Resection (EMR)/Endoscopic Submucosal Dissection (ESD)

Nearly 10 to 15% of all colon polyps are considered difficult polyps. Those located between two colonic haustra, cecum and right colon, ileocecal valve, appendix orifice or dentate line and the ones larger than 2 cm are in this category [32].

To recognize difficult polyps and standardize treatment options, they are classified in various categories such as size, morphology, placement and ease of access. Lesions less than 1 cm, 1–1.9 cm, 2–2.9 cm, 3–3.9 cm and 4 cm and above receive 1 point, 3 points, 5 points, 7 points and 9 points, respectively. Morphologically, pedunculated ones are scored with 1 point, sessile lesions with 2 points, and flat ones with 3 points. The lesions located in the left colon are scored with 1 point and those located in the right colon are scored with 2 points. Polyps that are easy to access are scored with 1 point and those with difficulty are scored with 3 points. Lesions graded in four main categories; if between 4 and 5 points they are classified as difficult polyps of grade 1, 6–9 points as difficult polyps of grade 2, 10–12 points as difficult polyps of grade 3, above 12 points as difficult polyps of grade 4 [33, 34].

For the treatment of difficult polyps, the endoscopist must perform complete resection and aim for preventing complications diligently. This situation requires some advanced therapeutic routes ranging from endoscopic interventions to surgical options in polyps considered as difficult polyps.

Endoscopic mucosal resection is a successful treatment option in 75% of complex colon polyps, with a low complication rate of 4.5% and a residual polyp rate of 4% [35]. Endoscopic mucosal resection is performed on the same basis as hot snare polypectomy. The procedure can be described as the excision of lesions larger than 20 mm by the use of electrocautery snare following submucosal saline injection.

The use of submucosal injection reduces the conduction of heat to deep structures (muscularis propria, serosa) and the risk of acute and late haemorrhage. Thus, complete resection of the sessile polyps becomes less complicated. The procedure on lesions larger than 20 mm may be rather complicated due to the bleeding. Excessive bleeding during operation may cause residual polyps go unnoticed. Submucosal injection enables resection as it decreases bleeding [36].

EMR has become the standard treatment for tumours larger than 2 cm and the tumours with flat or lateral spread. Successful results can be obtained with EMR performed piece by piece in non-invasive lesions that are raised with submucosal injection and even minimally invasive lesions [37]. Although the distance that can be accepted as clean surgical margin is considered as 1 mm, the preferred surgical margin is 2 mm [12].

It has been reported that colon perforation in diagnostic colonoscopies is rate 0.03–0.65% and in therapeutic colonoscopies is 0.073–2.14% [38]. Even after the procedure performed by the most experienced endoscopists, perforation can be seen in 1–2% of the cases after EMR. The majority of cases can be treated endoscopically. Like hot snare polypectomy; early bleeding and delayed bleeding can be expected. Bleeding usually develops from vascular structures in the submucosal area.

Bleeding that may require endoscopy for haemostasis, hospitalization and transfusion can be seen in 7% of the patients after the procedure. Haemostasis can usually be controlled by thermal coagulation. In thermally uncontrolled lesions, coagulation can be achieved by means of clips or bipolar forceps. In late-stage bleeding, it is generally seen in the geriatric patient group using anticoagulants and haemostasis can be achieved by using endoscopic methods [37].

Endoscopic submucosal dissection (ESD) was developed in Japan at the end of the 1990s and is a method that allows the removal of early gastric tumours in one piece [39]. Colorectal ESD is more difficult than gastric ESD as the anatomical features of the colon differ from the stomach and oesophagus; the colon wall is thin, lumen is long and narrow with sharp and limited angles. The most important advantage of ESD over endoscopic mucosal resection (EMR) is that it enables the removal of previously treated large lesions in one piece [40].

The indications of ESD procedure are polyps with lateral spread greater than 2 cm (especially pseudo depressed type), lesions likely to be submucosal infiltration, large puffy lesions suspected to be malignant, mucosal lesions fibrous due to

previous biopsy, sporadic tumours of ulcerative colitis and local residual early-stage cancer after endoscopic resection (without lymph node metastasis) [41].

Surgery in Colorectal Polyps/Difficult Polyps

In spite of all effective endoscopic procedures, there are wide range of surgical treatment options starting from colotomy to polyp excision or combined laparoscopic endoscopic surgery and transanal endoscopic microsurgery. Patients with polyps that are not suitable for endoscopic polypectomy are referred to surgical resection (Fig. 8.1). Cancer develops in 18% of these polyps [42].

Approximately 10% of cancers with submucosal spread have metastatic lymph nodes. Submucosal lesions that are endoscopically resected and diagnosed histopathologically as poorly differentiated require surgery. Focal invasive submucosal section classification in stemless and smooth lesions and Haggit classification of pedunculated polyps are referred to establish the treatment approach to focal invasive cancers. Lesions accepted as level 0 in the Haggit classification are limited to the mucosa or they are carcinoma in situ lesions in the intramucosal area, level 1 lesions are limited carcinomas only at the head of the polyp. Carcinomas spreading to the neck of the polyp are classified as level 2, carcinomas invading the polyp stalk are level 3, and carcinomas invading submucosa under the stalk is classified as level 4 [13].

Submucosal invasion (SM) of carcinoma is categorised into three main categories: Sm1, Sm2 and Sm3. Sm3 refers to the carcinoma that invades the deepest third of the submucosa. Sm2 refers to the carcinoma that invades the middle third of the submucosa. Sm1 refers to the carcinoma that invades the top third of the submucosa. Sm1 category is also divided into three subcategories based on the ratio of horizontal spread to the whole lesion: Sm1-a carcinoma invading with less than 25% horizontal spread, Sm1-b carcinoma with 25–50% horizontal spread and Sm1-c with horizontal spread to >50% of the total lesion [43, 44].

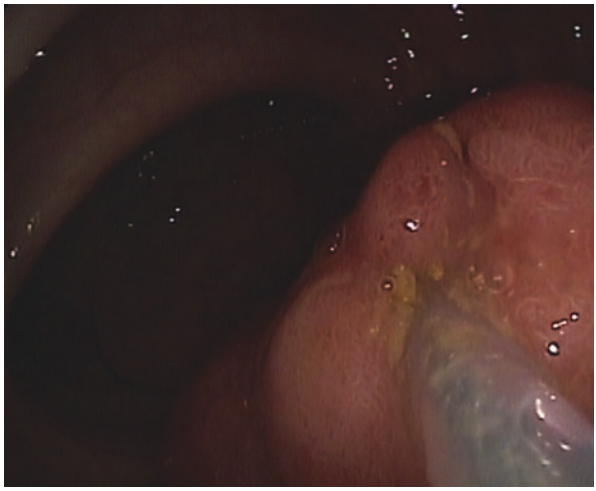

Fig. 8.1 Polyps that are not suitable for endoscopic polypectomy are referred to surgical resection

Endoscopic resection is considered sufficient in Haggitt type 3 and sm1a + b lesions. Haggitt type 4, sm 1-c and deeply invaded lesions are considered to have a high risk of lymph node metastasis. These lesions require surgical resection and appropriate lymph node excision [13].

Surgical options may be preferred for polyps evaluated within the category of difficult polyps. Surgery is also referred for poor differentiation and lymphovascular invasion. Poor differentiation is present in approximately 5–10% of colorectal cancers, and lymphovascular invasion is present in approximately 30% of all colorectal cancers [12].

Negative histological findings in malignant pedicle and non-pedicle colorectal lesions [12]:

For peduncle lesions

- Less than 2 mm distance between the tumour and cauterization limit
- Stalk invasion
- Poor differentiation
- Lymphovascular invasion
- Insufficient histological evaluation

For non-peduncle lesions

- Piecemeal resection
- Positive resection margin
- Invasion depth: 1000 μm
- Poor differentiation
- Lymphovascular invasion
- The tumour in the form of a bud
- Insufficient histological evaluation

Many surgical approaches, from open surgery and colotomy procedures to combined laparoscopic-endoscopic methods, can be preferred. It is important to take into account the location of polyps (difficult polyp at mesenteric wall), surgeon's experience, suspicion of malignancy, presence of lymph node and the patient's comorbid causes during the decision-making process [45].

In open or closed surgery, evaluation can be made with three procedures: extraction of colon polyp with colotomy, segmental limited resection and colectomies in accordance with oncological principles. In addition, if lymph node is positive and highly suspicious for malignancy, open or laparoscopic surgery in accordance with the oncological principles should be performed [46].

Polyp excision with colotomy is rarely preferred for the patients with polyps suspicious for malignancy as it carries the danger of tumour positivity at the surgical margin and peritoneal cultivation of tumour cells [45].

A key factor in both open and laparoscopic approach in preoperative evaluation is the precise detection and marking of the location of the polyp. Although there are not many problems expected in cecal polyps (right hemicolectomy?), there may be

localizations that will change the surgical approach in the transverse colon, descending colon and sigmoid colon.

Metal clips and the injection of paint solutions (methylene blue, Indian ink) should be used for marking. Carbon nanoparticle suspensions are safe for marking lesions. The permanence of the dye ensures the stability in localization and provides an opportunity for the check-up of the lesions for up to 1 year after colonoscopy or laparoscopy [46, 47].

While endoscopic procedures carry the risks of bleeding, perforation and residual tumour, open and laparoscopic colon surgeries have their own disadvantages; long duration of hospital stay, risks related to anaesthesia, pain, deterioration in nutritional status, bleeding, injury to adjacent organs and structures (ureter, veins, small intestine, spleen, etc.), wound infection, deep vein thrombosis, possibility of urinary or lung infections and even death [45, 48].

Laparoscopic Approach in Colorectal Polyps

The first laparoscopic right hemicolectomy was introduced by Jacobs in 1991 [49]. Shortly after, laparoscopic left hemicolectomy was performed successfully.

Over the years, it has been demonstrated that laparoscopic colectomies have an equally successful outcome to open surgery in oncological surgery, and it decreases the number of cases in terms of wound infection, haemorrhage, long hospital stay and analgesic need. In addition, bowel functions are restored faster.

However, by 2010, the ratio of laparoscopic colectomies to all colectomies reached only 41.6% [50]. Due to concerns on residual disease and problematic surgical margins, which is generally believed to be secured more efficiently via open surgery, laparoscopic techniques are questioned when it comes to oncological resection procedures. However, studies investigating the safety and efficacy of laparoscopic colectomy in comparison to open colectomy in patient groups with colon cancer shows that laparoscopic resection is as safe and effective as open resection [51, 52].

Decreased postoperative ileus, less postoperative analgesia requirement, smaller incisions, better cosmetic results, less wound infection and shortened hospital stay are the positive aspects of laparoscopic approach. On the other hand, there is a relative length of operation time (due to surgeons' experience) and increased costs with the use of laparoscopic instruments can be the case. In a randomized controlled study, it was shown that there is no significant difference between the recurrence rate between laparoscopic and open surgery for colorectal cancer. In both techniques, there is no difference between the complications seen perioperatively and postoperatively [13, 51, 53].

The long learning process of laparoscopic surgery and doubts in determining the surgical margin (diverticulitis, tumours) have brought up hand-assisted laparoscopic colon resections. It has been stated that colectomies can be performed with minimal incision in which the surgeon can insert his/her hand into the abdomen in addition to the standard laparoscopic trocar entry [54].

The rate of transition from laparoscopic surgery to open surgery is around 3.2% [55]. Studies show that colectomies performed with laparoscopy-assisted mini-laparotomy and hand-assisted laparoscopic colectomies are safer than open colectomies [56, 57].

The rapid recovery process, which is the advantage of laparoscopy over open surgery, is not possible with mini-laparotomy-laparoscopic surgery or hand-assisted laparoscopic surgery. In addition, the rate of incidence hernia was reported between 6% and 10% [50].

The switch from conventional open colectomies to minimally invasive colectomies such as single-incision laparoscopic, robotic and natural orifice transluminal endoscopic surgery are important cornerstones in the surgical process.

Combined Endoscopic-Laparoscopic Surgery

Combined endolaparoscopic surgery (CELS) (1993) has been described as a method that allows the detection of perforations that may occur during EMR and ESD and their repairment in the same session. It also allows precise detection of the location, which may be difficult to identify from the serosal surface, and their treatment.

This technique, which requires both the surgeon and the endoscopist at the same time, allows the endoscopist to easily access and resect difficult polyps, as the surgeon mobilizes and manipulates the column laparoscopically. Besides, perforation that may occur can be repaired quickly. In addition, synchronous polyps and cancers are treated with a minimally invasive method in a single session [13, 46, 58].

There are also other approaches diverging from this combined technique, such as laparoscopic-assisted colonoscopic resection, endoscopy-assisted laparoscopic wedge resection and endoscopy-assisted colonoscopic resection [55, 58, 59].

The CELS procedure enables the opening and manipulation of adhesions surgically by allowing the endoscopist to control the equipment intraluminally. It is possible to repair the full-thickness injury that may occur during the endoscopic procedure. If the polyp is not completely cleared endoscopically (in benign cases), the procedure can be completed by laparoscopic wedge resection. In the presence of malignancy, laparoscopy in accordance with oncological procedures is appropriate for resection [59, 60].

Monitors are placed by taking the location of the polyp into consideration, the surgeon should approach the patient accordingly. Although room air is used endoscopically in normal applications, intraperitoneal CO_2 insufflation is performed laparoscopically. CO_2 is also suitable for colonoscopy. CO_2 is absorbed faster than room air and obstructs vision less than room air laparoscopically. In addition, terminal ileum can be clamped to prevent bowel distention by air passing from ileocecal valve to proximal ileum. It is more convenient to start the procedure with colonoscopy first. By injection of indigo carmine solution, the polyp can be raised from the submucosa. In case of cancer suspicion or polyps that do not rise with submucosal injection, malignancy and surgical margin can be studied with frozen section following resection. If necessary, colectomy can be performed laparoscopically. After

resection and repair, SF can be filled into the abdomen and leak test can be performed by CO_2 insufflation with colonoscope [58, 60].

Transanal Endoscopic Microsurgery (TEM)

The surgical procedure for the treatment of adenomas and early-stage cancers in the rectum is called TEM. The TEM procedure has been applied for more than 30 years. It is especially preferred in T1N0M0 early-stage rectal cancer for its ease of application. However, the inability to excise the lymph nodes in the mesorectum with this the procedure makes a careful evaluation of the lesion by referring endoscopic examination and imaging methods like endoanal USG, pelvic MR absolutely necessary [61].

TEM can be processed with proctoscope, laparoscopic camera and laparoscopic instruments with a diameter of 4 cm and 12–20 cm in length for the lesions up to 25 cm from anal verge. While standard laparoscopy proceeds with dissection and retraction movements. TEM can be applied mostly with angled instruments.

The advantages of this method are shortened hospitalization time, early mobilization, and low complication rate, early oral intake, which even apply to patients with wide lesions and full-thickness resection.

While 8.1% of all patients have minor complications such as leakage, minimal bleeding, urinary retention and infections, serious bleeding that require treatment, rectovaginal and recto vesical fistula that require ileostomy, leaks that require a second intervention, ischiorectal abscesses and anal incontinence may be seen in 1.2% of the patients. Mortality has been reported as 0.3% approximately [62, 63]. Full-thickness TEM can provide curative treatment in early-stage rectal cancer, polyps and lateral spreading lesions. TEM may be reperformed in the case of local recurrence [64].

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Colon Polyps and Their Pathologic Characteristics

9

Dudu Solakoglu Kahraman and Sevil Sayhan

Introduction

Categorization of colon polyps according to 2019 classification of World Health Organization (WHO) [1, 2]:

- **Inflammatory Polyps:**
  - Inflammatory polyp usual tip (NOS, "pseudopolyp")
  - Prolapse-type inflammatory polyp
  - Inflammatory myoglandular polyp
  - Inflammatory cap polyp
  - Colitis cystica profunda/polyposa
  - Diverticular-disease-associated polyp
  - Inflammatory cloacogenic polyp
- **Hamartomatous Polyps:**
  - Juvenile polyps and juvenile polyposis
  - PTEN-hamartoma tumor syndrome (Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, and Proteus syndrome)
  - Peutz-Jeghers syndrome
- **Epithelial Polyps:**
  - Serrated lesions and polyps;
    Hyperplastic polyps
    Sessile serrated lesions
    Sessile serrated lesions with dysplasia
    Traditional serrated adenomas
    Serrated polyposis syndrome
    Serrated adenoma, unclassified

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  - Traditional adenoma:
    Tubular/tubulovillous/villous adenoma
    Flat adenoma
    Adenomas with misplaced epithelium (pseudoinvasion)
    Malign epithelial polyps
    Adenomatous polyposis syndromes (Familial Adenomatous Polyposis, Gardner, Turcot, AFAP, MYH-Associated Polyposis)
- **Lymphoid Polyps**
- **Mesenchymal Polyps:**
  - Ganglioneuroma
  - Neurofibroma
  - Granular cell tumor
  - Mucosal perineurioma
  - Mucosal Schwann cell hamartoma
  - Leiomyoma
  - Leiomyosarcoma
  - Lipoma
  - Gastrointestinal stromal tumor
  - Fibroblastic polyp
  - Inflammatory fibroid polyp
- **Miscellaneous Polypoid Lesions**
  - Pneumatosis coli
  - Endometriosis
  - Mucosal pseudolipomatosis
  - Systemic mastocytosis
  - Mucosal tag
  - Inverted appendix
  - Atheroembolus-associated polyp

Inflammatory Polyps

Inflammatory polyps are colon polyps consisting of nonneoplastic epithelial and stromal components with inflammatory cells. They are frequently associated with inflammatory bowel disease (Crohn's disease and ulcerative colitis), as well as ischemic colitis, severe infectious colitis and necrotizing enterocolitis [3–5]. These lesions occur after excessive regenerative and reparative changes after ulceration. Inflammatory polyps are not premalignant lesions, but may be indistinguishable colonoscopically from adenomatous polyps [4, 5].

Usual Type Inflammatory Polyp (NOS, "Pseudopolyp")

Inflammatory pseudopolyps are polyps that occur at any location of the colon and they are mostly associated with inflammatory bowel disease [5, 6].

Pathologic Features

Grossly, the inflammatory polyps are sessile or pedunculated. Some demonstrate worm-like or long finger-like projections. They can be single, multiple, with variable sizes from 0.5 to 10 cm. When they reach a large size, they are called giant inflammatory polyps [6–8]. These polyps show very small protrusions of the mucosa on the surface [8, 9]. Histologically, they are formed by an inflamed enlarged lamina propria, surrounded by colon mucosa with cryptitis and crypt abscesses. In addition, erosions and reactive changes in the epithelium, distortion, hyperplasia, and dilatation in the crypts are seen. Sometimes these polyps can be composed entirely of granulation tissue or pleomorphic reactive stromal cells similar to sarcoma cells [10–12] (Fig. 9.1).

To distinguish this reaction from malignancy, attention should be paid to the zonal separation of atypical cells, the rarity of mitosis, the absence of atypical mitosis, soleness, and small size of the lesion, and the presence of concomitant inflammatory bowel disease. Since stromal cells are stained with vimentin and smooth muscle actin, the cells are thought to originate from reactive fibroblasts or myofibroblasts [12]. Dysplasia and even carcinoma are rarely seen in patients with inflammatory bowel disease [13, 14].

Treatment

Surgical excision is indicated if the underlying inflammation is large and involves multiple foci, and if there is bleeding or obstruction [6].

Prolapse-Type Inflammatory Polyp

Solitary rectal ulcer syndrome is an unrelated localized protuberance of the mucosa. In its pathogenesis traction and distortion of the distended mucosa due to peristalsis

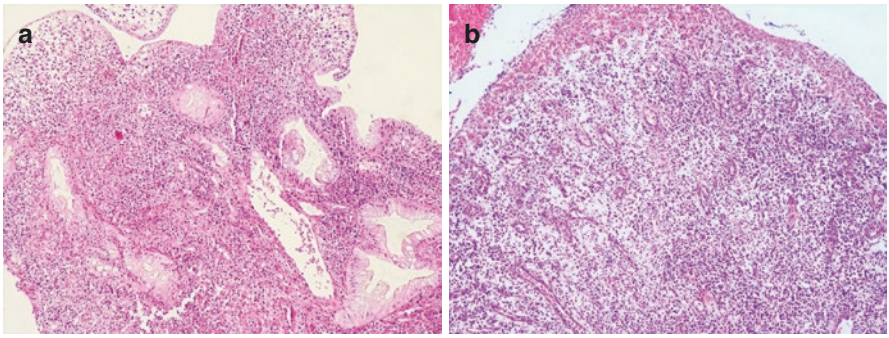

Fig. 9.1 Inflammatory pseudopolyps. (**a**) Composed of a mixture acute and chronic inflammatory infiltrate enlarged lamina propria, surrounded by colon mucosa with dilated crypts and cryptitis, surface erosion (H&E, ×100). (**b**) May be composed entirely of granulation tissue or pleomorphic reactive stromal cells (H&E, ×100)

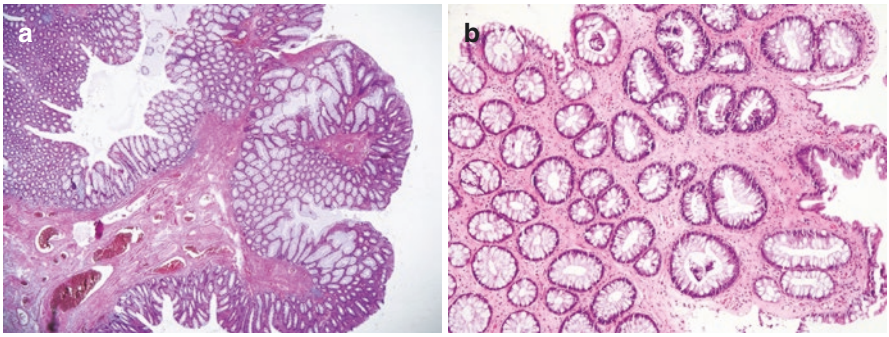

Fig. 9.2 Prolapse-type inflammatory polyp. (**a**) Polyp shows mucosal hyperplasia, strands of thickened and splayed muscularis mucosa extend around the crypt bases (H&E, ×20) and (**b**) into the lamina propria (H&E, ×100)

is implicated. It results in torsion of the vessels, with development of damage, ischemia, and fibrosis in the lamina propria [15].

Its histological features (Fig. 9.2);

1. Fibromuscular hyperplasia in lamina propria,
2. Thickening and extension of muscularis mucosa into lamina propria,
3. Elongation, hyperplasia, distortion, and serration of crypts,
4. Variable degrees of inflammation, ulceration, and reactive epithelial changes [16, 17].

Depending on the anatomical location of the injury and the underlying causes, these polyps are also called inflammatory polyps of the ileocecal valve, colitis cystica polyposa, polyps associated with diverticular diseases, and inflammatory clocogenic polyps of the anal transition region [17].

Inflammatory Cap Polyp (Cap Polyposis)

It is a rare, nonneoplastic lesion of any age first described by Williams et al. in 1985 [18, 19]. The etiology of inflammatory cap polyp (ICP) has not yet been fully elucidated. Repeated trauma to the colon mucosa caused by abnormal colonic mobility and difficulty in defecation have been considered as initial triggering events [18, 20].

Clinical Findings

Patients with ICP have diarrhea, mucous discharge, gastrointestinal (GI) bleeding, and tenesmus [21]. Endoscopically it is seen as small sessile, semipedunculated polyps with a diameter ranging from a few millimeters to centimeters. It is often located in the rectum or rectosigmoid [22].

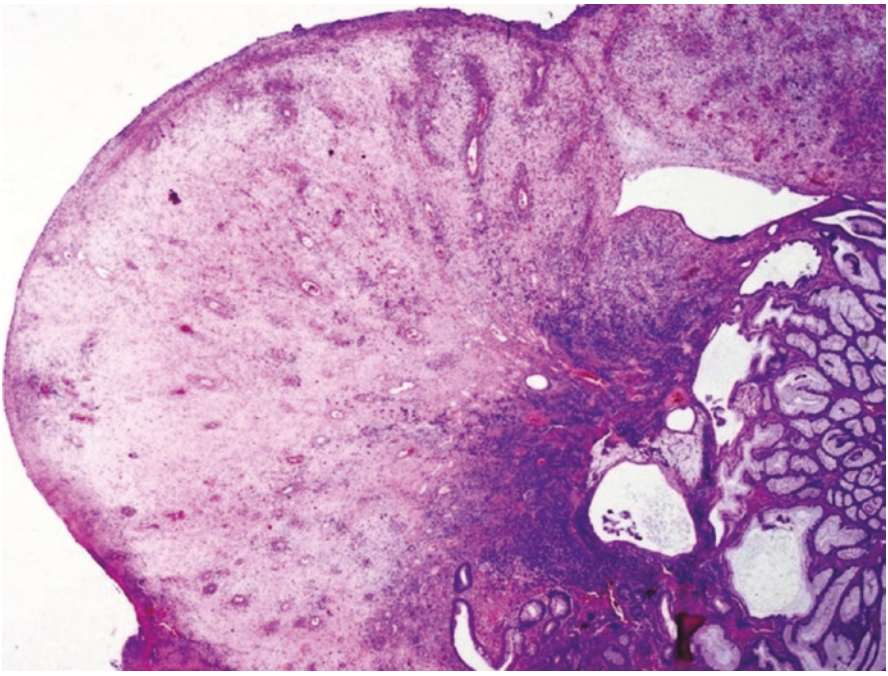

Fig. 9.3 Inflammatory cap polyp. A hematoxylin-eosin stain of inflammatory cap polyp shows the typical cap structure composed of the inflammatory granulation tissue. In addition, hyperplastic benign gland structures are observed under the cap (H&E, ×20)

Histopathological Features

Characteristic cap polyp is composed of ulcerated, inflamed granulation tissue, and its lamina propria contains severe inflammation, elongated hyperplastic, dilated, tortuous crypts [23, 24] (Fig. 9.3).

Treatment

These polyps may regress after the underlying disease (ulcerative colitis or nonspecific colitis) is treated [25]. Spontaneous regression or regression after treatment of *Helicobacter pylori* infection may be seen in some patients. Surgical excision is applied to multiple polyps [23, 26, 27].

Inflammatory Cloacogenic Polyp

Inflammatory cloacogenic polyps (ICPs) are rarely seen, often benign sessile polyps with a diameter of 1–5 cm located at the anorectal junction. Rectal bleeding is the most common symptom. It can occur with any disease that causes intestinal damage. Histomorphologically, ulcerated surface and tubulovillous growth are characteristic

features. Lymphoplasmacytic inflammation and fibromuscular hyperplasia are seen in lamina propria, and submucosa contains cryptic formations. Treatment consists of excision of the polyp, followed by colonoscopic surveillance [28].

Colitis Cystica Profunda/Polyposa

Colitis cystica profunda (CCP) is of clinical importance because it often mimics malignant colorectal lesions [29]. It has been associated with many acquired disease states as rectal prolapse, solitary rectal ulcer, inflammatory bowel disease, diverticulitis, local rectal trauma, and adenocarcinoma [29, 30].

Macroscopic Findings

CCP is seen as focal, segmental, or diffuse lesions in the colon. Its localized form has been described to be associated with solitary rectal ulcer syndrome, rectal prolapse, and its more prevalent types have been detected in patients with Crohn's disease, ulcerative colitis, radiation, and infectious colitis [29–32]. Mitsunaga et al. recently reported a single case of polypoid CCP lesion associated with adenocarcinoma [33]. Therefore, careful histopathological examination of all CCP specimens and exclusion of a related malignancy is recommended [34].

Histopathological Findings

It is characterized by the presence of multiple dilated, cystic mucin-filled crypts in colon submucosa, rarely muscularis propria and serosa. It differs from adenocarcinoma in that the crypts are lined with the normal or reactive epithelium. In addition, it is differentiated from carcinoma with its lobular structure, presence of lamina propria, and hemorrhagic areas/hemosiderin around the crypt [30, 33, 35].

Treatment

Surgical treatment is reserved for patients with severe symptoms of rectal prolapse and conservative management is appropriate in others [32, 36].

Diverticular Disease-Associated Polyp

They are rarely seen nonneoplastic polyps that develop on the ground of diverticular disease and are often located in the sigmoid colon [37]. Polyps associated with diverticulosis are classified into two types as inverted diverticular and polypoid prolapsing mucosal folds [38, 39]. Inverted colonic diverticula is characterized endoscopically as a 0.2–2 cm sessile/pedunculated lesion having the same color as its surrounding mucosa. Polypoid prolapsing mucosal folds are more common forms of polyps associated with diverticular diseases. The grossly bright red polypoid is slightly elevated and has a size of 0.5–3 cm [40, 41].

Histologically, early lesions have vascular congestion, hemorrhage, and accumulation of hemosiderin. Advanced lesions demonstrate edema, capillary thrombi, fibrosis of the lamina propria, and branching and dilatation of the crypts (Fig. 9.4). Most polyps undergo regression [37, 38].

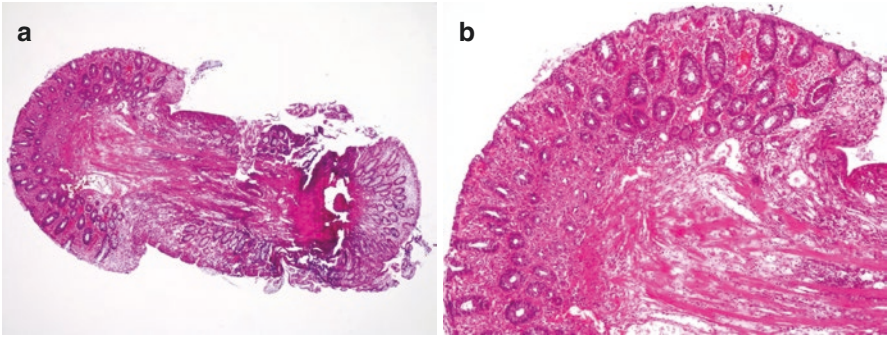

Fig. 9.4 Diverticular disease-associated polyp: Mucosal edema, congestion, fibromuscular expansion of lamina propria, epithelial hyperplasia (**a**, H&E, ×40 and **b**, ×100)

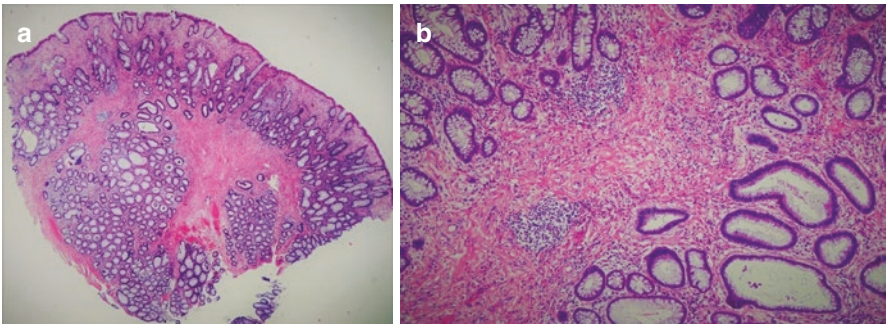

Fig. 9.5 Inflammatory myoglandular polyp. (**a**) Inflammatory granulation tissue in the lamina propria, smooth muscle proliferation and hyperplastic glands (H&E, ×20). (**b**) In the large magnification area, hyperplastic glands with variable cystic changes and smooth muscle proliferation (H&E, ×100)

Inflammatory Myoglandular Polyp

They are rarely seen polyps usually localized in the left colon and sigmoid [40]. They can occur at any age (15–78 years). Clinical symptoms are occult or rectal bleeding. Macroscopically they are 0.4–2.5 cm, mostly pedunculated spherical lesions. They appear as scattered mucin-filled cysts in dark brown stroma [42, 43].

Histopathological Findings

Inflammatory myoglandular polyps are characterized with inflammatory granulation tissue in the lamina propria, smooth muscle proliferation and hyperplastic glands with variable cystic changes. Surface epithelium may reveal regenerative changes in the form of serrated or hyperplastic formations, and loss in their mucin content (Fig. 9.5). The etiology of this type of polyp is not known, but may include chronic trauma from forced fecal passage and intestinal peristalsis [42, 43].

These polyps may be distinguished from juvenile polyps and inflammatory polyps by the presence of abundant smooth muscle cells in the mucosa of the inflamed lamina propria. Furthermore, it should be differentiated from Peutz-Jeghers polyps

that appear as hamartomatous structures by tree-like proliferation of muscularis mucosa covered with colonic mucosa without inflammatory granulation tissue. Their localization and macroscopic appearance differentiate these polyps from polyps developing after mucosal prolapse syndrome and colostomy. In addition, these new polyps are different from inflammatory cap polyps due to the absence of a fibrin cap [42–44].

Hamartomatous Polyps

Hamartomas are defined as overgrowths of cells and tissues specific to the anatomical region in which they originate from [45]. Hamartomatous polyps (HPs) in the gastrointestinal (GI) tract are rare compared to other GI polyps, but are the most common type of polyp in children. Symptoms are usually rectal bleeding, abdominal pain, constipation, anemia, and/or small bowel obstruction [46]. Hamartomas are usually solitary but may also occur as part of hamartomatous polyposis syndrome such as juvenile polyposis syndrome (JPS), Peutz-Jegers Syndrome (PJS), Cowden syndrome (CS), or Bannayan-Riley-Ruvalcaba syndrome (BRRS). Cowden disease and BRRS, phosphatase and tensin homolog (PTEN) are known as hamartoma tumor syndrome [46–48].

Juvenile Polyps and Juvenile Polyposis

Juvenile polyps (JPs) are rare hamartomatous malformations of the gastrointestinal tract that may occur in hereditary juvenile polyposis syndrome (JPS) or sporadically. Although they are observed in the first two decades of life, they are not also rarely seen in adults [49, 50].

Juvenile polyps are seen in four different types [51].

1. Sporadic/isolated juvenile colonic polyps
2. Infantile JP
3. Juvenile polyposis coli
4. Generalized JPS (involving stomach, small intestine, and colon)

These polyps are important because of their different clinical behaviors and the risk of malignancy. There is no increase in the risk of malignancy in sporadic JPs. However, JPS also has a variable risk for gastrointestinal (GI) carcinoma [51, 52].

JP is the most common autosomal dominant hamartomatous polyp of the gastrointestinal tract (GIT) and characterized by the presence of multiple juvenile polyps in the gastrointestinal tract. It usually occurs in the rectum during the first two decades of life. Children usually have painless rectal bleeding or polyps along the rectum. There is a significantly increased risk of colorectal cancer in advanced ages, and colorectal cancer develops in 30–40%, and upper GIT cancers in 10–15% of the cases [51–53].

World Health Organization criteria for the diagnosis of JPS require the presence of one of the following criteria [54, 55]:

1. Presence of more than 3–5 juvenile polyps in the colon and rectum;
2. Juvenile polyps throughout the GI tract; or
3. Any number of juvenile polyps in a person with a family history of juvenile polyposis

Molecular Characteristics

Fifty percent to 60% of JPS patients have germline mutations of SMAD4 or BMPR1A, TGF-β/BMP pathway genes. SMAD4 mutations are found in 15–20%, and BMPR1A mutations in 20–25% of the cases [51, 56].

In a large-scale study performed, foci of dysplasia were observed in 9% of typical juvenile polyps (type A-classical JP) and in 7% of atypical JPs (type B-epithelial phenotype). JPs with SMAD4 germline mutation express an epithelial phenotype with a relatively high crypt density, whereas JPs with BMPR1A mutation are generally the classic juvenile polyp phenotype with a pronounced stromal compartment. Importantly, similar rates were found for all degrees of dysplasia in juvenile polyps with SMAD4 or BMPR1A mutations [57].

Macroscopic Features

JPs are macroscopically pedunculated, rarely seen sessile lesions often smaller than 3 cm in diameter. The classic form JP is unilobulated lesion with smooth, red brown surface, while atypical juvenile polyps are lobular or multilobular [52, 57].

Histopathological Features

JPs are composed of numerous cystic, dilated, tortuous crypts, some of which contain thickened mucin, filled with neutrophils, and edema and lymphocytes, plasma cells, numerous neutrophils and eosinophils in the lamina propria. Glands are comprised of well-structured, mucin secreting cells (Fig. 9.6). Their epithelium

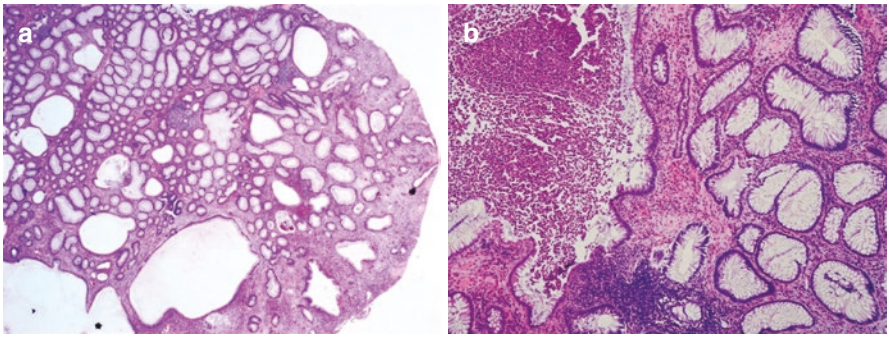

Fig. 9.6 Juvenile polyp. (**a**) Microscopic view of the whole polyp. At this magnification, cystic dilated glands and enlarged lamina propria can be observed (H&E, ×20). (**b**) At higher power, the crypts are cystic, dilated, tortuous, some of which contain thickened mucin, filled with neutrophils. The lamina propria is also expanded and contains edema and numerous of mixed inflammatory cells (H&E, ×100)

regenerates when it is ulcerated [58, 59]. Sometimes, silent osseous metaplasia can be seen [60]. Patients with JPS may have a combination of other polyps (juvenile polyp and adenoma) [57].

Treatment and Follow-Up

Polypectomy is an adequate treatment for solitary juvenile polyps when there is no potential malignancy [61, 62]. However, unlike other hamartomatous syndromes, JPS has a high malignancy potential without extraintestinal malignancy [51, 59]. Therefore, JPS requires endoscopic screening and prophylactic surgery in patients carrying a higher risk for colorectal carcinoma. If any of the SMAD4 and BMPR1A genes are identified, family screening should be performed [63].

Peutz-Jegher's Syndrome

Peutz-Jegher's Syndrome (PJS) is an autosomal dominant disease of the hamartomatous polyps carrying risk for stomach, small intestine, and colon malignancies accompanied by mucocutaneous pigmentation. However, 25% of these patients do not have a family history which suggests the presence of a spontaneous mutation. Its incidence is 1 in 50,000 to 1 in 200,000 births [64, 65]. The age of the patients ranges from 2 to 62 years. In 1998, the main gene responsible for PJS was determined as the STK11/LKB1 gene, i.e. a serine-threonine kinase gene localized on chromosome 19p13.3 [66, 67].

The diagnostic criteria for PJS are listed as follows [68]:

1. ≥3 histologically diagnosed Peutz-Jegher's (PJ) polyps
2. Any number of PJ polyps in an individual with a relevant family history
3. Characteristic mucocutaneous pigmentation with a family history or
4. Any number of PJ polyps accompanied by characteristic mucocutaneous pigmentation

Pathologic Features

Hamartomatous polyps of PJS occur throughout GIT. Their sizes range between 0.5 and 3.5 cm. They are sessile or pedunculated [69].

Microscopically, the most characteristic component of lamina propria is the distinct branching pattern (the same Christmas tree) of muscularis mucosa-derived smooth muscles which consists of branched crypts covered with hypertrophic goblet cells (Fig. 9.7). Lamina propria does not show significant inflammation at normal cellularity. The epithelium is hyperplastic and rarely dysplastic. However, it has been reported that it may contain adenomatous and carcinomatous transformation areas [68–70].

GI and extraintestinal neoplasms are increasing in frequency. Ishida et al. studied 583 Japanese patients with PJS and estimated the cumulative risk of a malignant tumor to be 83% at the age of 70 years. In another study, gastrointestinal, prostate,

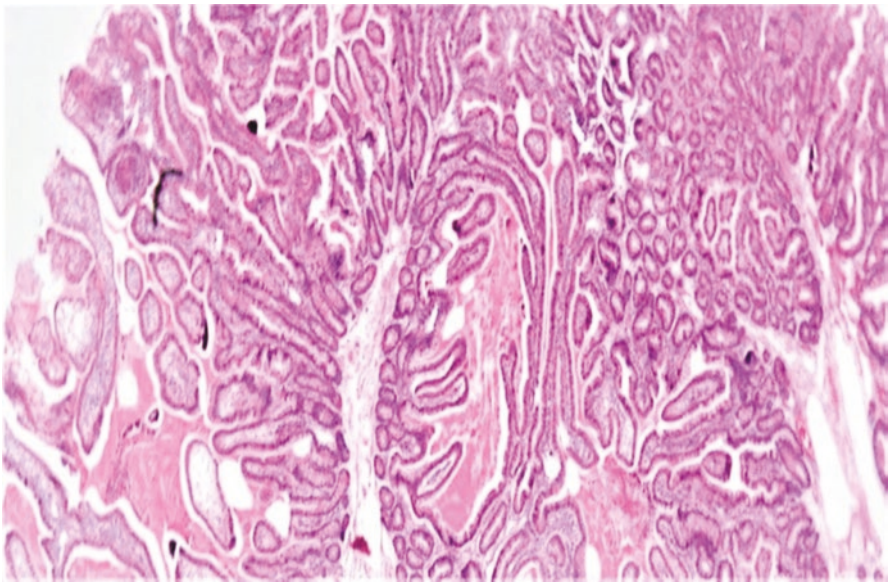

Fig. 9.7 Peutz–Jegher's polyp in the colon: At a low power; the polyp has a branching Christmas tree appearance. Branching smooth muscle fibers are derived from muscularis mucosa (H&E, ×40)

breast, lung, thyroid, hypopharyngeal and liver cancers frequently develop in patients with PJS [70, 71]. Endoscopic treatment is the main treatment. PJS patients should be followed up regularly because of increased risk of cancer and disease recurrence [72].

PTEN Hamartoma Tumor Syndrome

PTEN hamartoma tumor syndrome (PHTS) is a highly variable, often autosomal dominant condition associated with overlapping intellectual disability, overgrowth, and tumor susceptibility phenotypes.

PHTS includes a number of syndromes such as Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome and macrocephaly-autism/developmental delay syndrome. Many reviews in the literature have focused on PHTS in terms of predisposition to adult hamartomas and malignancies [73].

Cowden Syndrome

Clinical Features

Cowden syndrome is an autosomal dominant hamartoma/neoplasia syndrome termed by Lloyd and Dennis in 1963 [47]. In 1996, the focus of predisposition to Cowden syndrome was mapped at chromosome 10q22-23 [74]. In 1997, germline mutations in the PTEN gene on chromosome 10q23 have been reported in families with this syndrome [75–77].

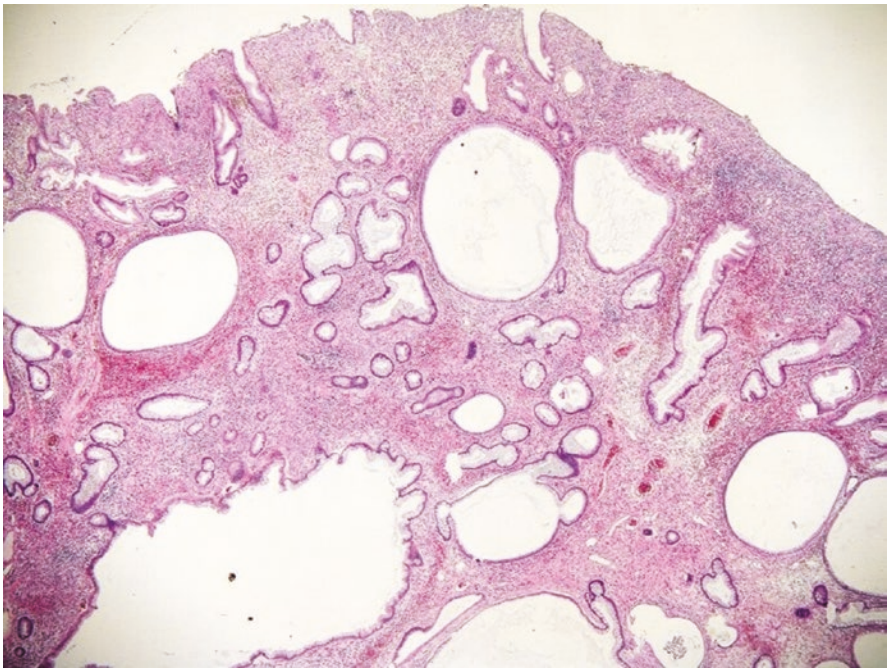

Fig. 9.8 Hamartomatous polyp from a patient with Cowden syndrome: Lamina propria contains cystic, dilated, mucin-filled crypts (H&E, ×20)

In Cowden syndrome hamartomas contain three germ cell lines. Mucocutaneous lesions, trichilemmoma, acral keratoses, and oral papillomas are present in almost all patients (90–100%). Multinodular goiter of thyroid diseases is found in 50–75% of the cases with follicular adenomas. Thyroid carcinoma occurs at a rate of 3–10%. There is an increased risk in endometrial and renal cell carcinoma [78, 79].

Pathologic Features

GI hamartomas in CS are found in the stomach, small intestine and colon at a rate of 35–40%. These polyps are histomorphologically similar to juvenile polyps (Fig. 9.8).

Lamina propria contains cystic, dilated, mucin-filled crypts [80, 81]. In addition, colonic lipoma, fibrolipoma, fibroma, ganglioneuroma and adenomas have been reported [82, 83]. The risk of colorectal adenocarcinoma in patients with CS with PTEN mutations is 10–15% [83, 84]. Therefore, endoscopic GIS examinations, breast and thyroid screening tests are important [82].

Cronkhite-Canada Syndrome

Clinical Features

Cronkhite-Canada Syndrome (CCS) is a rare, nonfamilial polyposis syndrome of unknown etiology. It was first described by Cronkhite and Canada in the year 1955

[85]. It mostly affects middle-aged people, and it is more frequently seen in men with a male/female ratio of 3:2. Colonic polyps are associated with ectodermal abnormalities (alopecia, nail atrophy, and skin hyperpigmentation). Patients frequently have symptoms of diarrhea, weight loss, nausea and vomiting, anorexia, and GI bleeding [86, 87].

Pathologic Features

Polyps occur throughout the GI tract in the CCS. Histologically similar to juvenile dilated mucin-containing cystic polyps that look like sawtooth are seen. Lamina propria contains edematous, mononuclear cells, and eosinophils. Colonic JPs are often pedunculated compared to CCS polyps [88].

Natural History

The malignancy potential for colonic CCS is controversial. Mortality is seen in 50–60% of the patients due to malnutrition, GI bleeding, or infection [86, 87].

Epithelial Polyps

Hyperplastic and Serrated Lesions and Polyps

Hyperplastic and serrated lesions and polyps have been recently reclassified in 2019 by the World Health Organization (WHO) [89].

1. Nondysplastic serrated lesions and polyps
   (a) Microvesicular hyperplastic polyp (MVHP)
   (b) Goblet cell hyperplastic polyp (GCHP)
   (c) Mucin-poor hyperplastic polyp (MPHP)
   (d) Sessile serrated lesions (SSL)
2. Dysplastic serrated lesions and polyps
   (a) Sessile serrated lesions with dysplasia (SSLDs)
   (b) Traditional serrated adenoma (TSA)
   (c) Conventional adenomas with serrated architecture
3. Unclassifiable serrated adenomas (USA)

Nondysplastic Serrated Lesions and Polyps

Hyperplastic Polyps

Clinical Features

Hyperplastic polyps are mostly benign, and constitute 75–90% of serrated lesions/polyps. These polyps can be found throughout the entire colon, but are particularly localized in the distal colon and rectum. They are common asymptomatic polyps in women over 50 years of age. It is seen endoscopically as pearly colonic papular lesions [90, 91].

Pathogenesis

Hyperplastic polyps develop as a result of irregular cell proliferation. In these patients, altered BCL2 and BAX gene expression, loss of chromosome 1p heterozygosity, APC gene, chromosome 3p and CDKN2A gene, overexpression of TP53, and KRAS mutations and altered CDKN1B expressions have been detected [92, 93].

Pathologic Features

Most hyperplastic polyps are macroscopically smaller than 0.5 cm and have smooth surfaces. Proximal HPs are poorly contoured. They have a rim with mucus caps and debris [94, 95].

The characteristic features of HPs include marked serration towards the luminal face, narrow-based simple elongated crypts, and maturation towards surface similar to normal mucosa, and proliferative activity in the basal one-third of the crypt. In HPs, there is a thickened basement membrane beneath the surface epithelium that is not regularly found in sessile and serrated lesions [90, 91].

HPs can be subclassified as microvesicular, goblet cell-rich, and mucin-poor types, but these subclassifications are currently not of clinical importance [94].

The microvesicular type is the most common type. These lesions contain abundant microvesicular mucin and a small number of goblet cells (Fig. 9.9a). These polyps are often characterized by an enlarged proliferative compartment and prominent luminal serration of half of the crypt base in the left colon. In Ki7 immunohistochemical staining, one-third of proliferating crypts are stained (Fig. 9.9b). There is no mitosis in the upper part of the crypt and surface epithelium. In addition, the surface epithelium is CK20 positive [92–94]. Nuclear atypia is minimal, but some polyps show mild stratification. Dystrophic goblet cells and round vesicular nuclei and prominent nucleoli are rarely found. These polyps show a mature surface with a small nucleus localized in the basal layer of the crypt, and abundant microvesicular mucinous cytoplasm. The basal layer of the crypts is lined with undifferentiated cells with small nuclei, and narrow cytoplasm MVHPs tend to harbor BRAF mutations (76%) and DNA methylation abnormalities (CpG island methylator phenotype (CIMP)) (45%) [93–97].

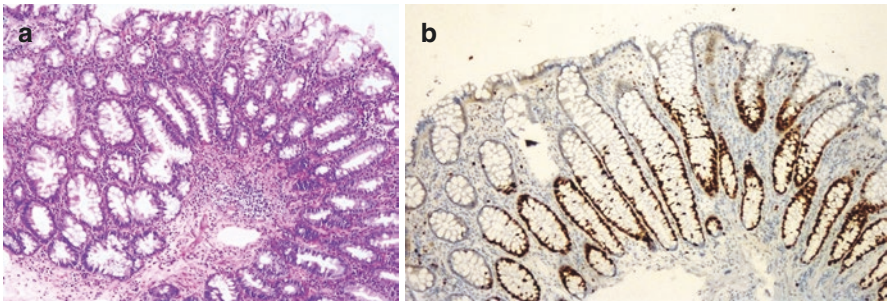

Fig. 9.9 Hyperplastic polyps, microvesicular type. (**a**) Prominent luminal serration and a columnar cells with microvesicular mucinous cytoplasm and goblet cells (H&E, ×100). (**b**) In Ki7 immunohistochemical staining, one-third of proliferating crypts are stained (DAB, ×100)

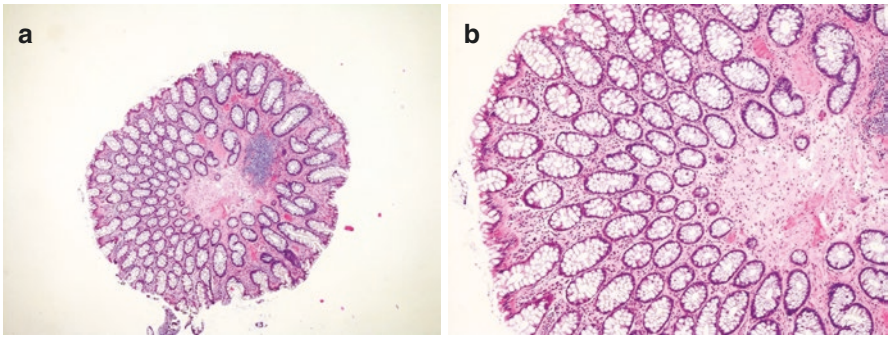

Fig. 9.10 Hyperplastic polyp, goblet cell-rich type, shows less luminal serration compared with the microvesicular type and the epithelium contains plenty of goblet cells, H&E, ×40 (**a**), ×100 (**b**)

Goblet cell hyperplastic polyps are among the second most common hyperplastic polyps. The sessile lesions less than 0.5 cm in diameter are often located in the left colon. These polyps consist of crypts rich in elongated goblet cells. They do not contain microvesicular mucin (Fig. 9.10). Normally they are sessile lesions with little serration on the surface and luminal serration at the upper part of the crypt. Nuclear atypia, pseudostratification, and mitosis are not seen [94, 98]. KRAS mutations in GCHPs are common (42%), while BRAF mutation (21%) is not [99, 100].

Mucin-poor hyperplastic polyps are less common. These polyps are prominently regenerative in appearance, and demonstrate mucin depletion, goblet cell-free, and micropapillary structure, small sessile lesions with small cells with lesser cytoplasm. The absence of mucin is the main feature of the hyperchromatic nucleus. There is inflammation in the lamina propria [94, 99].

Differential Diagnosis

As the potential for malignancy is clearly demonstrated in sessile serrated lesions (SSLs) and traditional serrated adenomas (TSAs) identification, accurate histological classification of these tumors is important [98].

They are differentiated from HPs, SSL, TSA, prolapse-type inflammatory polyps, and conventional adenoma with their structural and cytological features.

Unlike hyperplastic polyps, in SSLs structural changes in crypts are in the form of horizontal growth along the muscularis mucosa. These changes include dilatation at the base of the crypt (basal one-third of the crypt), full serration and proliferation spreading to the crypt base, branching in the crypts, increasing number of dystrophic goblet cells, focal nuclear stratification, and mitotic changes in upper crypt cells. If the lesion is a sessile polyp larger than 0.5 cm, and localized in the right colon, it is probably early phase SSL [98, 101].

TSAs are easily differentiated from HPs in that they are larger than HPs, and have villiform structure, and cytoplasmic eosinophilia at all levels of the crypt [98]. Prolapse-induced inflammatory polyps are inflamed and ulcerated. These types

have superficial ischemic type features, prominent regenerative epithelium, and they are characteristised by fibromuscular hyperplasia in lamina propria [15, 98]. Conventional adenomas have hyperchromatic, pseudostratified cigar-shaped atypical nucleus [98].

Treatment

HPs greater than 2 cm have a low risk of dysplasia and malignant transformation [94]. Small polyps should be excised during endoscopic biopsy. If large lesions show SSL-like serration and localized in the right colon, treatment is total excision [102].

Sessile Serrated Lesions

Clinical Features

SSLs are polyps larger than 5 mm, often located in the proximal colon, and consist of 15–25% of all serrated polyps. Endoscopically, they are generally flat-sessile polyps that have the same color of the mucosa, or slightly reddish.

Molecular Properties

SSLs demonstrate BRAF mutations (80%) with CpG island methylator phenotype (CIMP-H) (90–92%), which is highly DNA methylated. Less than 5% of the cases show low APC or KRAS mutation and TP53 abnormality. Morphologically microsatellite instability is absent until dysplasia or carcinoma develops. Today SSLs are believed to be the precursors of sporadic microsatellite-unstable colorectal carcinomas (MSI-H neoplasms) and CpG island-methylated microsatellite-stable cancers. Some of these lesions rapidly develop into dysplasia or invasive carcinoma showing lymphovascular invasion and lymph node metastasis [94, 100, 103].

Pathologic Features

SSLs are distinguished from HPs by their structural properties resulting from their manifestations of variable proliferation. In these lesions, the proliferation sites are usually irregular on one side of the crypts, rather than on the bottom. This feature can be demonstrated by Ki67 staining. There are often gastric-type mucin and serrations at the base of the crypts. Endocrine cells decrease or disappear [95].

The distinctive features of SSL include branching and dilatation in the basal part of the crypts, inverse T and L-like appearance, exaggerated mitosis on the basal layer of the whole crypt, vesicular nuclei in the upper crypts, deficient lamina propria between the crypts, hypermucinous epithelium and rarely growth towards submucosa [91, 93, 94]. Mature goblet and mucinous cells show irregular distribution on the basal layer of the crypt (Fig. 9.11).

SSLs can show varying degrees of nuclear atypia. SSA/P s have irregular, asymmetric, and characteristic Ki67 pattern [94] (Fig. 9.12).

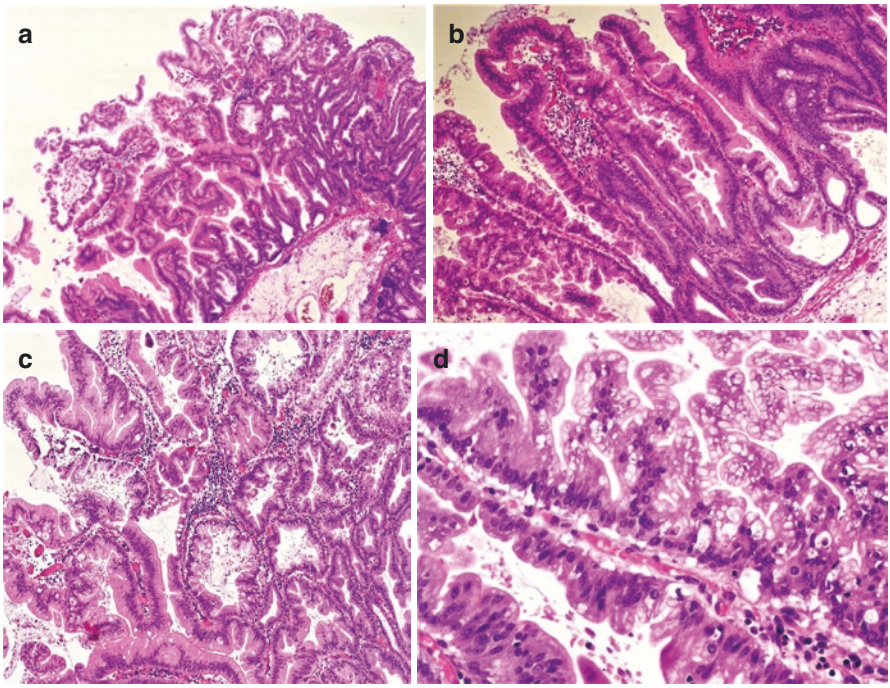

Fig. 9.11 Sessile serrated lesion (SSL). (**a**, **b**) SSL is characterized by many architecturally distorted serrated crypts with prominent basal crypt dilatation and basal crypt dilatation with lateral growth along the muscularis mucosae (H&E, ×40, ×100). (**c**, **d**) Mature goblet and prominent mucinous cells show irregular distribution on the basal layer of the crypts (H&E, ×100, ×200)

Dysplastic Serrated Lesions and Polyps

Sessile Serrated Lesions with Dysplasia (SSLD)

Previously, these lesions were called mixed hyperplastic/adenomatous polyps. Until recently, these lesions have been termed as sessile serrated adenoma/polyps with dysplasia, but they have been renamed as sessile serrated lesion with dysplasia according to the 2019 WHO classification [89].

Pathologic Features

SSLD is a morphologically heterogeneous lesion with dysplastic as well as hyperplastic changes of typical microvesicular polyps. The present changes are similar to conventional adenomas, but have differences in the level of the molecular pathway. Structurally, villous architecture, elongation of the crypts, complex branching, crowding of the crypts with cribriforming, and reduced or excessive luminal serration are observed. Serrated dysplasia which is typical of these lesions is

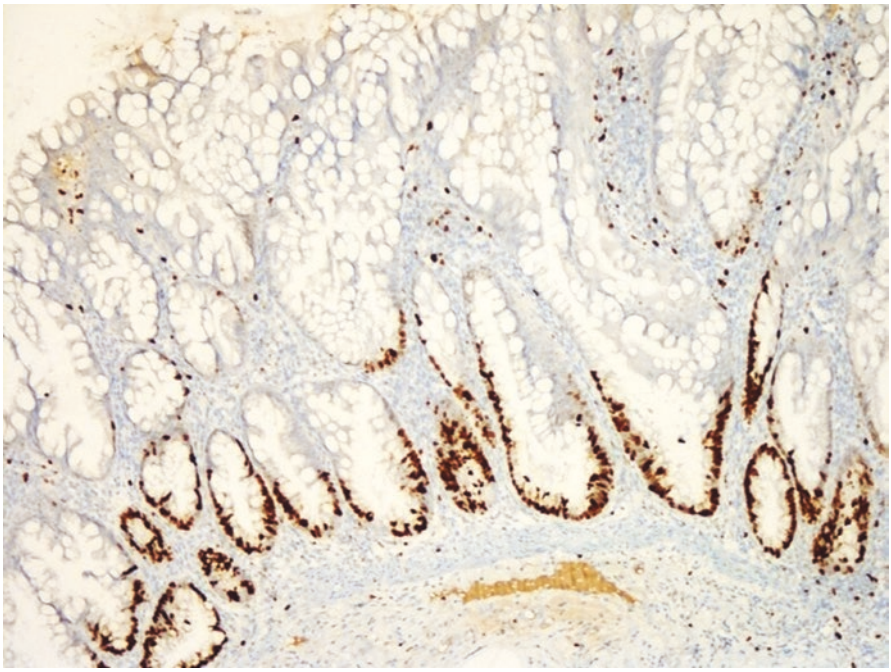

Fig. 9.12 SSLs have irregular, asymmetric, and characteristic Ki67 pattern (DAB; ×100)

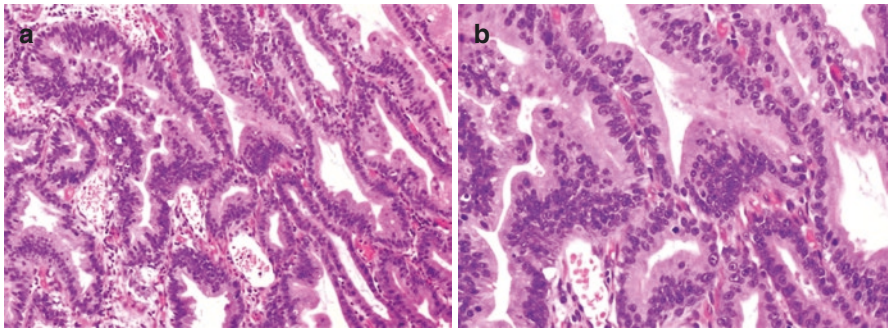

Fig. 9.13 Sessile serrated lesion (SSL) with dysplasia (SSLD). (**a**) Architectural features of SSLDs include crypt irregularite, complex branching, cribriforming, extreme or reduced luminal serration (H&E, ×100). (**b**) The serrated dysplastic epithelium shows with hyperchromatic, pleomorphic mild stratified nuclei, eosinophilic cytoplasm, and mitotic figures (H&E, ×200)

characterized by cuboidal cells with eosinophilic cytoplasm and round vesicular nuclei containing numerous mitoses when compared with conventional adenomas (Fig. 9.13). The cells have prominent nucleoli [89].

Cytologically, they may show dysplasia similar to that of conventional adenomas [104, 105]. Low or high stratification of dysplasia is not recommended and is not

reproducible due to lack of correlation between morphological heterogeneity and loss of MLH1 expression [106, 107].

Molecular Features

The molecular characteristic features of SSLDs are BRAF mutations, nuclear β-catenin accumulation, CIMP-H and MSI as a consequence of MLH1 gene silencing due to promoter hypermethylation [103].

SSLDs harbor activating mutations in BRAF (MGK7), a gene that promotes proliferation and eliminates the effects of apoptosis. These mutations do not allow cells to undergo apoptosis, they accumulate along the basement membranes and lead to serration [108]. Sessile serrated adenomas are prone to methylation of the promoter that can lead to inactivation of MLH1 leading to microsatellite instability or to methylation of various other genes leading to CIMP-H microsatellite-stable neoplasia [109].

Treatment

Endoscopic treatment, such as endoscopic mucosal resection or endoscopic submucosal dissection, is useful for these lesions. If endoscopic invasive carcinoma is suspected in SSL, surgical resection with lymph node dissection is necessary because they have a high risk of lymph node metastasis [110].

Traditional Serrated Adenoma (TSA)

TSAs were originally described by Longacre and Fenoglio-Preiser as mixed hyperplastic adenomatous polyps/serrated adenomas [98, 111]. Subsequently, Torlakovic et al. termed TSAs as hyperplastic polyps (HP), sessile serrated adenomas/polyps, and traditional serrated adenomas [111, 112]. In the WHO classification of colorectal serrated lesions and polyps in 2019, TSAs were included in the group of serrated lesions with dysplasia [89]. TSAs are generally defined as hypereosinophilic epithelial polyps with low or high dysplasia that develop into distinctly serrated, villiform structures. Unlike SSL, TSAs are pedunculated polypoid lesions [113].

Clinical and Epidemiological Features

TSAs are rarely seen polyps, constituting <1% of all colorectal polyps and 1–7% of serrated lesions in most series [108].

These lesions are more common in women and protuberant polyps manifest in the distal colon and rectum, and flat lesions in the proximal colon [95]. SSA/P and hyperplastic polyps are seen at a more advanced age and they are pedunculated rather than sessile lesions [113].

Pathogenesis

Their pathogenesis is not known exactly. In some studies, they were thought to develop from hyperplastic polyps or SSA/P [112]. However, some studies found the relationship to be insufficient and suggested that they develop through additional alternative pathways. In TSAs, very frequently RSPO3, RNF43, some degree of CIMP, relatively equal levels of BRAF and KRAS mutations and aberrant nuclear

localization of β-catenin were detected. All TSAs show retention of mismatch repair proteins [114, 115]. BRAF mutated TSAs are often associated with CIMP and progress to mismatch repair-proficient carcinoma which has a poor prognosis [114].

Pathologic Features

TSAs are similar to conventional adenomas as for their endoscopic and macroscopic features. These polyps are generally pedunculated and rarely large and filiform [113].

The histopathological characteristics of TSA are as follows (Fig. 9.14):

1. Typical slit-like clefted serration, complex villiform projections,
2. Ectopic crypt foci (ECF),
3. Centrally placed elongated, narrow pencillate nuclei with delicate dispersed chromatin and cytoplasmic hypereosinophilia [116].

Although TSA is a mucin/goblet cell type lesion, it contains small number of scattered goblet cells [117].

At least two of these three features are required for diagnosis. Besides, at least one feature should be present in 50% of the polyps [114].

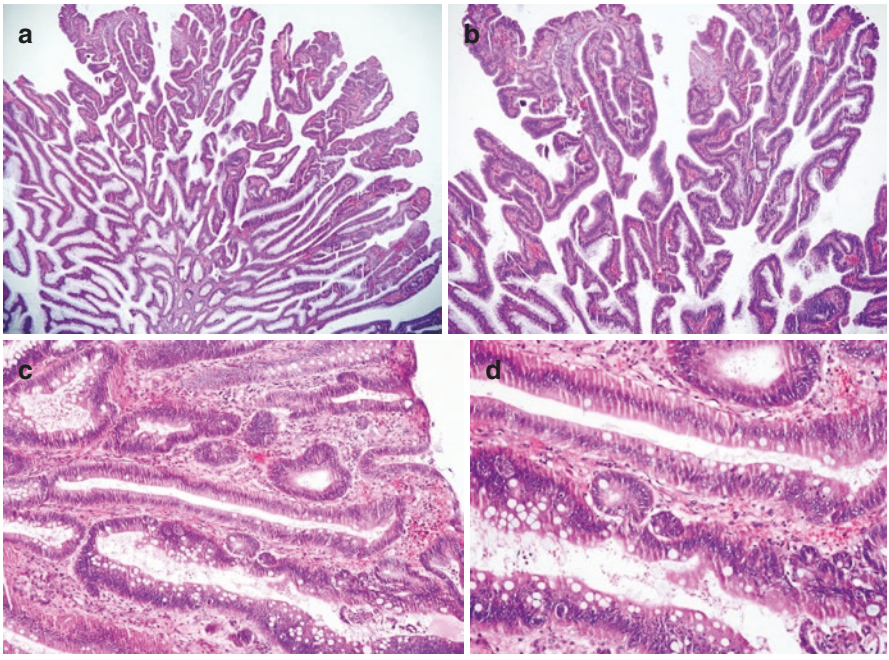

Fig. 9.14 Traditional serrated adenoma (TSA). (**a**, **b**) Typical slit-like clefted serration, complex villiform projections (H&E, ×20, ×40). (**c**) Ectopic crypt formation is seen in this magnification (H&E, ×100). (**d**) At high power, tall and columnar cells with abundant eosinophilic cytoplasm and centrally located oval nucleus with pseudostratification but absent mitotic activity (H&E, ×200)

TSAs have a protuberant growth pattern with villiform configuration and complex abnormal architecture in that the crypts do not "anchor" on the muscularis mucosae and they are randomly suspended (ectopic crypt formation) [112, 118].

Filiform TSAs contain elongations finger-like villous projections and often inflammation, ulceration and dilated lymphatic vessels in the lamina propria [113]. They have not prominent Ki67 immunoreactivity or mitotic activity and restricted Ki7 pattern in ECF [93, 112].

Based on their molecular heterogeneity, 50% of TSAs harbor MVHP, GCHP or SSL precursor lesions adjacent to them. In addition, they may manifest conventional adenoma-like areas and intestinal type high-grade dysplasia [119].

Treatment

Progression of TSAs to high-grade dysplasia has been reported in 37% of the cases [111]. Intramucosal adenocarcinoma has been reported in 11% of these patients [113]. Treatment is similar to conventional adenomas. Endoscopic extraction is required.

Unclassifiable Serrated Adenoma

Rarely, dysplastic serrated lesions cannot be differentiated from each other due to their overlapping features. In this case, the term dysplastic unclassifiable serrated lesion and nondysplastic unclassifiable serrated lesion can be used.

Conventional Adenoma with Serrated Features

Rarely, conventional tubular, tubulovillous, and villous adenomas may show areas of serration and they are separated from TSAs by their nuclear cytological features (Fig. 9.15). Conventional TVAs are larger than the serrated TVAs and located in the proximal colon. They contain higher rates of CpG island methylation and KRAS mutation. Serrated trait is associated with KRAS mutations. These adenomas are microsatellite-stable colorectal carcinoma precursor lesions [120, 121].

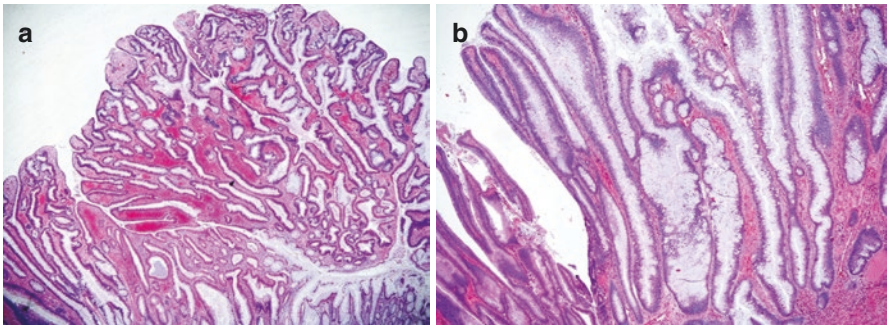

Fig. 9.15 Conventional adenoma with serrated features. (**a**) (H&E, ×20), (**b**) (H&E, ×40). In the field of low and high magnification, adenoma and serrated features are observed together

Serrated Polyposis Syndrome

It is a recently described rare disease. It is believed to be due to the overlap of clinical, pathological, and molecular heterogeneous diseases. It is seen equally among women and men. It has a higher prevalence of colorectal cancer at the time of diagnosis with estimates ranging between 25% and 40% [122].

Diagnostic criteria according to WHO classification are as follows [122–124]:

1. At least five histologically confirmed serrated lesions/polyps located proximal to the rectum, of which at least 2 are larger than 10 mm in diameter, all being at least 5 mm in size
2. More than 20 serrated lesions/polyps of any size distrubuted evenly throughout the colon, with of which at least five being proximal to the rectum.

The type of surgical procedure should be customized according to the distribution of polyps and patients' individualized factors. However, most patients are treated with segmental or extended resection (total colectomy with ileorectal anastomosis). Given the risks of colorectal cancer, it is reasonable to recommend colonoscopic surveillance to first-degree relatives of the patients with serrated polyposis syndrome every 5 years [122, 124].

Conventional Colorectal Adenoma (CCA)

Adenomas are defined morphologically as dysplastic colonal proliferation of the colon epithelium. The prevalence of colon adenomas varies in different parts of the world. These polyps, which are almost asymptomatic, are smaller than 1 cm and have a similar distribution throughout the entire colon. In fact, open or occult rectal bleeding is seen in most patients. The clinical significance of adenomas is associated with their almost entirely established premalignant characteristics [124, 125].

Pathologic Features

CCAs are macroscopically classified as sessile or pedunculated lesions. However, intermediary forms between the sessile and pedunculated forms may also develop. Tubular adenomas tend to be spherical (Fig. 9.16). Villous adenomas have a rough surface with prominent papillary protrusions [126].

Histomorphological features: CCA subtypes [126]:

1. Tubular adenoma, low/high grade
2. Villous adenoma, low/high grade
3. Tubulovillous adenoma, low/high grade
4. Advanced adenoma

Adenomas have a similar adenomatous epithelium regardless of their type. Adenomas are subtyped according to their general growth patterns. At least 75% of a villous adenoma, while less than 25% of a tubular adenoma should consist of villi. Twenty-five percent and 75% of a tubulovillous lesion should contain villi [126, 127].

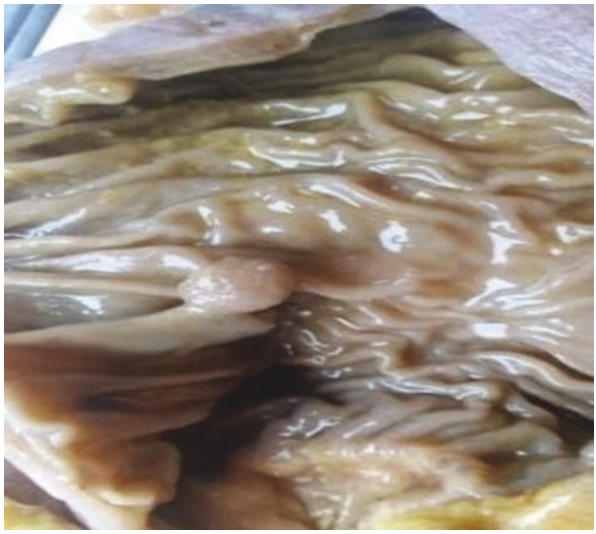

Fig. 9.16 Gross image of tubular adenoma

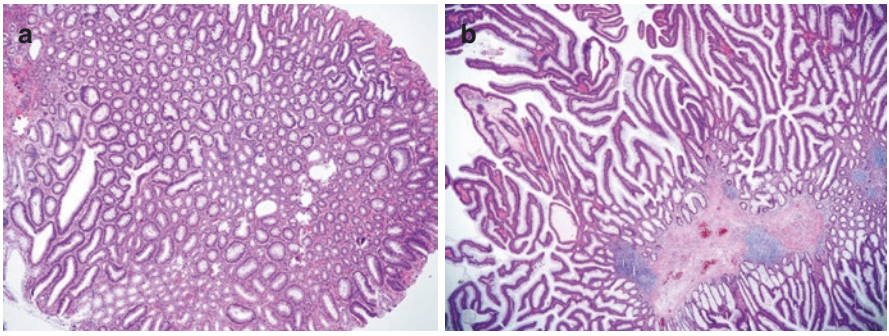

Fig. 9.17 Tubular adenoma and villous adenoma with low-grade dysplasia. (**a**) tubular adenoma is consisting of glandular or tubular formations, (**b**) villous adenoma with finger-like growth pattern (H&E, ×40)

Tubular adenomas are adenomatous epithelial proliferations showing glandular or tubular formations. The tubules are separated by lamina propria. Similar epithelium is seen in villous adenomas, but the growth pattern and configuration is in the form of a finger-like configurations extending vertically from the muscularis mucosa to the outer surface of the adenoma. Adenomas are formed from dysplastic epithelium. High- and low-grade dysplasias are seen [127, 128] (Fig. 9.17).

Low-grade dysplasia is defined by the presence of architecturally noncomplex crypts containing nuclei, which are either pseudostratified or partially stratified and detected only in lower half of the cell cytoplasm. Mitotic activity may be viable, but atypical mitoses, apparent loss of polarity, and pleomorphism are at least at a minimal level [127, 129, 130] (Fig. 9.18).

High-grade dysplasia is defined by the apparent pseudostratification or stratification of neoplastic nuclei, which are found in the luminal half of the cells and often

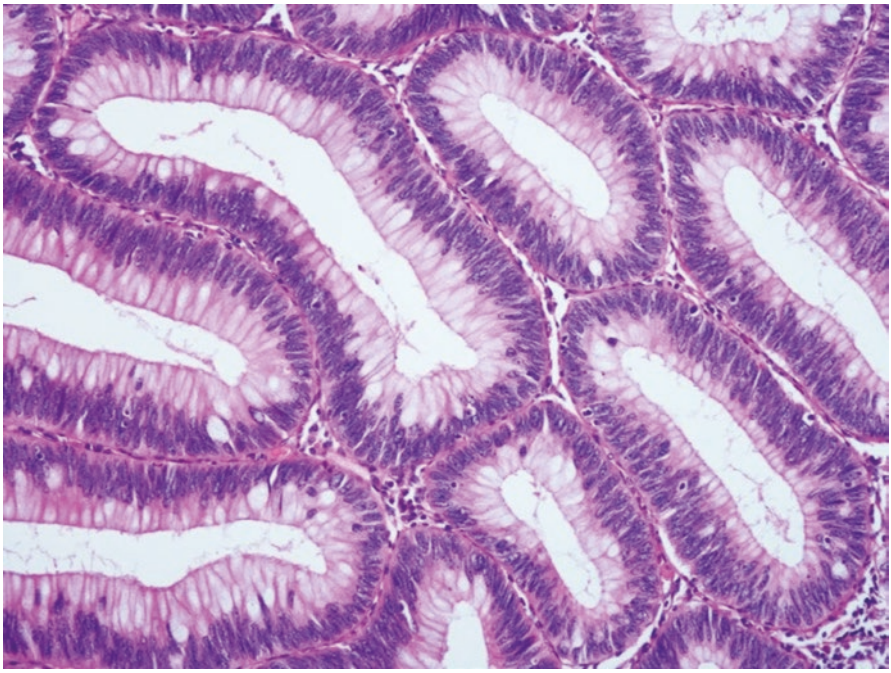

Fig. 9.18 Low-grade dysplasia in a tubulovillous adenoma: Features of low-grade epithelial dysplasia with mild cellular stratification of glands and no evidence of complex architecture (H&E, ×200)

involve significant pleomorphism, increased mitotic activity, atypical mitoses, and significant loss of polarity. Architectural changes such back-to-back gland configuration and cribriforming can also be noted (Fig. 9.19). The lamina propria of adenomas may be affected by variable degrees of acute and chronic inflammation and contain different numbers of eosinophils. Paneth cell and/or endocrine cell metaplasia is a common finding. Rarely, squamous metaplasia can be seen in adenomas [127, 129, 130]. Especially pedunculated adenomas, may contain dilated, and ruptured crypts due to extravasation of mucin into lamina propria. Generally, these cases are associated with misplacement of the epithelium within the submucosa [131, 132].

Adenoma is considered as an intramucosal adenocarcinoma when single-cell infiltration, small gland proliferation, desmoplasia, or consecutive glands with prominent cribriform formation are seen in the mucosa [131–133].

Advanced Adenoma

The term advanced adenoma refers to adenomas with more than three adenomas, one of them being 1 cm in size and having a villous structure, high-grade dysplasia, and requiring very aggressive clinical follow-up (e.g. recurrent colonoscopies at every 3 years) [134].

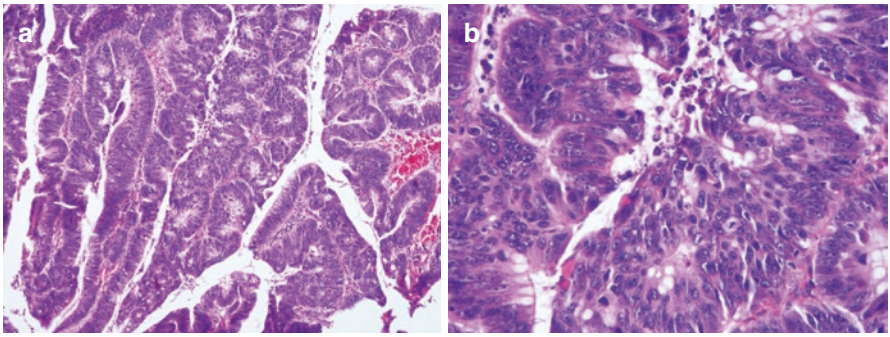

Fig. 9.19 High-grade dysplasia in an adenoma: At a low (**a**) and high (**b**) power area: Features representing high-grade dysplasia with complex glandular architecture prominent and cellular stratification of glands with hyperchromatic nuclei and loss of polarity from the base to surface of the mucosa (H&E, ×40, ×200)

Adenoma: Natural History and Treatment

The majority of adenomas show low-grade dysplasia. However, larger lesions are more likely to harbor high-grade dysplasia. The degree of dysplasia is an independent risk factor for malignancy in adenomas regardless of size [126].

Appropriate treatment for all colorectal adenomas, regardless of size, structural type, or degree of dysplasia, is complete removal with confirmation of tumor-negative mucosal and deep stalk margins. En bloc resection techniques, such as endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) or surgery, should always be the techniques of choice in case of suspected superficial invasive carcinoma. The EMR approach is safe and efficient [135, 136].

Adenoma with Epithelial Misplacement (Pseudoinvasion)

Pseudoinvasion is the prolapse of the adenomatous mucosa or epithelium of the polyp into its head, stalk, or deeper (submucosa) structures by misplacement which in some cases morphologically mimic a malignant polyp. This entity is also called epithelial misplacement, and hamartomatous inverted polyp [137]. The probability of pseudoinvasion in all adenomas ranges from 2.5% to 3.5%. These adenomas consist of often sigmoid polyps and stalked adenomas. They are differentiated from invasive carcinoma with their characteristic features [132, 137].

Histologically, they are composed of misplaced glands with surrounding nondesmoplastic lamina propria. The epithelium may be histologically normal, adenomatous or even demonstrate high-grade dysplasia [138, 139]. Usually acellular mucin pools or those lined by dysplastic epithelium of a grade similar to that of the surface of the polyp are associated with misplaced epithelium. Furthermore, mucin pools have typically smooth, and regular contours and usually associated with ruptured crypts with extravasated mucin in the surface of the polyp. In addition to them, bleeding and hemosiderin accumulation are often present in the submucosal area [137, 140] (Fig. 9.20).

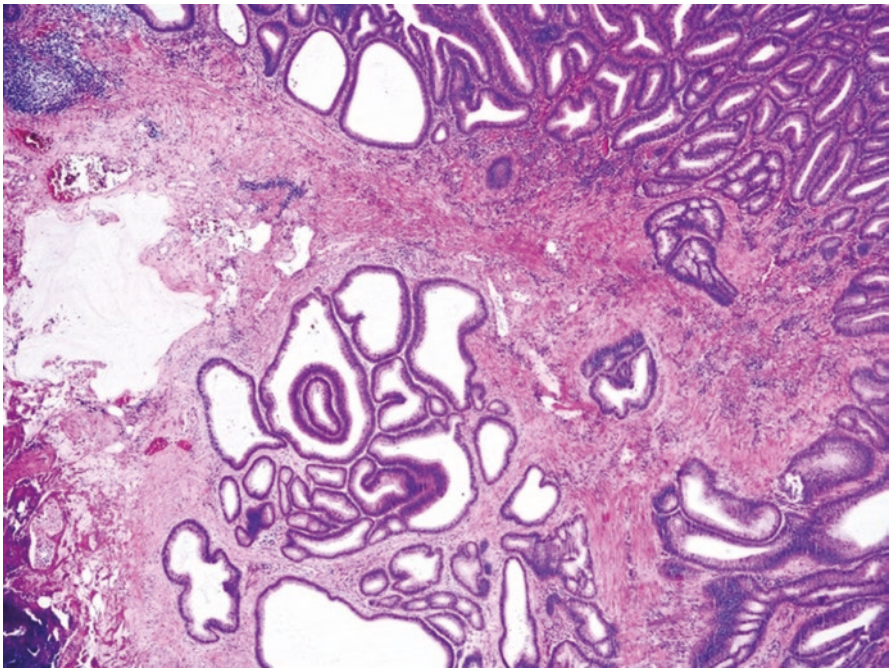

Fig. 9.20 Adenoma with epithelial misplacement (Pseudoinvasion): An adenoma with epithelial misplacement shows a well-demarcated lobule of misplaced glands in the submucosa, smooth corner pool of mucin, lined by low-grade dysplastic epithelium, hemorrhage, and hemosiderin-loaded macrophages (H&E, ×40)

In cases posing diagnostic difficulties, an increase in matrix metalloproteinase-1 (MMP-1) and or TP53 staining in the submucosal epithelium, a decrease both in e-cadherin staining and collagen deposition around the submucosal gland will aid in the diagnosis of adenocarcinoma [141, 142].

Treatment

Adenoma with epithelial misplacement should be excised ensuring tumor-negative mucosal and deeply cauterized margins. In cases that cannot be differentiated from adenocarcinoma the adenoma should be removed with complete polypectomy and/or surgical resection [142].

Flat Adenomas

These dysplastic noninvasive lesions without polypoid development, with slightly elevated margins and central depression, were first described in 1983. The clinical significance of flat adenomas relates to their potential malignancy, challenging diagnosis and their possible roles in interval cancers [143, 144]. Some reports have shown that the prevalence of high-grade dysplasia is increased in flat adenomas, and disease progresses more rapidly in adenocarcinomas than in traditional adenomas

[144, 145]. Frequently small polyps are located on the right side of the colon. They do not have the typical characteristic features of familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC) syndrome (Lynch syndrome) [146]. It has been also reported that high-grade dysplasia is more, but K-ras mutations are less seen in flat adenomas. In their study Owen et al. concluded that APC gene mutation is less often seen in flat adenomas than in polyps [147].

Histomorphologically, flat adenoma shows radial or lateral enlargement of the dysplastic epithelium in the surface mucosa without vertical expansion down to the base of the crypt (Fig. 9.21).

Histopathologic sections demonstrate very thin layers (≤1.3 mm) or thinner than twice the thickness of the contiguous mucosa [145].

Malignant Epithelial Polyp

Malignant epithelial polyp is a term used when an adenoma contains a focus of invasive adenocarcinoma. Endoscopically it has a polypoid or nonpolypoid structure. Approximately 0.2–11% of the endoscopically resected polyps are malignant polyps carrying a risk of metastasis [148, 149].

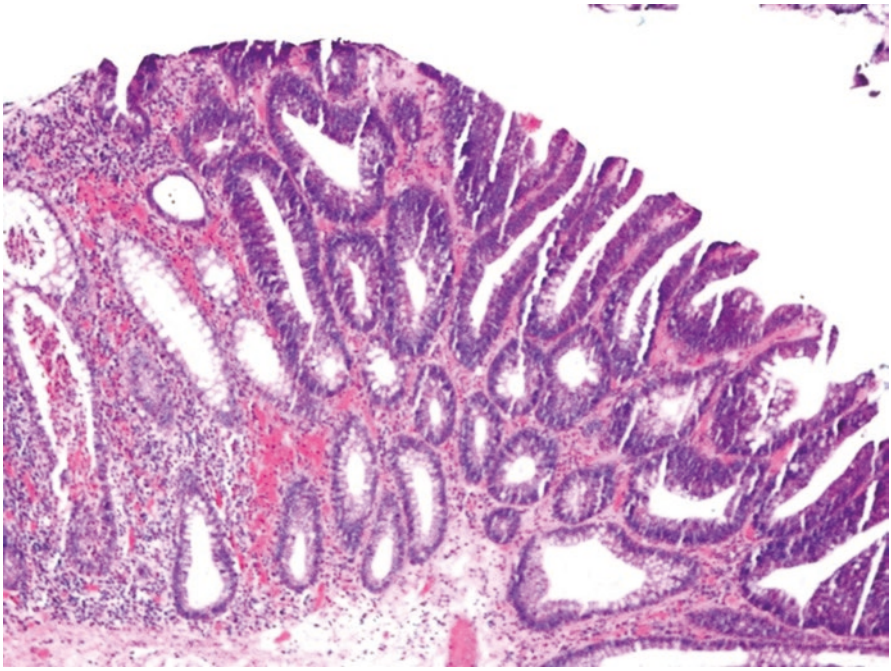

Fig. 9.21 Colonic flat adenoma: This polyp shows radial or lateral enlargement of the dysplastic epithelium in the surface mucosa without vertical expansion down to the base of the crypt (H&E, ×40)

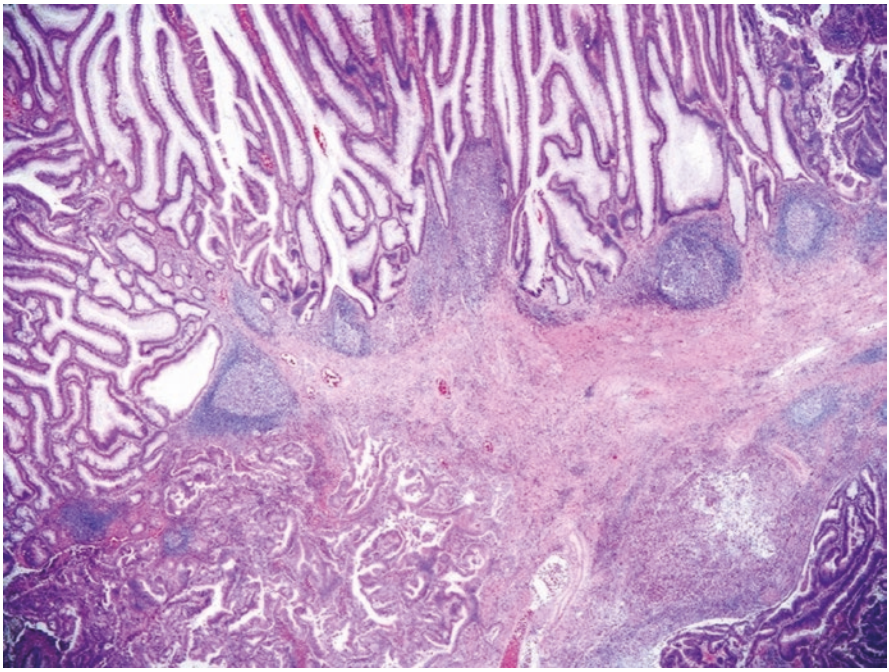

Fig. 9.22 Malignant epithelial polyp: Villous adenoma with invasive carcinoma. This image is showing tumor tissue as adenoid structure into the mucosa and or submucosa (H&E, ×20)

Pathologic Features, Natural History, and Treatment

Histomorphologically, there is invasion of the mucosa and or submucosa in an adenoma with low- or high-grade dysplasia (Fig. 9.22).

Malignant epithelial polyps are staged according to the grading of adenocarcinoma, and their glandular component is graded from 1 to 4 [149].

Several staging systems are recommended to assess the level of invasion. In the Haggit staging system, presence of adenocarcinoma in polyps is described according to the level of invasion [150];

0: limited to the mucosa
1: limited to the polyp head
2: limited to the neck
3: limited to the stalk of the polyp
4: limited to the submucosa

Invasion in sessile polyps is directly considered as Grade 4. It has been reported that depth of invasion is particularly important for prognosis [150, 151].

Evaluation of lymphatic invasion is important for lymph node metastasis. Vascular invasion should also be assessed for the prediction of prognosis [150, 152].

There are some criteria that should be evaluated histopathologically in terms of prognosis and treatment approach to malignant polyps. These criteria were

determined as favorable or unfavorable histological criteria. Favorable histological criteria are related to grade 1 or 2 polyps, carcinoma cells being at least at a distance of 2 mm to the nearest surgical margin and absence of vascular or lymphatic invasion.

Unfavorable histological features are associated with;

1. Invasive tumor cells at or <2 mm closer to the surgical margin,
2. Grade 3 carcinoma, or
3. Presence of a lymphatic/vascular invasion [138, 148].

Surgical resection should be performed to patients having unfavorable histological features due to the risk of lymph node metastasis and residual disease [153].

Adenomatous Polyposis Syndrome

Familial Adenomatous Polyposis (FAP)

FAP is a rare, autosomal dominant disorder induced by the inheritance of a mutated APC gene (located on chromosome 5q) or a new germline mutation in the same gene (up to a one-third of the cases). The APC gene serves as a tumor suppressor gene, and its absence at other genetic loci (i.e. KRAS, and TP53) induces development of additional mutations. Grossly, hundreds or thousands of polyps are seen in the colon [154, 155] (Fig. 9.23).

FAP is highly prone to transition to adenocarcinoma. Adenocarcinoma occurs in most patients in their 30s, but it may also become apparent at an earlier age. FAP accounts for approximately 1% of colon cancers [156]. CRC develops in 70% of the FAP patients older than 80 years of age [156, 157]. Upper GI tract adenomas, and adenocarcinomas may develop at a higher incidence in FAP patients. They are particularly prominent in the first and second parts of the duodenum and in the periampullary region [158, 159]. Gardner syndrome, Turcot syndrome, MUTYH-associated polyposis, and attenuated FAP are considered subtypes of FAP [154, 157, 160].

It has been advocated that endoscopic screening of FAP probands and relatives should be performed between 10 and 12 years of age in order to reduce the occurrence

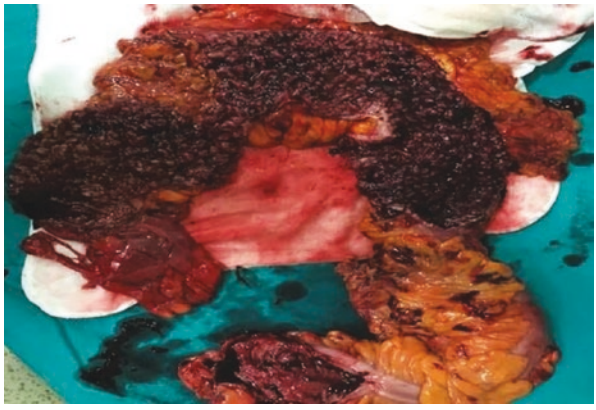

Fig. 9.23 Familial adenomatous polyposis: The colon includes hundreds of polyps, which are histomorphologically adenomas

of colorectal cancer. While colectomy remains the optimal prophylactic treatment, the choice of procedure (subtotal and proctocolectomy) is still controversial [160].

Gardner Syndrome

The syndrome, first described by Gardner in 1951, is a phenotypic variant of familial adenomatous polyposis. It is an autosomal dominant disease characterized by multiple adenomatous polyps covering the surface of intestinal mucosa. Tumors outside the colon are accompanied by multiple polyps in the colon. In 15% of the cases, aggressive desmoid tumors (fibromatosis), osteoma (especially involving mandibula, skull and long bones), epidermoid cysts, dental abnormalities, and congenital hypertrophy of the pigment epithelium of retina are seen [161]. It occurs secondary to mutations in the APC gene. It carries risk for colorectal carcinoma in 100% of the cases [154, 157, 160].

Turcot Syndrome

Turcot syndrome can arise from mutations in the APC gene (type II, associated with FAP) or in the MMR gene (type I, associated with HNPCC). Mutations of both genes may result in colorectal cancer and brain tumors. Most commonly, glioblastomas and medulloblastomas become manifest [162].

Attenuated Familial Adenomatous Polyposis (AFAP)

AFAP is a poorly understood syndrome, defined as the presence of synchronous adenomas in the colon in patients aged between 10 and 99 years, and considered as a phenotypic variant of familial adenomatous polyposis (FAP) [163, 164]. In AFAP, unlike classic FAP, APC mutations tend to occur mostly in the 5′ or 3′ directions of the gene [165]. In addition to being smaller in number, adenomas and adenocarcinomas develop at a later age (after 60 years) than classic FAPs. It carries 80% risk for colorectal carcinoma. Once mutations have been discovered, they require close endoscopic screening in order to remove polyps and prevent the development of adenocarcinoma in these patients [154, 164].

MYH-Associated Polyposis

In the year 2002, Al-Tassan et al. examined a family of multiple colorectal adenomas and carcinomas without any APC mutations [166]. They discovered that affected patients harbored biallelic mutations in the human MutY homologous gene (MYH or MUTYH localized on the short arm of chromosome 1), which encodes a base excision repair enzyme responsible for preventing mutations after oxidative DNA damage. Patients with more than 30 adenomatoid polyps without a history of familial polyposis had a higher incidence of polyposis related to MYH [166, 167]. The exact risk of colorectal carcinoma in patients with MYD-related polyposis is not known, but Farrington et al. found a 93-fold increased risk of colorectal cancer in a large-scale population-based study of 2239 cases compared to wild-type controls [168].

Hereditary Nonpolyposis Colorectal Cancer Syndrome (Lynch Syndrome)

Hereditary nonpolyposis colorectal cancer (HNPCC), also known as Lynch syndrome, is a common autosomal dominant syndrome characterized by early age at onset, neoplastic lesions, and microsatellite instability (MSI).

The Amsterdam-2 criteria for the HNPCC are as follows [169, 170]:

1. At least three relatives must have HNPCC-associated cancer
2. One of these individuals must be first-degree relatives
3. At least two consecutive generations must be affected
4. At least one of the tumors should be diagnosed before the age of 50
5. FAP should be excluded and
6. The diagnosis of the tumor should be confirmed histopathologically.

HNPCC is the most common form of colon cancer, accounting for approximately 5% of all colon cancers. Characteristically, right colon carcinomas develop at an early age compared to microsatellite-stable colorectal carcinomas, MSI-H carcinomas show a high medullar/microglandular growth pattern. It also contains mucinous and/or signet ring cell components [171].

Lymphoid Polyps

The prominent lymphoid follicles localized in the colorectal lamina propria can be seen as minute polyps during colonoscopy. Histologically, intense mature lymphoid cell infiltration is seen in the lamina propria and submucosa. The lymphoid tissue consists of germinal centered, well-contoured lymphoid follicles with fine mantle and marginal zones (Fig. 9.24). Lymphomatous polyposis shows multiple polyps in the colon. Most mantle cells are polyps developed secondary to lymphoma. They show an aggressive clinical course [172, 173].

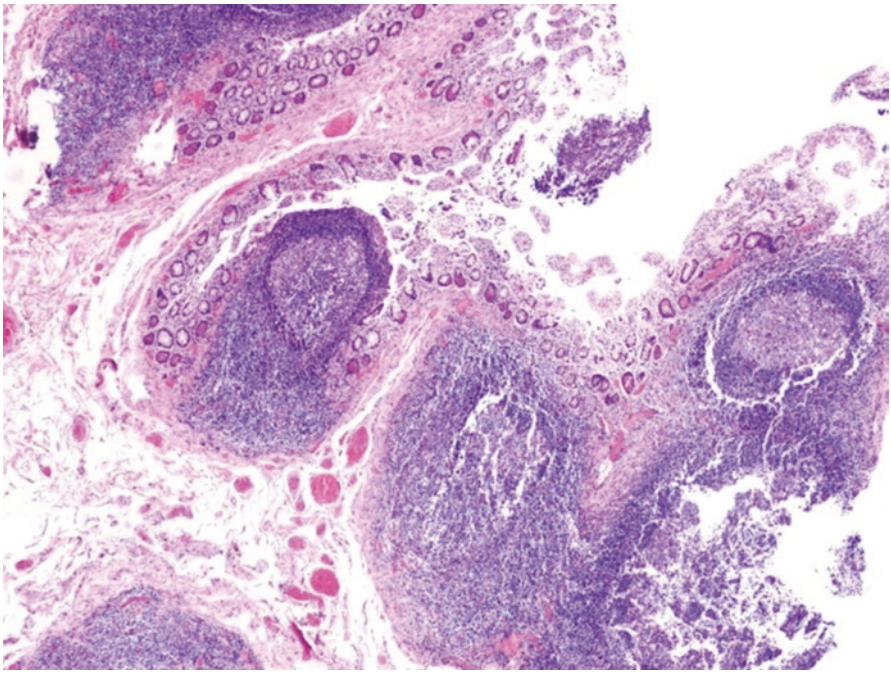

Fig. 9.24 Lymphoid colonic polyp: At low power, the polyp is composed of germinal centered lymphoid follicles (H&E, ×40)

Mesenchymal Polyps

Mesenchymal polyps are polyps that originate from colonic stromal cells. They are usually localized in mucosa and submucosa. Many polyps originate from adipose, smooth muscle, vascular, and neural tissue [174].

Fibroblastic Polyp

Fibroblastic polyps (FPs) are benign mucosal lesions detected incidentally during colonoscopy in middle-aged and elderly adults. They are endoscopically similar to hyperplastic polyps.

Histopathological Features

FPs have crypts similar to hyperplastic polyps. Polyps are composed of increased fibroblastic stroma in mucosa containing spindle-shaped cells with uniform nuclei, eosinophilic cytoplasm, and indeterminate nucleoli [174]. Immunohistochemically there is a perineural marker (EMA, claudin-1, glut-1) positivity, in addition to vimentin and focal SMA and CD34− positivity [175, 176].

Inflammatory Fibroid Polyp

Inflammatory fibroid polyps (IFPs) of unknown origin are rarely seen polyps localized in colorectal submucosa and occur at approximately 60 years of age. Endoscopically, they are solitary, sessile, or pedunculated formations approximately 1.5 cm in diameter.

Histopathologically, they contain many inflammatory cells in the highly vascularized fibromyxoid stroma. Inflammatory cells consist usually of eosinophils, some plasma cells, histiocytes and neutrophils. The characteristic histopathological feature of IFP is the arrangement of stellate or spindle-shaped fibroblastic cells around the blood vessels in an onion-skin pattern [177–179] (Fig. 9.25).

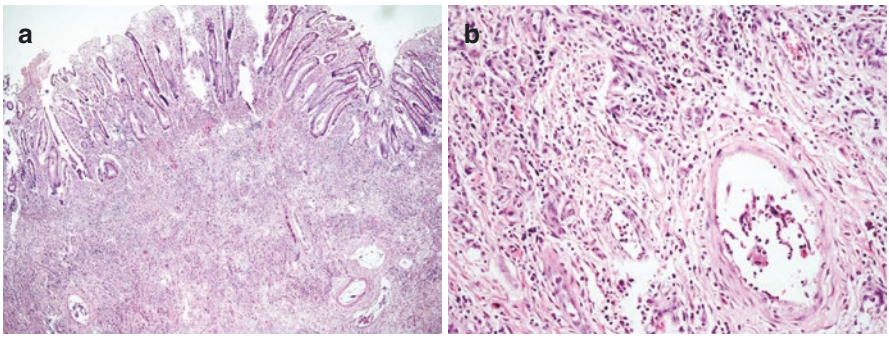

Fig. 9.25 Inflammatory fibroid polyp. (**a**) Histopathologically, they contain many inflammatory cells in the highly vascularized fibromyxoid stroma (H&E, ×40). (**b**) Arrangement of stellate or spindle-shaped fibroblastic cells around the blood vessels in an onion-skin pattern (H&E, ×200)

Immunohistochemical markers aid in the establishment of diagnosis. CD34, SMA, fascin, cyclin-D1, calponin, and PDGFRA-positivity, and S100, DOG1, desmin, and CD117-negativity are significant in differential diagnosis [179–181]. Recently, IFP is thought to be a completely benign lesion without any potential for malignancy or metastasis. Small lesions can be excised [180, 181].

Other Colorectal Mesenchymal Polyps

Other colorectal mesenchymal polyps and their properties are summarized in Table 9.1 [182–191].

Table 9.1 Other colorectal mesenchymal polyps

Polyp type	Size	Localization	Histological features	Immunohistochemical features
Ganglioneuroma (Fig. 9.26)	A few millimeters	Distal colon	Spindle-shaped cells, variable numbers of ganglion cells, coarse collagenous stroma	S100+, Synaptophysin+ (spindle cells) NSE+, Calretinin+, Synaptophysin+ (ganglion cells)
Perineurioma	Several millimeters	Rectosigmoid	Uniform, spindle cells proliferation, fine collagenous stroma, entrapment colonic crypts, whorling around crypts, serrated epithelial crypts	EMA+, Claudin-1+, Glut-1+, focal CD34+
Leiomyoma of the muscularis mucosae	Several millimeters	Colorectal region	Bundles of smooth muscle cells with uniform nuclei, abundant cytoplasm, rare mitosis	SMA+, Desmin+, CD34−,CD117−,DOG1−
Lipoma	<2 cm	Ascending colon and cecum	Submucosal benign-appearing adipocytes, colonic mucosa is normal, atrophic, hyperplastic, or ulcerated	No specific markers
Leiomyosarcoma	Larger size (mean, 6 cm)	Colorectal region	Variable pleomorphism, spindle cell-like smooth muscle cells, increased mitosis	Desmin+, SMA+

(continued)

Table 9.1 (continued)

Polyp type	Size	Localization	Histological features	Immunohistochemical features
Gastrointestinal stromal tumor	Variable size	Sigmoid colon	Spindle and epithelioid morphology, bland spindle cells with faintly eosinophilic cytoplasm, round cells with clear to eosinophilic cytoplasm	CD117+, CD34+, DOG1+
Granular cell tumor (Fig. 9.27)	A few millimeters to 2–3 cm	Right colon	Plump, rounded, or polygonal cells with eosinophilic granular cytoplasm, uniform small nuclei	S100+, NSE+, CD68+
Mucosal Schwann cell hamartoma	1–6 mm	Rectosigmoid	Uniform fusiform cells with elongated, wavy nuclei, abundant, dense eosinophilic cytoplasm, minimal intervening stroma, entrap crypts	S100+,Vimentin+,EMA-

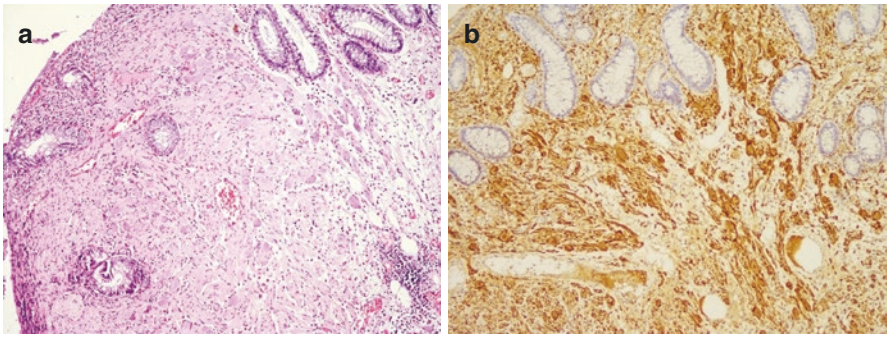

Fig. 9.26 Colonic ganglioneuroma. (**a**) This polyp consists of proliferated stromal spindle cells and ganglion cells (H&E, ×100). (**b**) Immunohistochemically, S100 positive in Schwann cells (DAB; ×100)

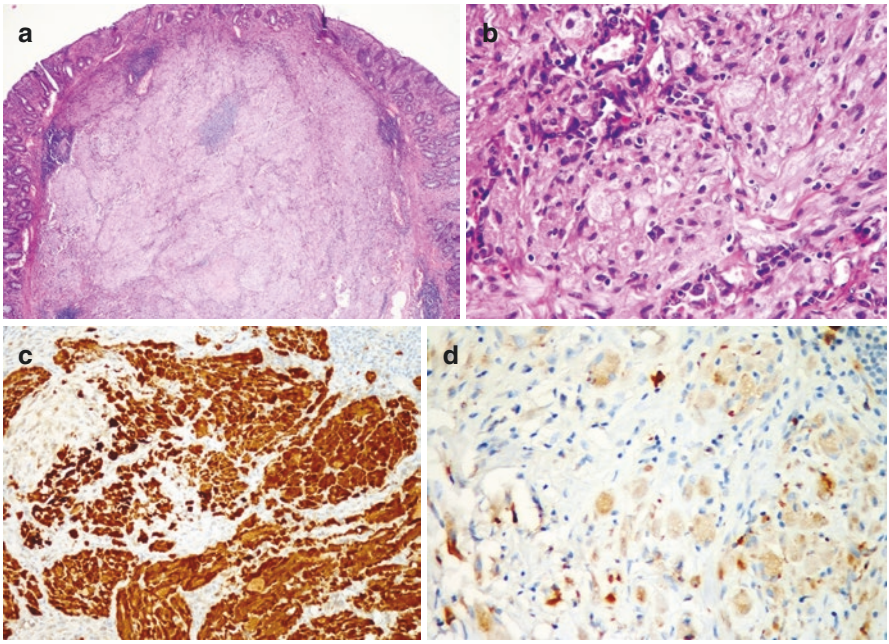

Fig. 9.27 Granular cell tumor. (**a**) Unencapsulated lesion is localized in the submucosa of right colon (H&E, ×40). (**b**) Lesional cells are swollen spindle shaped and redundant granular cytoplasm (H&E, ×200). (**c**, **d**) Immunohistochemical stain; S100 and CD68 positive (DAB, ×200)

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Trends, Risk Factors, and Preventions in Colorectal Cancer

10

Definition of Cancer

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Thousands of new cells proliferate in our body every day as many cells die. New cells locate in organs and tissues when adapting to their normal structures. Normally uncontrolled proliferation is not seen. Multiple genes are affected in most tumors. This may result in loss of function of the tumor suppressor genes or activation of the oncogenes [1, 2].

Cancer tissue is characterized by uncontrolled and limitless cell proliferation. It does not resemble the properties of the tissues that it originated. Cancer cell proliferation continues by disrupting the original tissue structure. With this proliferation, cancer cells exceed the organ borders and destroy the organs beside or spread into distant areas and begin to proliferate in distant tissues. Cancer cells need blood vessels for growing. This vascularization provides oxygen and nutritional elements to cancer cells and also helps in eliminating metabolic waste from the area through systemic circulation. Angiogenesis is the basic rule of disease in tumor growth. Vascular endothelial growth factor A is an important factor in this process [3].

Tumor cells continue uncontrolled proliferation and invade the blood and lymph vessels by destroying their wall. If the tumor cells invade the blood vessels, they continue to move with venous circulation. Inferior mesenteric vein drains to liver via portal vein. After the liver, circulation continues through the inferior vena cava to the right atrium and right ventricle. Blood flows from the right ventricle to the lung through the right pulmonary artery and then to the left atrium and from the left ventricle to the whole body. Therefore, the first step for colon cancer cells on this path is the liver, and the next place is lungs and the other organs of the body. According to this knowledge, liver metastases are common in colon cancer because the liver is the first organ in the pathway of tumor cells. If cancer cells pass through

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liver, they come to the lungs and then spread to the entire body. In lymphatic spread, the cancer cell invades the lymphatic vessel first and then comes to the first lymph node in the path of that lymphatic drainage. There, while the lymph fluid infiltrates, most of the tumor cells attack and metastasize. Cancer cells that do not settle that lymph node can continue to settle in later lymph nodes. The lymph circulation continues like this and eventually enters the systemic circulation. These flow paths will be explained in detail in the anatomy section of the colon and rectum [4, 5].

Breast cancer is the cancer type which most causes death in women, whereas in men lung cancer is the cancer type which most causes death. In some countries, colorectal cancer (CRC) is the second leading cause of cancer-related deaths. Colorectal cancer occurs more frequently in Australia, New Zealand, Europe, and North America, but less frequently in Africa and South-Central Asia [6, 7].

Risk Factors for Colorectal Cancer Family history, inflammatory bowel diseases (crohn, colitis ulcerosis), diabetes, smoking, alcohol use, red meat consumption, processed meat consumption, presence of colon polyps, obesity, low physical activity, and low vegetable and fruit consumption are risk factors that increase CRC incidence.

Risk Decreasing Factors Acetyl cysteic acid and multivitamin use (supplemental folate and calcium), physical activity, and calcium and milk consumption can reduce the risk for colorectal cancer [8, 9].

We will explain these issues in detail in the following of this chapter.

Risk Increasing Factors for Colorectal Cancer

Family History

People with family history of CRC or who have colorectal adenoma (CRA) have a high risk of developing CRC. Colorectal adenomas will be discussed in detail in other sections. Relatives of patients diagnosed with CRC at a young age also have high risk [10].

First-degree relatives of patients with CRC have a high risk for CRC than the second and third degree relatives. Patients that have CRC in first-degree relatives double the risk of having CRC [11, 12].

It has been shown that the incidence of colorectal cancer is reduced by removing the polyps detected during colonoscopic scans in patients with a family history of colorectal cancer. According to our knowledge, the removal of adenomatous polyps reduces the risk of developing colorectal cancer. Therefore, adenomatous polyps must be removed in patients with or without family history [13, 14].

The American College of Gastroenterology (ACG) and the American Society of Gastrointestinal Endoscopy (ASGE) and the American Association of Gastroenterology (AGA) generally recommend colonoscopy screening every 5 years after the age of 40

for first-degree relatives of patients with colon cancer before the age of 60 years. While ASGE and AGA recommend colonoscopic screening after the age of 40 to first-degree relatives of patients diagnosed with colon cancer after age 60, ACG recommends colonoscopy after age 50 [15].

Hereditary Syndromes

The risk of colon cancer is high in patients with hereditary syndrome. These syndromes are named familial adenomatous polyposis and hereditary nonpolyposis coli [16, 17].

Familial adenomatous polyposis (FAP) is an autosomal dominant disease. In this disease, there are many adenomatous polyps, and if these polyps are not detected and managed early, they can progress to colorectal cancer. Extraintestinal symptoms (osteomas, dental anomalies, etc.) may be present in 70% of the cases. In patients with the diagnosis of FAP or in family members with high-risk factors, annual sigmoidoscopy at 10–12 years of age is recommended for screening the lower gastrointestinal tract. If polyp is detected in sigmoidoscopy, total colonoscopy is recommended [18–20].

Hereditary nonpolyposis coli is also known as Lynch syndrome, and it is an autosomal dominant disease. It is a disease which many malignancies can accompany. The most common malignancy is presented as colorectal cancer. Other malignancies can be sorted as ovary cancer, endometrium cancer, intestinal cancer, hepatobiliary tract cancer, stomach cancer, urinary tract cancer, etc. In this disease, high-quality surveillance colonoscopy is recommended starting from the age of 20–25 every 1–2 years. Or screening colonoscopy is recommended to be performed 2–5 years before the earliest age of diagnosis in the family [21–26].

Gender

Advanced colorectal neoplasia is more common in men than in women [27]. Right colon cancer is more common in women than in men [28].

Previous Treatment for Certain Cancers

It is reported that the risk of colorectal cancer is increased in patients having radiotherapy due to testicular cancer. It is also reported that the risk of cancer is increased in men with prostate cancer. This may be due to radiotherapy given for prostate cancer. There is a relative risk for colorectal cancer development in women having pelvic radiation due to gynecological cancer. During radiotherapy, the rectum is exposed to radiation due to being nearer to gynecological organs. The American Cancer Society and other medical organizations recommend earlier screening for these patients with increased risk of colorectal cancer. Radiotherapy given directly to the abdomen is another risk factor that increases colon cancer [16, 29, 30].

Night Shift Work

There are researches that working on night shifts three times a month for 15 years may increase colon cancer in women. Studies have shown that melatonin levels may be effective in the risk of developing colorectal cancer. More clinical research is needed on this subject. Night shift work is also reported to increase risk for breast cancer, prostate cancer, and endometrial cancer [29, 31–33].

Presence of Multiple Primary Cancers

There are reports that approximately 10% of patients may develop a second primary tumor within the first 10 years after primary tumor development [34].

Multiple primary tumors can develop in the same patient at the same time or at a different time. It is reported to be between 0.7% and 11.7% of all carcinomas. Multiple primary tumors are more common in age older than 65. Although multiple primary cancers are rare, nowadays we see more common. The development of diagnostic techniques and longer survival than previous times has been shown to be factors in this increase in frequency. Multiple primary tumors can be divided as synchronous and metachronous. If the second primary tumor is detected within 6 months after the diagnosis of the first primary tumor, it is called synchronous tumor. If the second primary tumor is diagnosed after 6 months, it is called a metachronous tumor [35, 36].

Age

Although colon cancer may be seen at a young age, its incidence increases with age. It is very rare in pediatric ages. Annual incidence in pediatric age is approximately 1 case per million individuals. It is most commonly seen between the ages 60 and 75. In colorectal cancers, 90% of new cases and 94% of deaths occur in people older than 50 years [37, 38].

Inflammatory Bowel Diseases (Crohn, Colitis Ulcerosa)

The coexistence of chronic inflammation and cancer has been demonstrated by studies between inflammatory bowel disease and colon cancer. People with inflammatory bowel disease have a higher risk of developing colorectal cancer. Especially if the disease persists for a long time, if there is extensive colonic involvement, if the patient has pseudopolyps, and if the disease is associated with primary sclerosing cholangitis, patients have a higher risk for colorectal cancer. People with chronic ulcerative colitis or Crohn's disease have a five- to sevenfold increased risk of developing colon cancer compared to healthy individuals. It is generally accepted that this risk develops after 8 years of illness. Initial screening for colon cancer is

recommended in patients with inflammatory bowel disease 8 years after the onset of the disease [39–41].

The lifetime risk of developing colorectal cancer in patients with ulcerative colitis is between 5% and 13.5% [42, 43].

There is an increased risk for colorectal cancer and dysplasia in patients with Crohn's colitis and primary sclerosing cholangitis [44].

Diabetes Mellitus

Studies have shown that patients with type 2 diabetes have a 27% higher risk of colorectal cancer than non-diabetic patients. The risk of developing colorectal cancer in patients with diabetes is both validating for men and women. Type 2 diabetes creates risk factors such as hyperinsulinemia, insulin resistance, hyperglycemia, or hypertriglyceridemia for colorectal carcinogenesis. Insulin can stimulate cell proliferation. This stimulation can be directed with the insulin receptor or insulin like growth factor (IGF)-I receptor. Studies have shown that high levels of insulin, C-peptide (a marker of insulin secretion), or IGF-I may increase the risk of colorectal cancer. As intestinal transit time is prolonged in diabetes, it may lead to an increased risk of colorectal cancer. With prolonged bowel transit time, colon mucosa contacts potential carcinogenesis and fecal bile acids for longer periods. Even fecal acids have been shown to promote colorectal cancer in animal models. Some studies have reported increased colorectal cancer mortality in patients with diabetes, whereas some studies have not identified this risk. In a study, the risk of colon cancer recurrence is reported as similar in patients with and without diabetes at the time of diagnosis. There are studies reporting that type 2 diabetes is a potential risk for CRC to start at an early age in patients with type 2 diabetes, and early screening might be appropriate in patients with type 2 diabetes [45–50].

Smoking

There are many carcinogens in cigarette smoke. These carcinogens can cause changes in DNA, and they can even cause irreversible damage and colon cancer in the colon mucosa. Carcinogens in cigarette smoke can come to the colon mucosa through the blood circulation or they may come to mucosa because of ingestion of smoke-contaminated saliva [51].

Some studies showed that smoking duration is associated with colorectal polyps. Smokers have an 18% greater risk of developing colorectal cancer than nonsmokers. Proximal colon cancer risk is reported to be higher in these patients than distal colon cancer risk. However, other studies reported no significant difference between proximal and distal colon cancer risks. Therefore, colorectal cancer screening may be recommended more frequently in smokers. American College of Gastroenterology supports screening for colorectal cancer in older smokers at an age of 45 instead of 50 [7, 51–56].

Smoking is the cause of microvascular disease that leads tissue ischemia. Tissue ischemia may pose a risk for anastomosis. There are also clinical studies reporting that the risk of anastomotic leakage after colon surgery is higher in smokers than in other patients. Therefore, caution should be exercised against the risk of postoperative fistula [57, 58].

Alcohol Use

Individuals using alcohol have a modest increased risk for colon cancer. There is a connection between alcohol use and oral cavity cancer, pharynx cancer, larynx cancer, esophagus cancer, liver cancer, female breast cancer, and colorectal cancer. The risk of colorectal cancer associated with alcohol consumption is similar in both men and women. Alcohol consumption is divided into three groups as mild, moderate, and severe in the meta-analysis published by Fedirko et al. Heavy consumers are defined as who consume 50 g/day or more of alcohol, and there are 52% more likely to develop colorectal cancer than nonalcohol users. Moderate alcohol users are defined as those who consume 12.6–49.9 g/day ethanol, and the risk is 21% higher in these people. Those who consume mild alcohol are those who consume 12.5 g/day or less ethanol, and the risk is 0–7% compared to those who do not consume alcohol. These results show that the risk of colorectal cancer depends on alcohol consumption dose. In correlation with the amount of alcohol consumption, the risk of developing colorectal cancer increases. It has been reported that alcohol consumption is a risk factor for anastomotic leakage in patients who underwent anastomosis after resection due to colorectal cancer [58–62].

In a study, it was found that increased risk of disease recurrence and shorter time to disease recurrence was higher in patients who used alcohol in early-stage rectum cancer than those who did not use alcohol. Ethanol intake is associated with poor prognosis and lower overall survival counts in cases of CRC [63, 64].

Red Meat and Processed Meat Consumption

High rate red meat consumption is associated with a high risk of colon cancer occurrence. Higher green leafy vegetable (GLV) consumption may reduce this risk [65].

Possible biological mechanisms that may explain the increased risk of colorectal cancer associated with consumption of red meat and processed meats are indicated. Potential mutagenic effects of heterocyclic amines present in highly cooked meat may be a reason. The second mechanism is the endogenous formation of N-nitroso compounds in the gastrointestinal tract. Depending on the dose of red meat intake, endogenous formation of nitroso compounds occurs in humans. Nitrites or nitrates are used as additives to prevent spoilage of meat. These form exogenous nitrites which work just like endogenous nitrites. The risk of cancer caused by taking cured

meats and red meats is a moderate risk (20–30%). It is recommended not to eat more than 500 g of red meat per week and avoid processed meat [66–70].

Gallbladder Diseases

Cholecystectomy is a moderate risk factor for colon cancer. This risk has not been shown for distal colon and rectal cancer. Biological mechanisms associated with intestinal exposure of bile may be responsible for this risk. The presence of gallstone increases the risk of colonic adenoma. Chiong et al. reported in their meta-analysis that cholelithiasis increases the risk of rectal cancer. There are also studies reporting that reflux of bile into the stomach may be a risk factor for gastric cancer in patients with cholecystectomy [71–76].

Presence of Adenomatous Polyp

The presence of adenomatous polyps is a risk factor for colon cancer. Colonic adenomatous polyps may show malignant transformation. These risk factors can be classified as high risk and low risk.

Large size (especially >1.5 cm), sessile or flat formation, severe dysplasia, presence of squamous metaplasia, villous architecture, and polyposis syndrome (multiple polyps) are defined as high-risk factors for polyps. On the other hand, small size (especially <1.0 cm), pedunculated formation, mild dysplasia, no metaplastic areas, tubular architecture, and single polyp are identified as low-risk factors.

The cancer focus within the adenomatous polyp will progress and lead to invasive cancer; therefore, polyp excision prevents this risk [77–80].

Obesity

Obesity has been implicated as a risk factor for colorectal cancer. Obesity has also been shown to be a risk factor for postmenopausal breast cancer, endometrial cancer, kidney cancer, and esophageal cancer. In a study conducted in postmenopausal women showed that the existence and duration of obesity are risk factors for cancer development. In addition, there are also studies that reported this risk can be decreased with regression of the obesity [81, 82].

Obesity increases the risk of colon cancer in men more than in women. According to clinical studies, it is reported that the presence of abdominal obesity is more risky than subcutaneous fat tissue in colorectal cancer etiology [83–86].

Leptin secreted from adipose tissue controls the body fat storage and stimulates cell proliferation. Circulatory leptin levels increase as adipose tissue mass increases. Studies have reported that leptin may be responsible for the development of colorectal adenoma [87].

There are also studies that make obesity responsible for colorectal cancer recurrence, treatment outcomes, and survival [88].

Metabolic Syndrome

The condition consisting of three or more components is called metabolic syndrome. These components are defined as high blood pressure, increased waist circumference, hypertriglyceridemia, low level of HDL cholesterol, and diabetes. The risk of colon cancer, liver cancer, pancreas cancer, breast cancer, and endometrial cancer increases in metabolic syndrome [89–91].

Infections

Helicobacter pylori can settle in the stomach and cause gastritis, ulcers, and gastric neoplasia. Helicobacter pylori infection should be considered in the risk of colonic adenomatous polyps and colon cancer [92–95].

Schistosomiasis is a common parasitic disease in underdeveloped and developing countries. Contaminated water can cause infection. Chronic schistosomiasis can cause cystitis and fibrosis. It can also be a risk factor for bladder cancer, liver cancer, colonic adenomatous polyps, and colorectal cancer [39, 96].

Human papilloma virus infection is associated with cervical cancer. In clinical studies, association between human papillomavirus infection and colorectal cancer has been identified. The risk of colon cancer increases tenfold in people with human papillomavirus infection than in healthy individuals [97–99].

Human cytomegalovirus (HCMV) is a beta-herpes virus and can be found endemically. It can lead to life-threatening diseases in immunosuppressive individuals. Studies have shown that CMV nucleic acids and proteins can be found in neoplastic cells in colorectal polyps and adenocarcinomas. It is informed that this virus infection may have an important role in colon cancer [100, 101].

There are also studies that indicate an increased risk of colorectal cancer in people with HIV infection [102, 103].

Organ Transplantation

Organ transplantation increases the risk of cancer in other organs. Adami et al. reported the risk of colorectal cancer fourfold higher in patients undergoing organ transplantation. In addition, in a study, it was reported that proximal colon cancer increased in patients who underwent organ transplants, whereas there was no increase in distal colon cancer [104, 105].

Nonalcoholic Steatohepatitis

Nonalcoholic fatty liver disease is a risk factor for colorectal neoplasm and colorectal cancer. Also nonalcoholic fatty liver disease has an additive effect on the development of colorectal cancer. In a study published in 2011, Wong et al. reported that nonalcoholic steatohepatitis was highly associated with colorectal adenoma and advanced neoplasm. They also reported that these adenomas were more common in the right colon, and they recommended colorectal cancer screening for these highly risked patients [106, 107].

Gallbladder Polyps

There are studies suggesting the association between gallbladder polyps and proximal colon polyps [108].

Risk-Reducing Factors for Colorectal Cancer

Acetylsalicylic Acid

The use of prophylactic aspirin is currently recommended for the possible risk of thromboembolism. On the other hand, aspirin use can cause bleeding complications and hemostasis problems [109].

The use of aspirin also reduces the recurrence of adenomatous polyps. The mechanism on this issue is not fully known. There are studies reporting that low-dose (75–300 mg/day) aspirin use reduces colon cancer incidence by 76% and mortality by 65% in the long term (median time 18 years). Aspirin is known to reduce the incidence and mortality of colorectal cancer. In another study, it was suggested that the use of intermittent aspirin or naproxen inhibits the progression of colon adenomas to colonic invasive adenocancer [109–113].

Statins

Statin is used in the treatment of hypercholesterolemia. Some studies have reported that statin use reduces proximal colon cancer in men and rectal cancer risk in both genders. Another case-control study has shown that statin reduces the risk of colorectal cancer. However, in most cohort studies, the benefit of statin could not be found [114, 115].

Bisphosphonates

Bisphosphonates are often used in treatment of osteoporosis. Some studies have reported that the use of bisphosphonates for more than a year reduces the risk of colorectal cancer by 59% [116].

Calcium and Vitamin D

It was suggested that calcium combined with secondary bile acids and ionized fatty acids reduced the risk of colon cancer by forming insoluble soap in the colon lumen. It is also reported that colon cancer is associated with vitamin D deficiency. Studies showed that vitamin D deficiency increases the risk of colorectal cancer, whereas vitamin D intake reduces the risk of colorectal cancer [117–120].

Physical Activity

Physical activity has a risk-reducing effect for many types of cancer (e.g., breast cancer, endometrial cancer, prostate cancer, colon cancer). Physical activity can prevent about 15% of colon cancers. For cancer prevention, 30–60 min of moderate-vigorous intensity physical activity is recommended 5 days in a week. Since physical activity increases bowel movements, it may be effective in reducing the risk of colon cancer by reducing the passage duration of the carcinogenic substances [121–126].

Fish Consumption

Some studies showed that consuming more than two servings of fish each week may reduce the risk of colorectal cancer recurrence [127].

Serum Cholesterol Level

In a clinical study, it was reported that high concentration of serum HDL reduces the risk of colon cancer [128].

Dietary Fiber

There are studies reported that meals with fiber-rich grain reduce the risk of colorectal cancer. Especially the cereal fibers and whole grains are mentioned to reduce the risk of colorectal cancer. The contact time of toxic substances with the colon mucosa is reduced by reducing the intestinal passage time and constipation with taking fibrous foods [129–131].

Postmenopausal Hormone Therapy

It is reported that hormone therapy given to postmenopausal women reduces the risk of colorectal cancer [132–135].

Screening Program

Screening programs have an important role in decreasing the incidence and mortality of CRC. There is a generally accepted opinion that the age of onset of CRC screening should be 50 years. However nowadays, some groups advise that CRC screening starts from 45 years old. The side effects of colonoscopy are rare, but these side effects may increase in the elderly individuals due to their comorbidities. For this reason, some guidelines recommend the screening program to terminate at the age of 75, while others recommend it to end at the age of 80. Major risk factors for CRC are defined as family history, medical history, presence of colorectal polyps, and chronic inflammatory bowel disease history. Also familial adenomatous polyposis and hereditary nonpolyposis colorectal cancer (Lynch syndrome) are determined as high-risk factor for CRC. Smoking increases the development of adenomatous polyps, and smokers have a higher incidence of rectal cancer. The success of screening programs may increase with the increase of the general population education [8, 136].

In addition, colorectal cancer can be prevented by removing adenomatous polyps which can cause cancer with screening colonoscopy. Another advantage of the screening program is the early recognition of CRC. Early diagnosis of CRC has a higher chance for treatment. Colorectal cancers usually develop in 10–15 years. It typically begins as a noncancerous polyp; then, the polyp may become cancerous. Such polyps are called adenomatous polyps or adenomas. Ten percent of adenomas can develop to cancer. Adenomas are quite common and one third or half of individuals can have one or more adenomas. Ninety-six percent of colorectal cancers are adenocarcinomas, and most of these cancers develop from adenomatous polyps. When cancer occurs, it begins to grow in the colon wall and tries to invade blood and lymph vessels. The tumoral cells make lymph node, liver, and spleen metastasis due to these vascular and lymphatic invasions. On the other hand, tumor can invade the organs in abdominal cavity according to its localization [137–140].

Green Tea Consumption

There is a weak relationship between more green tea consumption and a reduced risk of male colon cancer [141].

Prevention of Colorectal Cancer

Colonoscopy screening reduces colorectal cancer risk by 90%. Screening colonoscopy can prevent cancer by detecting precancerous polyps. There are studies reporting that the prevalence of adenomatous polyps at the age of 50 is 25% in men and 15% in women. The majority of these polyps are found as asymptomatic, and the excision of these polyps during colonoscopy is important in preventing colon cancer [142, 143].

Some studies report that changing lifestyle reduces the risk of colorectal cancer [144].

It has been reported that consumption of fiber-rich fruit and vegetables reduces the risk of colorectal cancer. It has been suggested that the fibers contained in our food absorb or dilute fecal carcinogens, modulate colonic transit time, even alter acid metabolism, decrease colonic pH, and increase short-chain fatty acid production. High intake of fiber or vegetables is reported to reduce the risk of colon cancer by 40–50%. Red meat consumption is also known to increase the risk of colorectal cancer. Instead of red meat, alternative animal proteins such as fish can be taken. Reduction or discontinuation of alcohol intake will reduce the risk of colorectal cancer. Smoking is strictly forbidden. Also, obesity should be avoided, visceral fat mass should be reduced, and regular sports should be done. There are studies reporting that colorectal cancer can be reduced by 24% by doing physical activity. Calcium is thought to reduce the risk of colon cancer by binding to toxic secondary biliary acids [117, 145–149].

The most important risk in colon cancer is older ages. The greatest success in preventing colorectal cancer depends on screening tests. Precancerous lesions such as adenomatous polyps can be detected by screening tests before the cancer appearance, and the cancer can be prevented by polypectomy.

Colorectal cancer screening tests can be divided into two groups:

1. Stool tests: occult blood and exfoliated DNA tests
2. Structural examinations: colonoscopy and virtual colonoscopy

Stool tests for occult blood test are known as guaiac test and fecal immunochemical test (FIT) [150].

Guaiac Test

The Guaiac test is a test that measures occult blood in the stool. Some foods may affect this test result. Therefore, before 3 days of the test, patients must stop eating red meat, cantaloupe, uncooked broccoli, turnip, radish, and horseradish. Nonsteroidal anti-inflammatory drugs, vitamin C, aspirin, ibuprofen, and naproxen may also affect the test result. A negative test means that there is no blood in the stool, whereas a positive result indicates that there is too little blood to be seen in the stool. There are studies reporting the false-positive rate as 11% with normal diet. Also false-negative results can reach up to 48% [151, 152].

Fecal Immunochemical Test (FIT)

This test is known as a new fecal occult blood test. This test is performed with monoclonal antibodies that produced against human hemoglobin beta subunit. If the test result comes normal, it means that there is no blood in the stool. The sensitivity of this test is high, and FIT is seen more sensitive to colorectal cancer than guaiac test [153, 154].

Exfoliated DNA Test

Stool DNA test can detect colorectal cancer and large adenomas with high sensitivity. This enables the patient's early diagnosis and curability. Serrated sessile polyps greater than 1 cm can be recognized by this method [155, 156].

Colorectal screening is recommended in women and men. However, colonoscopy should be performed within the indications mentioned in Chap. 3.

Screening options may vary depending on risks, patient preference, and access. FOBT and FIT can be done once a year. The stool DNA test is a newly recommended test, and the interval for this test is uncertain. If adenomatous precancerous condition is detected in colonoscopy, colonoscopy must be performed more frequently (see Chap. 3) [157–160].

For positive results, indirect tests, such as the occult blood test, require the lesions in the colon to bleed and to pass this blood with feces. Therefore, it is not possible to identify non-bleeding lesions with these tests. For this reason, colonoscopic examination is thought to be more effective in detecting bleeding and non-bleeding colonic lesions early.

American Cancer Society Guideline for Colorectal Cancer Screening recommends people at average risk of colorectal cancer to start regular screening at age 45. For screening, people are considered to be at average risk if they do not have one of the following criteria:

- A personal history of CRC or certain types of polyps
- A family history of CRC
- A personal history of inflammatory bowel disease (ulcerative colitis or Crohn's disease)
- A confirmed or suspected hereditary colorectal cancer syndrome, such as familial adenomatous polyposis (FAP) or Lynch syndrome
- A personal history of getting radiation therapy to the abdomen or pelvic area to treat for a prior cancer [161]

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Anesthesia Practices in Colorectal Cancer Surgery

11

Yucel Karaman

The Effect of Anesthetic Technique, Anesthetic Agents, and Preoperative Anesthesia Practices on Prognosis in Colorectal Cancer Surgery

Today, the incidence of neoplasm cases is globally increasing. As in all cases of neoplasm, the incidence of CRC is also increasing. The incidence of CRC is increased by 38% from 2007 to 2017. One of the main reasons for this increase is shown to be the increase in population and average age. According to a recent study conducted in 135 countries and 29 cancer categories, of the 25 million cancer cases identified in 2017, nearly two million were colorectal cancers. The mean mortality rate is 47% in colorectal cancers, and in cancer-related deaths, it ranks third after breast and lung cancers in women and fourth after lung, liver, and stomach cancers in men [1].

As in all cancer groups, the decision of what anesthetic and analgesic techniques along with what anesthetic agents and doses will be most optimally used in CRC patients requires evaluation of many multifactorial characteristics for the anesthesiologist depending on the patient and facilities. Preanesthetic evaluation of patients preoperatively and correct planning of anesthesia procedures based on this evaluation affect mortality, morbidity, and success of operation in all patient groups. CRC patients are mostly geriatric patients, and they constitute the comorbid patient group with cardiovascular, hepatorenal, cerebrovascular, and metabolic comorbidities. In addition to the risks posed by systemic diseases, the drugs used also affect many systems, altering the pharmacokinetics and pharmacodynamics of anesthetic agents. Oncologic patient groups have some additional risk-increasing factors specific to themselves. Anemia occurs in approximately half of CRC patients due to occult bleeding. Apart from that, depression, anxiety, general weakness, tumor size-related

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venous compression findings, and metastasis-related organ failures may occur. Thrombocytopenia, leukopenia, immunodeficiency findings, and acid-base imbalance may arise due to chemotherapy and corticosteroids. A detailed systemic examination should be performed preoperatively in CRC patients, which mostly represent a geriatric, comorbid, and oncologic patient group, and if necessary, further tests and consultations from different branches should be carried out. The patient should be optimally prepared in a multidisciplinary consensus by oncology, surgery, and anesthesia and then operated [2].

Central venous cannulation is performed in the presence of tumor size-related major venous insufficiency or lymphatic compression-related insufficiency or ascites and in cases of fluid electrolyte and acid-base imbalance due to severe nausea, vomiting, and diarrhea. Blood and blood products are prepared depending on the anemic status of the patient and the extent of the operation. In the postoperative period, mechanical ventilation and intensive care conditions are provided for advanced care and follow-up in patients with a high risk of respiratory failure [3].

As in all patient groups, risk classification is made to determine the anesthetic approach, monitoring techniques, and postoperative conditions in the preoperative anesthesia assessment of CRC patients. The American Society of Anesthesiologists' (ASA's) physical status classification system is widely adopted and used worldwide. The ASA classification includes six groups, and as the value increases, the risk increases. With increasing risk, invasive techniques such as invasive arterial pressure measurement and central venous catheterization are preferred instead of standard noninvasive monitoring techniques and peripheral venous cannulation. ASA I physical status is defined as a normal healthy patient, examples include nonsmoking and no or minimal alcohol use. A patient with mild systemic disease is considered as ASA II physical status and has no activity restrictions, with the examples of current smoker, pregnancy, well-controlled diabetes mellitus, and hypertension. A patient with severe systemic disease is considered as ASA III and has substantive functional limitations such as poorly controlled diabetes mellitus, hypertension, morbid obesity, alcohol dependence, or abuse. ASA IV physical status is defined as a patient with severe systemic disease that is a constant threat to life; examples include recent myocardial infarction, ongoing cardiac ischemia, severe valve dysfunction, sepsis, disseminated intravascular coagulation, and acute respiratory distress syndrome. A moribund patient who is not expected to survive without the operation is considered as ASA V physical status; examples include ruptured abdominal/thoracic aneurysm, massive trauma, and intracranial bleed with mass effect. A declared brain-dead patient whose organs are being removed for donor purposes is considered as ASA VI physical status [4].

As in oncologic patient groups, depression and anxiety are common in CRC patients. The prevalence of depression ranges between 1.6% and 57%, and the prevalence of anxiety ranges between 1.0% and 47.2% among patients diagnosed with CRC. According to the studies, anxiety and stress lead to depression in cancer patients, and the release of stress hormones worsens immune system inhibition and postoperative prognosis. Informing the patient in the preoperative period, sedation

with premedication, and successful management of pain in the postoperative period may reduce stress and anxiety [5, 6].

Electrocardiography (ECG), noninvasive arterial blood pressure, and standard noninvasive monitoring with pulse oximetry (SpO2) that measures the level of oxygen in the blood and peripheral cannulation are first performed on patients transferred to the operating table. Severe hypotension or even cardiac arrest may occur in patients with hemodynamic failure during the induction period when hypnotics, analgesics, and muscle relaxant anesthetic agents for endotracheal intubation are administered. Therefore, radial artery cannulation, which is an invasive procedure, is performed on patients with hemodynamic and organ failure and acid-base and fluid-electrolyte imbalance for instant arterial blood pressure measurement. Because of the high incidence of hemodynamic failure due to inappetence, anemia, nausea, vomiting, and excessive and rapid weight loss in CRC patients, invasive arterial cannulation is commonly preferred to follow-up hemodynamics during induction and to perform preoperative arterial blood gas analyses [7].

Due to the use of neuromuscular-blocking agents in all major abdominal operations, as in CRC surgery, endotracheal intubation is indicated to maintain ventilation and protect the airway from aspiration. Endotracheal intubation may be challenging or cannot be performed due to obesity, short neck and limited movement of the neck, small mouth, large tongue, inadequate mouth opening, and many other reasons. The presence of findings that will complicate the intubation procedure is also investigated during the preoperative assessment. The simplest method used for this is the Mallampati scoring with four classifications based on the visibility of the uvula, hard palate, and soft palate, in which the patient opens his mouth as wide as possible and protrudes the tongue (Fig. 11.1).

Difficult intubation is expected in patients with a Mallampati score of 3–4. In the case of a Mallampati score of 3–4, techniques and tools such as video laryngoscopes

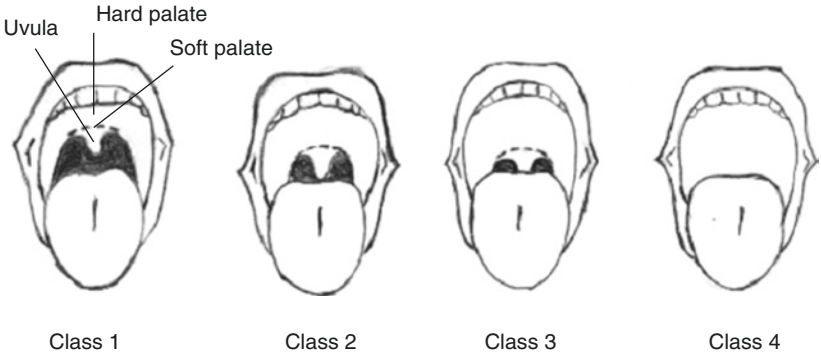

Fig. 11.1 Mallampati classification of mouth opening
Class 1: Uvula, soft palate, and hard palate visible
Class 2: Major part of uvula, soft palate, and hard palate visible
Class 3: Base of uvula, soft palate, and hard palate visible
Class 4: Only hard palate visible

in addition to conventional laryngoscopes and laryngeal mask airway (LMA) Fastrach through which an endotracheal tube could be inserted or awake fiberoptic intubation are kept ready. In order to simply describe the endotracheal intubation technique for our surgeon colleagues, the laryngoscope is held with the left hand, and the blade is advanced to displace the tongue to the left of the laryngoscope when the blade is inserted in the mouth. When the blade is slightly elevated after the epiglottis is seen, the vocal cords are seen, and intubation is performed by advancing the intubation tube held with the right hand between the two vocal cords. The endotracheal tube is advanced approximately 21 cm from the lip edge in females and 23 cm in males. If the tube is advanced too deeply, it enters the right pulmonary bronchus due to the suitable angle of the right bronchus, and the left lung is not ventilated. Therefore, it should be checked that both lungs are ventilated equally after intubation. In abdominal surgery, factors such as urgent operation (ileus is common in patients with CRC), high ASA score (III and above), preoperative low albumin levels, over 60 years of age, operative time of 2 h or longer, anemia (Hb $\leq$ 10 g/dL), upper respiratory tract infection and asthma attack in the last month, the presence of chronic obstructive pulmonary disease (COPD) are the risk factors for postoperative pulmonary complications. Patients with a high risk of respiratory failure in the postoperative period are transferred to level 3 intensive care units. Patients who cannot achieve adequate respiratory function at the end of the operation due to preoperative severe cardiac, renal, hepatic, cerebrovascular, and respiratory diseases are transferred to the intensive care unit with mechanical ventilation support without being extubated. Patients who are planned to be transferred to the surgical ward postoperatively are followed up in level 1 intensive care units (postop) for a short time until they achieve adequate hemodynamic, respiratory, and consciousness levels or in level 2 intensive care unit (post-anesthesia care unit-PACU) for 24 h. Recovery scores are used for the decision to transfer patients from these units to the ward. These scoring systems assess motor activity, breathing, circulation, consciousness, and O_2 saturation [8, 9].

Anesthesia Practices in Colorectal Cancer Surgery

Enhanced recovery after surgery (ERAS) offers effective, safe, and practical protocols for accelerating recovery of patients, preventing infection, shortening the length of hospital stay, and returning to normal life as quickly as possible in colorectal cancer surgery. According to these protocols:

- Bispectral index (BIS) and train of four (TOF) neuromuscular monitoring to provide optimal perioperative sedation and muscle relaxation.
- Avoiding hypoperfusion and high volume overload with targeted fluid therapy, and use of inotropes instead of fluid load when necessary,
- Prevention of hypothermia (detailedly explained in the following sections)

- Preferring analgesics such as NSAID, paracetamol, dexmedetomidine with multimodal analgesia due to the possible side effects of opioids such as urinary retention, respiratory depression and postoperative ileus. Use of short-acting opioids such as remifentanil.
- Supporting general anesthesia with regional anesthesia and analgesia techniques such as epidural block and transversus abdominis plane (TAP) block.
- In the postoperative period, maintaining analgesia in the form of continuous infusion by epidural catheterization using morphine and local anesthetic mixtures.
- Restriction of opioid use in all patients, especially in non-smoker females with a sedentary lifestyle, to prevent postoperative nausea and vomiting (PONV). Prophylaxis and treatment with droperidol, dexamethasone, ondansetron, metoclopyramide [10, 11].

Immune System

Anesthetic agents used during general anesthesia procedures may positively or negatively affect the functions of the immune system at different stages, which allow for the recognition of tumor cells and the prevention of their growth, invasion, and metastasis to the surrounding tissues. Due to these effects, anesthetic agents and practices used in CRC operations have been shown to alter tumor-related prognosis postoperatively [12].

The immune system confronts tumor cells at both the cellular and humoral levels. This fight starting with the recognition of the molecular structure of tumor cells by specific receptors continues with the release and activation of cytokines such as interleukin (IL 4-6-10) and tumor necrosis factor (TNF-α) from T lymphocytes. In particular, Toll-like (TLRs) and Nod-like (NLRs) receptors are considered to have important effects on recognition of tumor and immune system activation [13, 14].

Natural-killer (NK) cells play an important role in the cellular response induced by cytokines to tumor cells. NK cells are large granular lymphocytes that exhibit a lytic activity against tumor cells and make up 5–15% of all lymphocytes. Besides their antitumoral activities, they have antiviral properties. Although their mechanism of action is not fully known, the decrease in their number has resulted in increased tumor formation in mouse experiments. Natural-killer T cells (NKT), one of the subgroups of T cells that activate NK cells and NK cell receptors, are an important component of the immune system in the fight against tumor cells [15]. Apart from NK cells, tumor-associated macrophages (TAMs), which can especially invade into the tumor, are highly effective in cellular immunity to tumor cells. Cytokines and interleukin (IL) convert macrophages into their subgroups showing different effects against tumor cells. Cytokines such as lipopolysaccharide (LPS) and TNF-α first convert such macrophages into M1-like macrophages (M1) and then T-helper1 (TH1) macrophages, which inhibit the proliferation of tumor cells.

Interleukins (especially IL10) allow the transformation of M2-like macrophages (M2) and T-helper2 (TH2) cells. TH1 cells are effective in cellular immunity, and TH2 cells are effective in humoral immunity. Unlike TH1 cells, TH2 cells increase the proliferation of tumor cells and cause tissue damage. These two macrophage groups can differentiate into each other under certain conditions. The balance between the two groups (TH1/TH2) is of great importance for the prognosis of cancer in CRC patients [16].

Surgical operation itself may produce stress response, resulting in inhibition of immune systems of patients. Factors such as anxiety, fear, pain, blood transfusion, and hypothermia lead to the release of stress hormones. Glucocorticoid, prostoglandin, and catecholamines arising in stress response decrease the number of NK cells or inhibit their functions and increase the TH1/TH2 ratio in favor of TH2, which increases the proliferation of tumor cells. Such a suppression of immune response to tumor cells develops independently of gender, age, extent of operation, or tumor stage and is considered to increase the risk of postoperative tumor recurrence and metastasis [17].

Anesthetic agents and techniques used for anesthesia and analgesia and perioperative practices may affect the immune system functions in colorectal cancer surgery more or less depending on the selected agent and technique. Lymphocytes, leukocytes, macrophages, NK, and TH1 cells may alter the immune system activity at the cellular level; proinflammatory cytokines such as interferon (IFN), interleukin (IL), and TNFα may alter the immune system activity at the TH2 humoral level and the target receptors level affected by these factors [17].

Anesthetic Technique

Anesthetic agents used in general anesthesia are considered to prevent the perception of pain in the central nervous system during the operation with mechanisms of action such as reticuloendothelial system (RES) inhibition, gamma aminobutyric acid (GABA) activation, and *N*-methyl-D-aspartate (NMDA) receptor antagonism. On the other hand, epidural, spinal, or regional blocks block the pain through the conduction pathways of the spinal nerve roots or nerve fibers. According to some studies, the prevention of pain before reaching the central nervous system reduces the negative effects on the immune system. Since pain is a stimulating signal, its perception by the central system causes many mechanisms to be activated in response to this stimulus even if the patient does not feel it. The secretion of stress hormones such as adrenaline and noradrenaline leads to the suppression of the immune system that fights against tumor cells. A weakened immune system facilitates the proliferation, distant spread, and metastasis of residual tumor cells in the postoperative period [18].

There are studies showing that the negative effects of using epidural anesthesia and regional analgesia techniques alone or in combination with general anesthesia on the immune system are milder compared to general anesthesia.

According to these studies:

1. Epidural or regional anesthesia limits the activation of the sympathetic system by preventing afferent transmission of stimuli. With the reduced secretion of stress hormones, the inhibition of NK cells is prevented, and the TH1/TH2 ratio is maintained as much as possible.
2. It reduced the use of perioperative and postoperative opioid with regional anesthesia. Although controversial, according to some studies, opioids play a role in decreasing NK cell activity, increasing tumor metastasis, and decreasing the incidence of postoperative survival when used at high doses.
3. Anti-inflammatory effects of local anesthetics contribute to wound healing by reducing postoperative inflammation.
4. The negative effects on the immune system are reduced by allowing the use of anesthetic agents at lower doses in general anesthesia procedures.
5. Regional anesthetic techniques provide postoperative analgesia in addition to perioperative anesthesia. They reduce opioid consumption. Since they provide comfortable analgesia, they reduce pain-related stress and anxiety which suppress the immune system [19–21].

Although the level of evidence of epidural anesthesia is better, the evidence of the positive effects of epidural, spinal, and regional anesthetic practices on colorectal cancers is not sufficient for definitive results. The studies have generally indicated that regional and epidural anesthesia have less adverse effects on the immune system; thus they increase the survival rate, but they do not reduce tumor recurrence or metastasis. However, it has been stated that the studies on this issue are retrospective and have a small sample size and that prospective, randomized, controlled, and extensive studies are needed for definite results [22–24].

Anesthetic Agents

While there is generally a positive or negative consensus on the effects of some of the anesthetic on CRC cells, the study results are contradictory for some. The reason for this may be due to the fact that CRC cells have a series of stages that determine the prognosis such as proliferation, apoptosis, invasion, migration, metastasis, and anesthetic agents may exhibit different effects at different stages. In the future, we will perhaps be able to get more specific responses from in vivo and in vitro studies regarding the effects of anesthetic agents at different stages.

Inhalation Anesthetics

Although the mechanism is not fully known, in vitro and animal experiments have shown that inhalation anesthetics inhibit the proliferation and activity of NK cells and reduce the formation of TH1 cells. Many studies have demonstrated the suppressive effects of sevoflurane, desflurane, isoflurane, and halothane on the immune system. In particular, this effect of halothane is dose-dependent,

and as its concentration increases, its inhibition effect increases. However, the effects of inhalation agents on the prognosis of colorectal cancer cells in humans are controversial [25, 26].

While it is expected to worsen the prognosis of the tumor due to its suppressive effects on the immune system, there are also studies on the beneficial effects of sevoflurane and desflurane in colorectal surgery in the postoperative period. In a very recent two in vitro studies, it was reported that sevoflurane suppressed colorectal cancer cells via complex cellular pathways. Sevoflurane can affect the prognosis through microRNAs (miR), which are capable of increasing or decreasing the function of messenger RNA (mRNA) that is encoded (transcription) for the production of amino acid and polypeptide chains to be synthesized to perform certain functions and which transmit them to the cell ribosome (translation). Sevoflurane has been reported to be able to inhibit the proliferation, spread, and metastasis of tumor cells by activating miR-34, miR-124, and miR-203 [27–29].

Manipulations performed to achieve hemostasis in CRC operations lead to reperfusion injury in tumor tissue, and this injury leads to IL-8 secretion that attracts neutrophils to the region. Matrix metalloproteinase-9 (MMP-9) released from the neutrophils increases cancer recurrence. Sevoflurane and desflurane have been reported to decrease MMP-9 release and thereby tumor recurrence by reducing reperfusion injury [30]. A study on IL-6 and IL-10 concentrations found no difference between patient groups receiving total intravenous anesthesia (TIVA) and isoflurane [31].

Nitrogen protoxide (N2O nitrous oxide) is used to increase the concentration ability of inhalation anesthetics in general anesthesia procedures. This both provides faster induction and saves on inhalation anesthetic dose. However, its use is gradually decreasing because of the high number of side effects, the rapid induction of new inhalation anesthetics, and a considerable saving from inhalation anesthetics with low-flow anesthetic techniques. Nitrogen protoxide itself is teratogenic and is not used in pregnant women. It inhibits B12-dependent enzymes. Of these enzymes, the inhibition of methionine synthase disrupts methionine and folic acid metabolism and suppresses the synthesis and functions of mononuclear and neutrophil cells, which are required for the activity of the immune system. Despite all these adverse side effects of nitrogen protoxide, there is no evidence that it may adversely affect the prognosis of CRC [32].

Xenon has the lowest blood/gas partition coefficient compared to other inhalation anesthetics. Therefore, it is an inhalation anesthetic with the fastest induction and recovery. According to the studies, it has neuroprotective properties. Although there is no specific study on its effect on CRC cells yet, it has been reported to inhibit the proliferation and migration of breast cancer cells. This mechanism of action of xenon has not yet been solved, and its very expensive price prevents its use in routine [33].

Intravenous Anesthetics

Propofol

Many studies have demonstrated that propofol suppresses the proliferation of CRC cells and increases apoptosis with multiple mechanisms. It increases both the number and activity of NK cells that fight against CRC cells. It inhibits the aerobic glycolysis metabolism of CRC cells. It reduces the release of IL-13, which increases mesenchymal spread of CRC cells, and cytokines such as TNF-α, IL-6, and IL-1β, which lead to inflammation. It is also thought that its anti-inflammatory and antioxidant effects have positive effects on the prognosis of CRC. On the other hand, the effect of propofol on CRC metastasis is unclear [34–37].

Dexmedetomidine

It is an α2 agonist agent with sedative and analgesic effects. Conflicting results have been reported about its effect on CRC cells. Some studies have reported that it increases the proliferation of CRC cells, while some studies have reported no effect. This is probably due to the fact that the studies were conducted on different types of cancer. In current studies on dexmedetomidine and CRC cells, it has been advocated that it is a safe anesthetic agent that can be used in combination with propofol in CRC operations [38].

Etomidate

It is an anesthetic agent that has minimal hemodynamic effects and is often used for induction in cardiovascular failure and hypotensive patients. According to the studies, it increases the spread of CRC cells in both in vivo and in vitro tests. Therefore, it is recommended to be used with caution in CRC operations by considering this effect [38].

Ketamine

It is an anesthetic agent widely used in anesthesia procedures as an NMDA receptor blocker for hypnotic purposes. As with dexmedetomidine, there are different views on its effect on CRC cells. Several studies have demonstrated that ketamine reduces both the number and activity of NK cells and increases TH2 cells. However, while it is expected to suppress the immune system with these properties, ketamine has been reported to inhibit the proliferation of CRC cells in recent publications [39].

Benzodiazepines

Midazolam and diazepam have inhibitory effects on the immune system with the inhibition of IL-2, IL-8, and TNF-α. However, the effects of these properties on CRC cells are not clear. The studies are mainly on the results of its chronic use for sedative purposes. There is a need for studies on the effects of benzodiazepines on CRC cells after anesthesia [40, 41].

Opioids

Unlike other anesthetic agents, opioids are used in the majority of CRC patients not only perioperatively but also postoperatively. The dose of opioid used varies depending on the patient, the facilities of the clinic, and the practitioners. The reports about tumor prognosis in CRC patients according to the opioid dose used are conflicting. Fentanyl has been reported to inhibit NK cells in mice dose-dependently. On the other hand, a retrospective study on 1679 patients found no difference between the groups to whom high or low doses of fentanyl were administered. In another study, it was reported that fentanyl and remifentanil decreased serum levels of IL-6, IL-8, CRP, and TNF-α and reduced oxidative stress. No effect of sufentanil on CRC cells has been found. Intermittent administration of morphine has been shown to reduce CRC metastasis in mice, but have no effect in rats. According to the results of a study that analyzed 501 studies including colon, rectal, and colorectal cancer patients treated with opioids between 1950 and 2018 in the literature, the evidence on not using opiods in CRC patients is insufficient. Until proven otherwise, opioids appear to remain an important part of perioperative and postoperative multimodal analgesia [42, 43].

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

They reduce prostaglandin synthesis via cyclooxygenase (COX) enzyme inhibition. They inhibit the synthesis of bradykinin and the chemotaxis of lymphocytes, monocytes, and macrophages. According to the studies, COX-2 enzyme plays a role in the rapid transformation and proliferation of colonic and intestinal mucosal cell changes into cancer cells. The risk of developing CRC has been found to be lower in patients using NSAIDs for various reasons than in the normal population. Likewise, aspirin use has been found to reduce the risk of CRC in women without a family history of CRC [44, 45].

Aspirin and NSAIDs significantly inhibit CXCR4. The C-X-C Motif Chemokine Receptor 4 (CXCR4) is not present in normal tissue but causes an increase in tumor tissues. Therefore, CXCR4 is considered to play an important role in the proliferation and metastasis of CRC cells and is a preoncologic marker for CRC [46].

Local Anesthetics

One of the mechanisms by which regional anesthesia techniques reduce cancer recurrence in CRC patients is thought to be due to the suppressive effects of local anesthetics on cancer cells. Many in-vitro studies support this view and show that local anesthetics can be used safely in CRC patients. Lidocaine can suppress the proliferation of CRC cells via microRNAs and increase apoptosis. This effect of lidocaine increases with dose and duration. Ropivacaine inhibits the proliferation of CRC cells only at high doses. Bupivacaine and levobupivacaine can inhibit both proliferation and migration [47–49].

β blockers

Several studies have shown that stress hormones such as adrenaline and noradrenaline increase the risk of recurrence and metastasis in CRC patients. It has been thought that these hormones can be suppressed by the use of β blockers and may produce positive effects on cancer prognosis. There are also experimental and epidemiological studies supporting this view that β blockers may reduce the metastasis of tumor cells in CRC patients in the postoperative period. However, recent studies do not support this hypothesis. Perhaps β blockers may support long-term survival rates in other types of cancer, but such evidence has not been found in CRC tumors [50].

Peroperative Anesthetic Practices

Blood Transfusion

Preoperative anemia is common in CRC patients due to chronic inflammation-related Fe^{2+} metabolism disorder and occult bleeding. This rate is 38–59% in colon cancers and 18–50% in rectal cancers. It is thought that preoperative anemia-induced immune system dysfunction may be as effective as a preoperative blood transfusion in the worsening of postoperative cancer prognosis. Therefore, the effects of blood and blood product transfusion alone on tumor recurrence rate and long-term survival are controversial. However, blood and blood product transfusion is known to cause an increase in postoperative inflammatory response, suppression of the immune system's ability to fight against infective and cancer cells, and an increase in the length of hospital stay, long-term mortality risk and incidence of cancer recurrence [51].

There is an increasing number of studies suggesting that transfusion-related increased postoperative inflammatory response in CRC patients may adversely affect the prognosis. However, these studies report to take into consideration that preoperative anemia, which is common in CRC patients, is associated with larger and advanced-stage tumors, metastasis, advanced age, comorbidity, higher ASA scores and longer operative times. The question of whether transfusion itself or the factors causing transfusion is important is controversial. Nevertheless, considering CRC patients without preoperative anemia or metastasis, the general view is to question the requirement for perioperative blood and blood product transfusion and to avoid unnecessary and excessive transfusion [52].

Hypothermia

It is supported by studies that mild hypothermia of 20 °C increases postoperative infections threefold and leads to NK cell inhibition by causing the release of stress hormones. The in-vitro studies have shown that hypothermia suppresses the immune system at both cellular and humoral levels. However, the studies on the effects of

hypothermia on proliferation, recurrence and metastasis in CRC patients are limited. These studies found no statistically significant difference between normothermic and hypothermic groups in terms of long-term survival rates. Since anesthetic technique, anesthetic agents, blood and blood product transfusion and many patient and tumor-related factors are involved during the operation, hypothermia alone cannot be considered as a factor that would affect the prognosis. Nevertheless, as in every patient, the necessary measures should be taken in order to maintain perioperative normothermia in CRC surgery. These measures include temperature monitoring with esophageal lower-end probes for continuous control of core temperature, and warming of the patient himself/herself and intravenous and irrigation fluids using appropriate warming systems [53, 54].

Postoperative Analgesia

The in vivo studies have shown that acute postoperative pain suppresses the immune system by causing the release of stress hormones, increases the metastatic ability of tumor cells, and reduces long-term survival. It is known that patients with acute pain develop depression and anxiety at a higher rate, leading to immune system dysfunctions. Moreover, the effects of opioids, the most commonly used analgesic agent for postoperative acute pain, on tumor cells are also controversial [55].

Given the in vivo and in vitro results, it seems reasonable to manage postoperative acute pain with local anesthetics by using regional anesthetic techniques. The studies on this found a lower incidence of postoperative ileus, nausea, urinary retention, earlier mobilization and oral nutrition, lower pain scores, and higher patient satisfaction in patients whose analgesia is provided by an epidural catheter. However, no evidence has been found to support hypotheses about its effects on increasing metastasis of tumor or reducing long-term survival [56, 57].

In Conclusion

The anesthetic technique and anesthetic agents selected in CRC surgery as well as perioperative anesthetic practices may affect the prognosis of patients. They may play an inhibitory or excitatory role in the proliferation, invasion, migration, and metastasis ability of tumor cells.

Sevoflurane, desflurane, xenon, propofol, nonsteroidal anti-inflammatory drugs (NSAIDs), epidural block, or regional blocks with general anesthesia and local anesthetics used in these blocks can be safely used in CRC patients. The results on the effects of dexmedetomidine, ketamine, opioids, and β blockers are conflicting. Blood transfusion and hypothermia are known to have adverse effects in all surgical procedures.

Most of the studies on anesthetic practices in CRC surgery are in vivo or in vitro. The human studies are small scale and retrospective. The results revealed should be supported by randomized, prospective, and larger studies. However, according to

the present results, the determination of anesthetic practices may have the potential to change the behavior of tumor cells positively in CRC patients and may be a source of data for future studies.

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Cardiac Assessment in Noncardiac Surgery

12

Hatice Solmaz and Oner Ozdogan

The mean age of patients undergoing surgery and the number of cardiac risk factor they possess have increased worldwide in parallel to an increase in the number of patients undergoing surgery [1]. Major cardiac complications account for at least one third of perioperative mortality in patients undergoing noncardiac surgery. This affects prognosis in the medium and long term and thus raises the importance of preoperative cardiac risk assessment [2, 3]. For this reason, clinical risk of a particular patient and cardiovascular factors that might require long-term follow-up must be identified. An individualized, evidence-based, staggered assessment must be targeted and cardiac risk be assessed after the administration of cardiac risk indices, establishing the stress level of the surgical procedure and interpretation of the test results, and surgical requirements must be determined accordingly [4].

Preoperative Assessment

Cardiac complications occurring after noncardiac surgery are related to the type of surgery, surgical conditions, and risk factors of the patient [5, 6].

At the beginning of the preoperative assessment, the presence of cardiac symptoms such as angina, dyspnea, syncope, palpitation, and the patient's medical history of cardiac disease must be enquired. Patients with a history of myocardial infarction (MI) in the last 60 days or patients with unstable angina, decompensated heart failure, high-grade arrhythmia, and those with hemodynamically significant valvular heart disease are at high risk for MI, heart failure, ventricular fibrillation, primary cardiac arrest, complete heart block, and cardiac death [7]. These patients must receive optimal therapy and referred to a cardiologist for further assessment, where possible.

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Cardiac Response to Surgical Stress

Surgical intervention produces physical and psychological stress, and it could lead to deterioration in the autonomous, endocrine, metabolic, and cardiovascular systems. An increase is observed in the sympathetic activity, systemic vascular resistance, and blood pressure during and after surgery. The workload of the heart increases with the addition of increased heart rate secondary to an increased sympathetic activity leading to increased cardiac afterload. Blood loss secondary to the surgery and vasospasm due to increased sympathetic activity may cause myocardial infarction as a result of imbalance between myocardial oxygen supply and demand [8].

In addition to an increased level of circulating catecholamines due to surgical stress, a hypercoagulable state occurs secondary to the activation of hypothalamic-pituitary-adrenal axis. On the other hand, variation of the balance between prothrombotic and fibrinolytic factors could also increase the risk of acute coronary syndromes caused by the rupture of the vulnerable plaques [9]. All these factors together with the patient's position, body temperature management, bleeding, and the type of anesthesia lead to hemodynamic impairment.

Surgical stress response varies according to the type of anesthesia. Less invasive anesthesia techniques may reduce mortality in the early period in patients with moderate-to-severe cardiac risks and limit postoperative complications [10]. For this reason, factors specific to the surgery should not be overlooked while the importance of patient-specific factors is obvious in determining the cardiac risks.

Surgical Emergency

The importance and value of preoperative cardiac assessment will also depend on the urgency of surgery. The American College of Cardiology (ACC) and the American Heart Association (AHA) [11] defined emergency procedure as one in which life or limb is threatened if the patient is not moved to the operating room within less than 6 h. There is no time for clinical evaluation or only minimal clinical evaluation can be performed. Cardiac risk assessment in such emergency conditions does not alter the course or the outcome of the procedure but may guide the treatment in the early perioperative period [11].

An urgent condition was defined as a condition that threatens life or limb if the patient is not moved to the operating room within 6–24 h. The mortality and morbidity rate of a condition that requires urgent intervention may overweigh potential cardiac risks associated with the procedure [11].

Patients requiring emergency or urgent care have an increased risk of perioperative cardiac events that are independent of the scoring systems administered for risk assessment and comorbid conditions they possess [12]. The clinician must be accessible to assist in the management of cardiovascular complications in high-risk patients in the postoperative period.

A time-sensitive procedure is one in which a delay of 1–6 week for the assessment and management of disease negatively affects the outcomes. Many oncological procedures fall into this group. Elective procedure is defined as an intervention that can be postponed until 1 year [11].

Surgery-Specific Risk

The type of procedure, body area involved, degree of invasiveness, body temperature, fluid changes, and blood loss are surgical factors affecting the cardiac risk [13].

Surgical procedures, including open and endovascular procedures, are divided into three groups as low risk, intermediate risk, and high risk, in an attempt to provide clearer definition of cardiac risk. The risk estimate for cardiac death or myocardial infarction within 30 days for these groups is <1%, 1–5%, and >5%, respectively [14].

Surgical procedures or interventions that impart low cardiac risk (<1%) include dermatological, dental, and ophthalmological procedures, minor urological procedures as transurethral resection of the prostate, minor orthopedic procedures as meniscectomy, carotid endarterectomy or carotid artery stenting in an asymptomatic patient, minor gynecological procedures, and thyroid surgery, breast surgery, and reconstructive surgery [14].

Surgical procedures or interventions that impart intermediate cardiac risk (1–5%) include splenectomy, hiatal hernia repair, intraperitoneal procedures as cholecystectomy, carotid endarterectomy or carotid artery stenting in a symptomatic patient, peripheral arterial, angioplasty endovascular aneurysm repair, head and neck surgery, major neurological or orthopedic procedures as hip and spine surgery, major urological procedures as kidney transplant, major gynecological procedures, and non-major intrathoracic procedures [14].

Procedures that impart higher than 5% cardiac risk include aortic and major vascular surgery, open lower limb revascularization and amputation or thromboembolectomy, duodenopancreatic surgery, liver resection, bile duct surgery, esophagectomy, repair of perforated bowel, adrenal resection, total cystectomy, pneumonectomy, and lung or liver transplant surgery [14].

In general, endoscopic and endovascular less invasive methods are associated with faster recovery when compared to classical open surgical methods. Emergency major operations particularly in the elderly patients, aortic or other major or peripheral vessel surgeries, and prolonged surgical interventions that result in excessive fluid or blood loss are associated with high cardiac risks. Ophthalmological and plastic surgery procedures, transurethral resection of the prostate, and minor surgical interventions as orthopedic procedures are associated with low rate of complications in patients with a heart disease, provided that the patient remains hemodynamically stable. Laparoscopic procedures have a number of advantages, such as reduced length of hospital stay, decreased intraoperative blood loss, decreased rate of postoperative pneumonia, and faster restoration of normal bowel movement. Laparoscopic

procedures are preferred over open surgical procedures when considering less incisional pain, less extensive tissue trauma, and better postoperative lung functions as the advantages. Considering the need for pneumoperitoneum and using the Trendelenburg position in an elderly, frail, and obese patient with cardiac comorbidities, laparoscopic procedures that are well tolerated in otherwise healthy patients do not reduce the cardiac risks when compared to open surgery [15]. The reason for this is that pneumoperitoneum and Trendelenburg position required for this procedure increases intra-abdominal pressure but also mean arterial pressure, central blood pressure, mean pulmonary artery pressure, pulmonary capillary wedge pressure, and systemic vascular resistance, decreases venous return, and thereby impairs the cardiac functions [16]. Therefore, laparoscopic procedure in a patient with heart failure does not reduce cardiac risks when compared to open surgery, and both approaches must be considered the same.

Functional Capacity

Functional capacity of a patient is a reliable predictor of perioperative and long-term cardiac events. Functional capacity is measured with metabolic equivalent of task (MET). One MET equals to basal metabolic rate and reflects the basal oxygen consumption-metabolic demand. If a recent exercise test is not available for a patient who is to undergo noncardiac surgery, functional capacity can be evaluated by enquiring daily life activities [17]. Swimming, tennis, football, and basketball are more than ten MET activities requiring higher exercise capacity, whereas climbing two flights of stairs of walk up a hill is four MET activities. If the exercise capacity is poor (<4 MET), the patient is able to groom, eat, use the toilet, and dress but cannot climb two flights of stairs, and this is associated with increased rate of postoperative cardiac complications [18, 19]. Asymptomatic patients with good functional capacity can undergo scheduled surgery without performing advanced cardiac evaluation.

Risk Indices

The use of risk indices aims to reduce the risk of perioperative cardiac complications. The assessment must be limited mandatorily if emergency surgery is required. An approach involving more comprehensive and systematic cardiac risk assessment can be followed depending on the characteristics and type of surgery in the absence of an emergency situation.

Patients found to have low cardiac risk following comprehensive assessment can safely undergo surgery without further delay. The option of medical therapy must be prioritized in patients suspected of having increased cardiac risk.

Various imaging techniques can be employed to determine whether a particular patient is at high risk. However, attention must be paid to select techniques; the results of which have the potential to change or modify the management. The Lee

index [20], also called the revised cardiac risk index (RCRI), which was developed in the last three decades, and the intraoperative-postoperative myocardial infarction and cardiac arrest (MICA) model that was developed using the database of the National Surgical Quality Improvement Program (NSQIP) of the American College of Surgeons to predict myocardial infarction and cardiac arrest are the most commonly used risk indices [21].

The Lee index is a simple model that was developed to predict the risk of major cardiac complications such as major perioperative myocardial infarction, pulmonary edema, ventricular fibrillation, cardiac arrest, and complete heart block [20]. This risk index comprises six variables, including the type of surgery, history of ischemic heart disease, history of heart failure, history of cerebrovascular disease, preoperative use of insulin therapy, and preoperative creatinine >170 mmol/L (>2 mg/dL). Suprainguinal vascular surgeries and intraperitoneal and intrathoracic surgeries have been defined as high-risk surgeries, which is one of the variables of this risk index (Table 12.1). Patients with "0" or "1" predictor are classified as having low cardiac risk, whereas patients with more than "2" predictors are defined as having increased risk for cardiac events.

The NSQIP MICA model was developed to predict the risk of intraoperative-postoperative myocardial infarction or cardiac arrest within the first 30 days after surgery. Five factors were identified as the predictors of perioperative myocardial infarction and cardiac arrest: type of surgery, functional status, increased serum creatinine (>130 mmol/L or >1.5 mg/dL), American Association of Anesthesiologists (ASA) class (Class I, a normal healthy patient; Class II, a patient with a mild systemic disease; Class III, a patient with a severe systemic disease that is not life-threatening; Class IV, a patient with a severe systemic disease that is a constant threat of life; Class V, a moribund patient who is not expected to survive beyond the next 24 h without surgery), and age [21].

Different from other risk indices, the NSQIP MICA model is not a scoring system; however, it predicts the individual risk of myocardial infarction and cardiac arrest. Unlike the Lee index, this system does not include pulmonary edema and complete heart block. Complementary prognostic data is obtained when the NSQIP MICE model is used in combination with the Lee index.

Although atrial fibrillation and obesity are not included as a criterion in these risk indices, they are related to increased perioperative risks. Obese patients are at increased risk of cardiac events during noncardiac surgery [22, 23].

Table 12.1 Clinical risk factors according to the revised cardiac risk index

Ischemic heart disease
Presence of insulin-dependent diabetes mellitus in the preoperative period
High-risk surgery
Presence of the history of congestive heart failure
Presence of the history of cerebrovascular disease
Serum creatinine level >2 mg/dL in the preoperative period

Biomarkers

There is a paucity of data from prospective controlled studies regarding preoperative use of biomarkers.

Cardiac troponins including cardiac troponin T (cTnT) and cardiac troponin I (cTnI) are markers that are preferred in the diagnosis of myocardial infarction as these markers have higher sensitivity and specificity than other biomarkers [24]. Available evidence suggests that even small increases in the level of cTnT in the perioperative period point toward a clinically significant myocardial damage and poor cardiac prognosis and outcomes [25]. For this reason, evaluation of cardiac troponins must be considered before and 48–72 h after major surgery [26].

Brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-proBNP) are produced by the cardiomyocytes in response to an increased myocardial wall stress. This can occur at any stage of heart failure, independently of myocardial ischemia. Plasma BNP and NT-proBNP are important prognostic indicators of many heart diseases in nonsurgical conditions. Preoperative BNP and NT-proBNP levels have additional prognostic value in terms of long-term mortality and cardiac events following major noncardiac vascular surgery [27].

In a recent meta-analysis of 18 studies involving 2179 patients, it was determined that a cut-off value of 300 ng/L for NT-pro-BNP and a cut-off value of 92 mg/L for BNP before noncardiac surgery are associated with increased 30-day mortality and increased risk of nonfatal myocardial infarction. In this meta-analysis, the rate of patients with NT-proBNP and BNP values at and above these thresholds was 7.6%. The rate of 30 mortality and increased risk of non-fatal myocardial infarction was 4.9% in patients with NT-proBNP and BNP values below the thresholds, while this rate was 21.8% in patients with values at and above the thresholds [28].

The markers of inflammation may detect patients at high risk for unstable coronary plaque in the preoperative period; however, there is no data on how the inflammatory markers will change risk-reducing strategies in surgical conditions [29]. Based on the available data, routine use of serum biomarkers employed in patients undergoing noncardiac surgery may not be suggested as an index of cell damage; however, their use can be considered in high-risk patients (MET < 4) or in patients with a revised cardiac risk index of >1 for vascular surgery and >2 for nonvascular surgery [30, 31].

Noninvasive Tests for Heart Disease

These tests must be performed if the results are anticipated to change perioperative management. Patients with excessive stress-related ischemia constitute a high-risk population in which standard medical therapy fails to prevent perioperative cardiac events. Patients who are recommended to undergo preoperative testing include patients undergoing high-risk surgery, patients with poor functional capacity (<4 MET), and individuals having more than two clinical risk factors. Considering the fact that patients scheduled for low-risk surgery will also have low rate of events, test results are not anticipated to change perioperative management in patients with stable heart disease.

ECG

The main purpose of running noninvasive tests is to identify cardiac events that lead to an increased risk of perioperative cardiac complications. A 12-lead ECG can be considered a part of preoperative cardiac risk assessment in patients with moderate and high risk who possess clinical risk factors according to the revised cardiac risk index. ECG predicts long-term prognosis in patients with ischemic heart disease. Routine preoperative ECG recording is not recommended in patients who do not have the risk factors and who are candidates for low-risk surgery.

Echocardiography

Although routine echocardiography is not recommended in preoperative evaluation of ventricular function, it can be considered in asymptomatic high-risk surgical patients due to the relationship between major cardiac events and preoperative left ventricular systolic dysfunction, moderate-to-severe mitral insufficiency, and high aortic valve gradient [32].

Noninvasive Imaging in Ischemic Heart Disease

Ischemic heart disease is an important component of the risk indices and the predictors of perioperative cardiac adverse events. Exercise test is important to determine functional capacity in this group of patients. Furthermore, blood pressure and heart rate of the patient are also determined during the exercise test. A risk stratification based on the exercise test is not appropriate in patients with limited exercise capacity, as such patients are not able to reach the ischemic threshold. At the end of the exercise test, a myocardial ischemia response starting at low exercise workload is associated with a significant increase in the risk of cardiac events in the perioperative period and in the long term, while a myocardial ischemia response starting at high exercise workload is attributed only to a low level of risk. Nuclear perfusion imaging or echocardiography together with pharmacological stress test is more appropriate for patients with a limited physical capacity. The extent of myocardial ischemia detected by pharmacological myocardial perfusion imaging technique is associated with high risk of perioperative cardiac events [33]. Stress imaging technique is recommended for asymptomatic patients who have more than two clinical risk factors and poor functional capacity (<4 MET) before undergoing high-risk surgery. Stress imaging technique is not recommended before a low-risk surgery regardless of the clinical condition of the patients [11].

Perioperative Cardiac Risk-Reducing Strategies

Coronary Revascularization Prior to Noncardiac Surgery

An important number of patients undergoing noncardiac surgery may have ischemic heart disease. Preoperative angiography is not recommended for patients with stable cardiac condition undergoing low-risk cardiac surgery [34].

Emergency angiography is recommended for patients with previous acute ST-segment-elevated myocardial infarction who are to undergo nonemergency noncardiac surgery [35]. Urgent or early invasive strategies are recommended depending on the risk assessment in patients with a history of non-ST-elevated acute coronary syndrome and who are to undergo nonemergency noncardiac surgery [36].

Patients with documented myocardial ischemia and unstable angina pectoris that is treated sufficiently (Canadian Cardiovascular Society Class III–IV) who are candidates for nonurgent noncardiac surgeries are recommended to undergo preoperative angiography [37].

Dual antiplatelet therapy is mandatory in patients who have undergone coronary angiography followed by stenting procedure. It would be ideal to postpone surgery in these patients as long as the risks posed by stopping antiplatelet therapy outweigh the risks of postponing noncardiac surgery [38].

Pharmacological Therapy

Acetylsalicylic Acid

In a meta-analysis of 41 studies involving 49,590 patients that compared the relationship between perioperative discontinuation of aspirin and the risk of bleeding associated with aspirin therapy, aspirin therapy was found to increase the risk of hemorrhagic complications by 50% without resulting in severe hemorrhagic complications. In a systematic review of patients at risk of ischemic heart disease (IHD) and those diagnosed with IHD, a threefold increase was demonstrated in the risk of major adverse cardiac events with discontinuation of aspirin therapy [39].

The POISE-2 study randomized 10,010 patients undergoing noncardiac surgery to either placebo or aspirin groups. Aspirin therapy did not reduce the rate of death and nonfatal myocardial infarction during 30-day follow-up period. The study did not encourage routine use of aspirin in patients undergoing noncardiac surgery [40].

Routine initiation of aspirin therapy is not recommended to avoid perioperative cardiac events. Similarly, routine continuation of aspirin therapy is not recommended to avoid perioperative cardiac events except for patient undergoing carotid surgery or those who have recently undergone coronary stenting [31].

The decision of using low-dose aspirin in noncardiac surgery should be made on an individual basis, outweighing the risk of thrombotic complications against the risk of perioperative bleeding. Aspirin must be discontinued if the risk of bleeding outweighs potential cardiovascular benefits. Aspirin must be discontinued at least 7 days before surgery in patients undergoing high-risk surgery in terms of bleeding complications [41].

Dual Antiplatelet Therapy

Current guidelines recommend elective noncardiac surgery be postponed until 1-year course of dual antiplatelet therapy has been completed and performed without discontinuation of aspirin therapy, where possible, in order to reduce the risk of bleeding and transfusion in patients who have undergone drug-eluting stent

implantation. However, the procedure must be performed without discontinuing dual antiplatelet therapy if surgery is emergency or urgent. In patients who have undergone bare-metal stent implantation, surgery must be delayed for 4–6 weeks ideally up to 3 months, the procedure must be performed without discontinuing aspirin therapy if possible, and dual antiplatelet therapy must be temporarily interrupted if there is high risk of bleeding [42].

Dual antiplatelet therapy is recommended up to 1 year independently of the type of stent in patients undergoing revascularization due to high-risk acute coronary syndrome (ACS). In general, the benefits of early surgery for a specific pathology (e.g., malignant tumors, vascular aneurysm repair) should be balanced against the risk of stent thrombosis in patients who have recently undergone stent implantation or have suffered ACS [42].

Independently of the acute status of the coronary disease and in conditions where surgery cannot be delayed further, minimum acceptable duration of dual antiplatelet therapy is 1 month in bare-metal stents and 3 months in new-generation drug-eluting stents [42].

Current ESC guidelines recommend discontinuation of clopidogrel and ticagrelor 5 days before surgery and prasugrel 7 days before surgery in patients requiring surgical intervention within a couple of days unless there is a high risk of thrombosis [43].

An intravenous bridging therapy with eptifibatide or reversible glycoprotein inhibitor as tirofiban should be considered in patients with high risk of stent thrombosis in whom antiplatelet therapy has been discontinued [44]. Bridging with a low-molecular-weight heparin (LMWH) must be avoided in such patients. Dual antiplatelet therapy must be started at the earliest date and within 48 h, if possible. Platelet transfusion is recommended if there is excessive and life-threatening perioperative bleeding in patients receiving antiplatelet therapy [45].

Vitamin K Antagonists (VKA)

Warfarin, which is a vitamin K antagonist, is used for prophylaxis against stroke in patients with atrial fibrillation (AF), protection against thrombotic and thromboembolic complications in patients with prosthetic heart valves, treatment purposes in patients with deep vein thrombosis (DVT), and prophylaxis against DVT in patients who are at risk [46].

The use of anticoagulants is associated with increased risk of bleeding during noncardiac surgery. Thus, VKAs must be discontinued 3–5 days prior to surgical intervention. The follow-up of international normalized ratio (INR) on a daily basis is recommended until INR is measured to be <1.5. If surgical intervention with high risk of bleeding is to be performed in patients with prosthetic valvular heart disease, patients with AF and high risk of thromboembolism, and patients with a history of thromboembolic event in the past 3 months, bridging therapy with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) must be administered after discontinuing warfarin therapy, and INR decreases below 2 [47, 48].

Reliable evidence is available for the use of intravenous (IV) UFH in patients with mechanical prosthetic heart valve and with an INR < 2; for this reason, such

patients are hospitalized in some centers to administer UFH until 4 h prior to surgical intervention, and UFH therapy is resumed until INR reaches the therapeutic range after surgery [47].

When INR is <2.0, the administration of LMWH is recommended twice daily, at therapeutic doses, in patients with high risk of thromboembolism and, once daily, at prophylactic doses, in patients with low risk of thromboembolism. These patients should receive the last dose of LMWH 12 h prior to the intervention [48]. Surgery can be performed safely if INR is <1.5. Fresh frozen plasma (FFP) and vitamin K or prothrombin complex concentrates can be administered in conditions where emergency reversal of the effects of vitamin K antagonists is required.

Direct Oral Anticoagulants (DOAC)

Patients receiving direct oral anticoagulants (DOACs) such as dabigatran, rivaroxaban, apixaban, and edoxaban should discontinue their medications before the intervention and 2–3 half-lives if surgery has normal risks for bleeding and 4–5 half-lives before high bleeding risk surgery [49].

A bridging therapy with heparin is not indicated due to short half-lives of these medications in patients using direct oral anticoagulant agents if there is no high risk of thromboembolic events. Only exception is the patients who are at high risk for thromboembolic events and in whom surgery is delayed for a few days (Table 12.2) [50].

Resuming the therapy should be delayed for 1–2 days (3–4 days in some patients) following surgery due to rapid onset of action in DOACs (compared to VKAs).

Management of Specific Conditions

Heart Failure

Heart failure has a known predictive value for perioperative cardiac events and is an important factor in clinical risk indices. The preoperative prognostic value of heart failure in the presence of preserved left ventricular (LV) ejection fraction is not known for certain. The use of angiotensin-converting enzyme (ACE) inhibitors as the first-line therapy, or angiotensin receptor blockers (ARBs), aldosterone antagonists, and β-blockers at optimal doses in patients who do not tolerate ACE inhibitors is strongly recommended to reduce mortality and morbidity [51].

It is recommended that an intermediate- or high-risk surgery be postponed for at least 3 months to allow titration of recently initiated drug doses and potential improvement in left ventricular function become apparent in patients with newly diagnosed heart failure [52]. If there is no sufficient time for drug titration in the perioperative period, initiation of these drugs at high doses is recommended.

Table 12.2 Biological half-lives of non-vitamin K antagonist oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Biological half-lives (h)	12–17 h	5–9 h (young) 11–13 h (elderly)	12 h	9–11 h

It is stated that a therapy with beta-blockers can be continued in the perioperative period, and a dose of ACE inhibitor or ARB can be skipped 1 day prior to surgery if the patient is prone to hypotension [53, 54]. The drugs for heart failure should be resumed at the earliest convenience to the extent that the clinical condition permits. These patients must be euvolemic before elective surgery; blood pressure must be stable with optimal end-organ perfusion [55].

Hypertension

There is no evidence to suggest that one antihypertensive therapy is superior to another in patients undergoing noncardiac surgery.

There is no evidence suggesting the benefits of delaying surgery to optimize management in hypertensive patients with stage 1 [systolic blood pressure 150–159 millimeters of Mercury (mmHg)/diastolic blood pressure 90–99 mmHg] and stage 2 (systolic blood pressure 160–179 mmHg/diastolic blood pressure 100–109 mmHg) hypertension [30]. Antihypertensive medications must be continued in the perioperative period in these patients.

Potential benefits of delaying surgery to optimize pharmacological treatment should outweigh potential risks of delaying surgery in patients with stage 3 hypertension (systolic blood pressure ≥180 mmHg/diastolic blood pressure ≥110 mmHg). Blood pressure can be controlled with intravenous nitroglycerin, labetalol, or nitroprusside if emergency surgery is required.

Sympathetic hypertension occurring during the induction of anesthesia is more significant and deserves close attention in patients with untreated hypertension. Because the risk of hypertensive encephalopathy, pulmonary edema, and myocardial infarction is higher in elderly patients with low reserves. On the contrary, more than 20% decrease in the systemic blood pressure for a duration of longer than 30 min or mean blood pressure of less than 60 mmHg during surgery is associated with increased rates of postoperative MI, stroke, and death [30, 56].

Aortic Stenosis

Patients with severe aortic stenosis should undergo emergent noncardiac surgery accompanied by hemodynamic monitorization. Severe adverse cardiac events in the presence of severe aortic stenosis arise from hemodynamic impairment caused by the anesthetic agents and surgical stress. The development of hypotension and tachycardia may result in a decrease in coronary perfusion pressure, induction of arrhythmia and ischemia, myocardial damage, heart failure, and death. Aortic valve replacement should be considered before elective surgery in symptomatic patients [47]. Noncardiac surgery should be performed only if it is indicated in a patient in whom valvular replacement surgery cannot be performed due to high risk of severe comorbidities and lack of patient's consent for the procedure. Balloon aortic valvuloplasty or transcatheter aortic valve implantation can be among the options before surgery in such patients [47]. Low-risk and moderate-risk noncardiac surgery can be performed safely in patients with asymptomatic severe aortic stenosis. More comprehensive clinical evaluation is required for aortic valve replacement if high-risk surgery will have to be performed.

Arrhythmias

A patient should be investigated for the presence of a structural heart disease in case that arrhythmias are observed, such as AF and ventricular tachycardia (VT).

There is no clear evidence to suggest that ventricular premature beats and non-sustained VT alone are associated with poor prognosis. Ventricular extra beats require detection and correction of treatable causes such as hypoxia, anemia, and electrolyte disturbances. Sustained monomorphic VT should be treated by electrical cardioversion if the patient is hemodynamically stable [57]. Intravenous amiodarone can be used in stable patients.

Emergency defibrillation is required to terminate sustained polymorphic VT and ventricular fibrillation [57]. A beta-blocker therapy is useful in patients with recurrent sustained polymorphic ventricular tachycardia (SPVT) if ischemia is suspected or cannot be ruled out [58].

In rare instances of Torsades de Pointes, discontinuation of the culprit medications and correction of electrolyte abnormalities are recommended [59].

Supraventricular arrhythmias and AF are more common than ventricular arrhythmias in the perioperative period. Potential triggering factors such as respiratory failure or electrolyte disturbances should be checked and corrected. Vagal maneuvers can cease supraventricular tachycardia (SVT) in some cases [60].

Supraventricular tachycardias often respond well to adenosine therapy; SVTs that are refractory to adenosine therapy can be ceased by short-acting beta-blockers or a non-dihydropyridine calcium channel blocker (such as diltiazem and verapamil) or intravenous amiodarone [61]. Catheter ablation can be considered taking into account the characteristics and urgency of the proposed surgery in rare cases of Wolf-Parkinson-White syndrome and in patients with preexited AF [62].

Permanent Pacemaker and Presence of ICD

Symptomatic patients and those with significantly impaired left ventricular ejection fraction (<30%) are at high risk for cardiovascular complications, and these patients should undergo noncardiac surgery only if it is required.

Patients with permanent pacemaker can safely undergo surgery by taking appropriate measures. The use of unipolar electrocautery may pose some risks in pacemaker-dependent patients. Electrical stimulation of the electrocautery may cause inhibition of pacemaker device or reprogram these devices. Such problems can be reduced by keeping the electrocautery away from the pacemaker device and using fires with the lowest amplitude for short duration [63].

Electrical current from the electrocautery during noncardiac surgery may also cause problems in the functions of implantable cardioverter defibrillator (ICD). Implantable cardioverter defibrillator must be switched off during surgery. Patients with deactivated ICD device should be monitored along the period of deactivation. External defibrillation devices must be made available. ICD must be reactivated before moving the patient to the ward [64].

Extended Thromboprophylaxis Following Abdominal or Pelvic Surgery

Venous thromboembolism (VTE) involving pulmonary embolism and deep vein thrombosis is commonly observed after abdominal surgery [65]. Particularly cancer patients are at increased risk of VTE following intra-abdominal surgery both due to surgery-related and cancer-related factors [66]. These patients should therefore receive routine prophylaxis against VTE using low-molecular-weight heparin (LMWH) [67]. Out-of-hospital prophylaxis for VTE is not common. The need for extended out-of-hospital prophylaxis has been examined in recent years due to an association between VTE and 30-day mortality after intra-abdominal and pelvic surgery [68]. One study found that 40% of VTE events following cancer surgery occur after 21 days [69]. In another recent randomized and controlled study, patients undergoing laparoscopic colorectal cancer surgery were divided into two groups to receive postoperative LMWH therapy either for 1 or 4 weeks. The study established that extended prophylaxis is safe and reduces the risk of VTE [70]. In a recent review of seven randomized controlled studies that evaluated patients receiving 14-day extended course of prophylaxis against thromboembolism using LMWH versus placebo and control groups after abdominal and pelvic surgery, extended thromboprophylaxis was found to reduce the risk of VTE significantly without increasing bleeding complications only when compared to in-hospital administration [71]. In light of all these studies, American College of Chest Physicians, the National Cancer Care Network, and the American Society of Clinical Oncology recommend routine administration of extended out-of-hospital VTE prophylaxis following major abdominopelvic cancer surgeries [67, 72, 73]. VTE prophylaxis with enoxaparin is administered subcutaneously at a dose of 30 mg in every 12 h or 40 mg once daily; VTE prophylaxis with deltaparin is administered subcutaneously at a dose of 2500 or 5000 IU/kg once daily. A prophylaxis with tinzaparin is not recommended.

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13 Surgical Treatment Approaches to the Colorectal Cancers in the Light of the Current Guidelines

Cebrail Akyuz and Oguzhan Sunamak

Treatment Approach to the Malignant Polyps

Malignant polyps are T1 cancers in TMN classification which means they invade muscularıs mucosae and submucosa but not muscularıs propria. However, every T1 cancer is not polyp-originated cancer [1, 2]. In evaluatıon of the polyps, high-resolution endoscopy with narrow-band imaging or dye spray should be preferred. A majority of the malignant polyps can be treated endoscopically without necessitating major surgery. The proper selection of the lesion for local excision by the experienced endoscopists is very important in providing a potentially curative surgery. The pedunculated malignant polyps are classified by the Haggitt classification [3]. According to this classification, adenocarcinoma invasion is restricted to the head of the polyp in level 1; the tumor infiltration extends to the neck of the polyp in level 2; there is the stalk invasion in level 3; the invasion extends to the root of the polyp but restricted to the submucosa in level 4 (Fig. 13.1). This classification is the pathological one and applied after the polyp excision. Generally, if there are no unfavorable factors, level 1–3 polyps can be managed endoscopically. However, the polyps with unfavorable factors are frequently candidates for colon resection. The unfavorable factors are lymphovascular invasion, poorly differentiated tumor, and the surgical margin less than 2 mm. The standard surgical resection is necessary for level 4 adenocancers where the adenocancer invades submucosa [4, 5].

Haggitt classification is described only for malignant pedunculated polyps. Sessile polyps have no stalk; thus, the classification described by Kudo is used for the malignant sessile polyps [6]. Here, the adenocancer invasion is restricted to the

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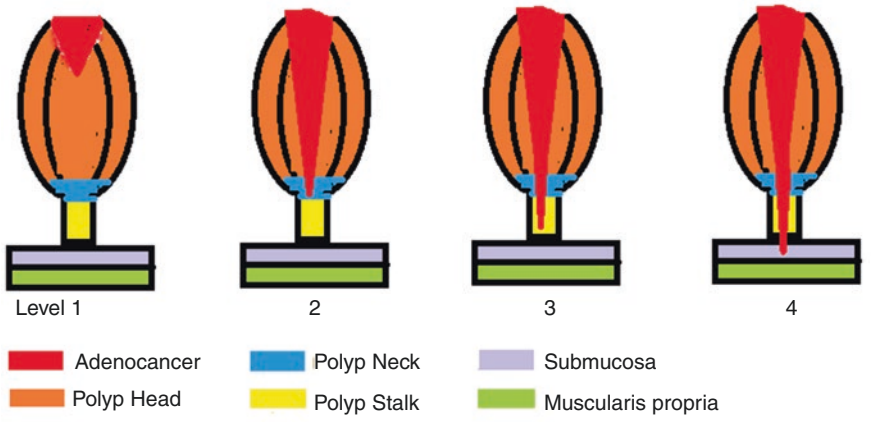


Fig. 13.1 Haggitt classification

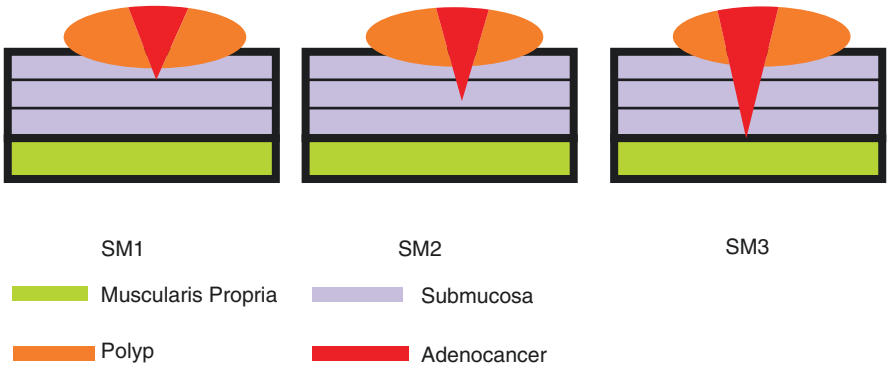


Fig. 13.2 The invasion depth according to the Kudo classification

upper 1/3 of the submucosa in SM1 and invades middle 1/3 of the submucosa in SM2 and lower 1/3 of the submucosa in SM3 (Fig. 13.2). Following the endoscopic resection, the absence of muscularis mucosa on the pathological examination might cause trouble in the application of the classification. Thus, the degree of invasion can only be predicted. The SM1 and SM2 lesions without unfavorable factors can be treated by endoscopic resection. As the metastasis rate of the malignant polyps in SM3 level or with unfavorable factors is very high (25%), standard colon resection must be offered [5, 7].

The most important step in managing the possible malignant polyps is to determine the invasion depth as it is a critical point in assessing the risk for local recurrence and lymph node metastasis. Surgical indications in malignant polyps are given in Table 13.1.

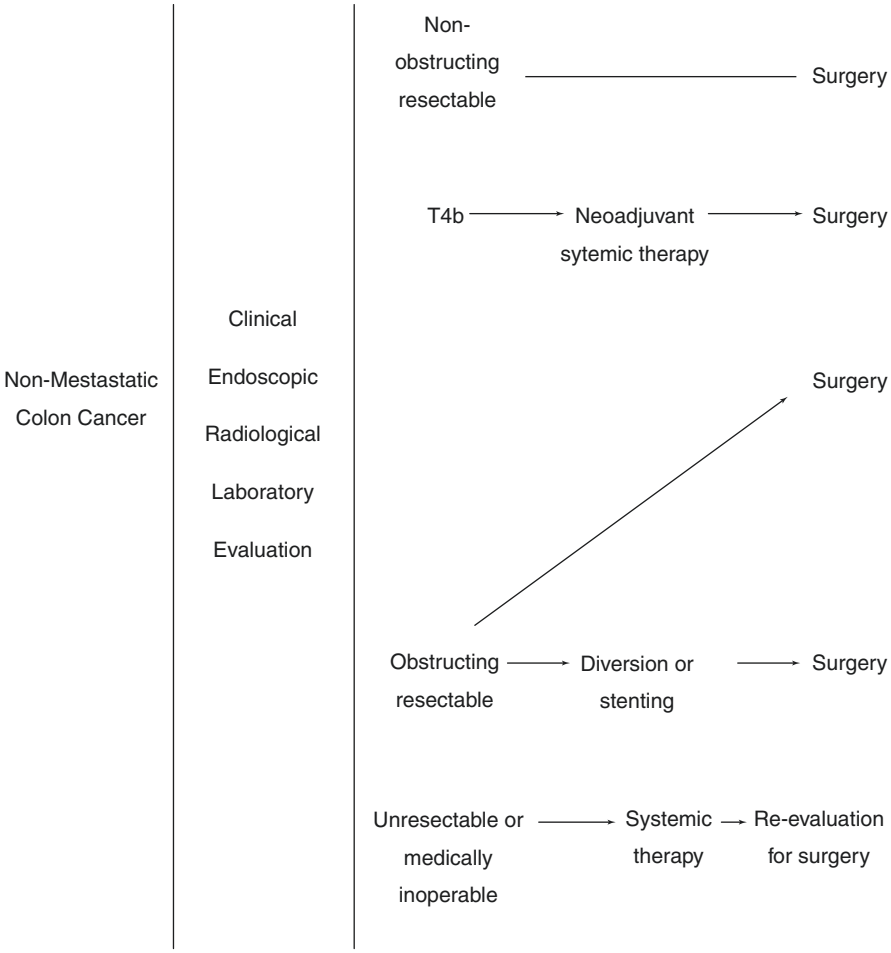
Surgical Treatment Approaches to the Colon Cancers

Surgical resection has still been the main treatment in colon cancers and necessitates a multidisciplinary team approach. This team should involve gastrointestinal or general surgeons, pathologists, medical or radiation oncologists, radiologists, dietitians, and stoma-care nurses [8]. Surgical treatment algorithm for the

Table 13.1 Surgical indications in malignant polyps

The endoscopic resection margin is less than 2 mm
Lymphovascular invasion is present
Inability to evaluate resection margin on pathological analysis
Haggitt stage 4 polyp
Sessile polyp with the level SM3
Tumor budding is present
Poorly differentiated tumor

Table 13.2 Treatment algorithm in non-metastatic colon cancers



nonmetastatic colon cancers was given in Table 13.2. TNM staging is the main one in staging and the treatment approach of both the colonic and the rectal cancers (Tables 13.3 and 13.4).

Table 13.3 American Joint Committee on Cancer (AJCC) TNM staging classification for colorectal cancers (8th ed., 2017)

T Primary tumor	**N Regional lymph nodes**
TX Primary tumor cannot be assessed **T0** No evidence of primary tumor **Tis** Carcinoma in situ **T1** Tumor invades the submucosa **T2** The muscularis propria invasion **T3** Pericolorectal tissue invasion **T4** The visceral peritoneum invasion or invasion or adherence to the adjacent organ or structure **T4a** Tumor invades the visceral peritoneum (tumor perforation involved) **T4b** Tumor directly invades or adheres to adjacent organs or tissues	**NX** Regional lymph nodes cannot be assessed **N0** Regional lymph node metastasis is not present **N1** One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative **N1a** One regional lymph node is positive **N1b** Two or three regional lymph nodes are positive **N1c** Regional lymph nodes are not positive, but subserosal, mesenteric, pericolic, perirectal/mesorectal tumor deposits are present **N2** More than four regional lymph nodes are invaded **N2a** 4–6 regional lymph nodes are invaded **N2b** More than seven regional lymph nodes are invaded
M Distant metastasis	
M0 There is no evidence of distant metastasis on radiological imaging **M1** Peritoneal metastasis or at least one organ metastasis is present **M1a** One organ or site metastasis without peritoneal metastasis **M1b** More than one organ or site metastases without peritoneal metastasis **M1c** Peritoneal metastasis with or without organ metastases	

Table 13.4 Pathological staging-based treatment approach following surgery in colon cancers

Stage	T	N	M	Treatment
Stage 0	Tis	N0	M0	Observe
Stage 1	T1	N0	M0	Observe
	T2	N0	M0	Observe
Stage 2A	T3	N0	M0	Observe or systemic therapy[a]
Stage 2B	T4a	N0	M0	Systemic therapy or observe[b]
Stage 2C	T4b	N0	M0	Systemic therapy or observe[b]
Stage 3A	T1, T2	N1/N1c	M0	Systemic therapy
	T1	N2a	M0	Systemic therapy
Stage 3B	T3-T4a	N1/N1c	M0	Systemic therapy
	T2, T3	N2a	M0	Systemic therapy
	T1-T2	N2b	M0	Systemic therapy
Stage 3C	T4a	N2a	M0	Systemic therapy
	T3-T4a	N2b	M0	Systemic therapy
	T4b	N1-N2	M0	Systemic therapy
Stage 4A	Any T	Any N	M1a	Systemic therapy
Stage 4B	Any T	Any N	M1b	Systemic therapy
Stage 4C	Any T	Any N	M1c	Systemic therapy

[a]In patients with no high risk for recurrence

[b]High-risk patients for recurrence (poorly/undifferentiated cancer, lymphatic/vascular invasion, bowel obstruction, less than 12 lymph node resected, perineural invasion, localized perforation, close, indeterminate, or positive tumor margin).

Colonoscopy is the gold standard in the diagnosis of colon cancers, which allows exactly locating the disease and taking biopsy as well as providing histopathological analysis and detecting the synchronized presence of polyps or tumors. It was reported that the patients with the sporadic colon cancers had another synchronized colon cancer by 4% and adenomatous polyps by 30% [9–11]. In patients in whom the colon could not be evaluated completely due to obstruction or an emergency, a total colonoscopy must be performed at the end of postoperative 3rd month. Elective colorectal cancer patients must be evaluated with contrast abdomen and thorax computed tomography (CT) for local extension and metastasis. The sectional CT images provide information on the tumor's relationship with the neighbor tissues. The detection of synchronized tumor or metastases might necessitate making modifications on the treatment plan [12, 13]. Magnetic resonance imaging (MRI) or positron emission tomography/computed tomography (PET-CT) can be beneficial where contrast sectional CT imaging is insufficient or to detect the presence of undiagnosed lesions [14]. Preoperative measurement of carcinoembryonic antigen (CEA) is suggested, increased level of which is correlated with worse prognosis and recurrence. CEA levels should be measured on the follow-up period for early detection of recurrence [15].

Mechanical bowel preparation in elective colorectal surgery has still been controversial. Cochrane meta-analysis, published in 2011, reported that mechanical bowel preparation was not beneficial. However, another meta-analysis proposed that mechanical bowel preparation and oral antibiotic administration decreased surgical site infection. American Society of Colon and Rectal Surgeons suggested elective bowel preparation and oral antibiotic administration in 2017 guidelines [16].

The main aim of colorectal cancer treatment is to resect the tumor and tumor-related lymph nodes with proper anatomical surgical margin [8, 17]. The extension and margin of surgical resection are determined according to the location of the tumor and the situation of the main vessels supplying the segment with the tumor. As the lymphatic drainage parallels arteries, the vascular supply of the colonic segment should be considered in determining the surgical margin [18]. If neighboring tissue or organ invasion is present, as in case of locally advanced tumors, the complete specimen should be resected en bloc along with the tumor.

The proximal, distal, radial, and mesenteric surgical margins must be taken into consideration during surgical resection. Having at least a longitudinal surgical margin of 5–10 cm might decrease epicolic and paracolic lymph node metastasis risk. When a sufficient surgical margin is provided, the lymph node metastasis risk is less than 1% [19]. The radial surgical margin also is an important prognostic factor in colon cancer. Its positivity is related to worse prognosis [20]. As we pointed, if any invasion of the surrounding tissues is present, these tissues should be included in en bloc resection. The mesenteric surgical margin is the margin important for sufficient lymph node resection. The survival was reported to correlate with the number of resected lymph nodes. The total number and the number of resected positive lymph nodes are of prognostic importance. According to the AJCC guidelines, the minimum number of resected lymph node should be 12 for a correct staging of the disease [13, 21, 22].

In recent years, the concept of total mesocolic excision (TME) has become popular, which means the resection of the tumoral segment with proper proximal and distal margins and the mesocolon involving the vasculature and lymphatics of the segment and possible micrometastases within it. In this resection, the main artery and vein of the colonic segment must be ligated and cut at the root, and en bloc mesenteric resection is done including the vessels. Thus, TME provides more lymph node resection in number, compared to the conventional colectomy [23]. Although there are concerns that the TME might cause increased peroperative morbidity and mortality, the studies showed that there is no significant difference in terms of morbidity, mortality, and anastomotic leakage rates between the TME and conventional colectomy [24–26].

Surgical Techniques in Colon Cancer

Right Hemicolectomy

It is the standard treatment for the tumors located in the right (caecum and ascending) colon. In this operation, ligating and cutting the ileocolic, right colic, and right branches of the middle colic arteries, en bloc resection of distal 10 cm segment of the terminal ileum, caecum, ascending colon, hepatic flexure, and proximal one-third of the transverse colon is performed [27].

Extended Right Hemicolectomy

This technique is used for hepatic flexure and proximal transverse colon tumors. In addition to the right hemicolectomy procedure, the middle colic artery is ligated and cut at its root originating from the superior mesenteric artery (SMA). Thus, proximal two-thirds of the transverse colon is involved in the resection, and the distal one-third remains which is supplied by Riolan arc [27].

Transverse Colectomy

It is used for the tumors located in the middle of the transverse colon. Midcolic vessels are ligated at the root and cut. Remained colonic segments are anastomosed between each other [27].

Left Hemicolectomy

It is the standard technique for the distal transverse colon, splenic flexure, and the descending colon tumors. The left branch of the middle colic artery is ligated and cut. The left colic artery is ligated at the root where it origins from the inferior

mesenteric artery (IMA). Distal transverse colon, splenic flexure, descending colon, and proximal sigmoid colons are resected [27].

Extended Left Hemicolectomy

Extended (radical) left hemicolectomy might also be preferred in the distal transverse colon, splenic flexure, ascending colon, and sigmoid colon tumors. The aim is to resect the diseased segment with a wide surgical margin which involves the lymphatic tissue draining the segment. IMA is ligated and cut at its root originating from the aorta. Thus, the blood supply of all colonic segments between the distal half of the transverse colon and proximal rectum (i.e., the distal transverse colon, splenic flexure, the descending colon, and sigmoid colon) is disrupted. Following the resection of these segments, the proximal transverse colon is anastomosed to the proximal rectum [27].

Sigmoid Colectomy

Although some surgeons prefer extended left colectomy for the tumors located in the sigmoid colon, routinely performed resection is the sigmoid colectomy. The bowel continuity is provided by anastomosing the descending colon and upper rectum for the tumors locating in the distal part of the sigmoid colon, and it is called high anterior resection. The continuity is provided with the resection and anastomosis between the descending colon and the rectosigmoid junction for the tumors locating in the upper part of the sigmoid colon. In sigmoid colectomy, left colic artery, the first branch of the IMA, is protected. Distal to this artery, IMA and the sigmoid and hemorrhoidal arteries, which are the branches of the IMA, are ligated and cut. As the descending colon is supplied by the left colic artery, its perfusion is not disrupted [27].

Subtotal and Total Colectomy

At the end of the colonic resection, only distal sigmoid colon or intraperitoneal proximal one-third of the rectum remains, the procedure is so-called subtotal colectomy. If all the intraperitoneal colonic segments are resected and only the rectum distal to the peritoneal reflection remains, it is called total colectomy [27].

Minimal Invasive Surgery

Minimal invasive surgery options in colorectal cancers have become popular for the last three decades. Laparoscopic and robotic colectomies are performed as alternative techniques in colorectal cancers. Having the advantages of shorter hospital stay

period, lower infection rates, and less postoperative pain, these techniques have been used increasingly [28–30]. Recently, a study on randomized 1248 colon cancer patients compared laparoscopic and conventional colectomy. It was showed that there is a shorter hospital stay period, less post-operative pain, and less pulmonary complication rate in laparoscopic group [31]. Another study involving 872 patients reported that there is no difference in terms of intraoperative and postoperative complications, recurrence rate, and disease-free and absolute survival rates between laparoscopic and conventional colectomy. Similarly, less analgesics dose need and shorter hospital stay periods were found [32].

Although there is no absolute contraindication for minimally invasive techniques in colon surgery, a history of multiple abdominal surgeries, severe pulmonary or cardiac failure, and locally advanced tumors which might necessitate complicated surgical procedures are the relative contraindications [31].

Emergency Colon Surgery

In spite of increasing use of the screening programs, an important number of the patients are admitted with emergency symptoms as obstruction, perforation, and bleeding which might necessitate emergency surgery. Compared to the electively operated patients, postoperative complication and stoma formation rates are higher [33]. As the diameter of the right colon is bigger than the left one, the tumors located in the left colon are generally admitted to the hospital because of obstruction [13]. Whether a tumor is diagnosed or not, obstructive colon pathologies with emergency surgery indication must be operated without compromising the principles of oncologic surgery [33, 34]. However, the surgical treatment plan for risky patients should be patient-specific. Especially, in the patients with high risk, opening a loop colostomy would be the most proper way to relieve the obstruction for obstructing left colon tumors. In locally advanced tumors or when the oncological resection of the tumor is not possible in an emergency operation, diversion ostomies can be preferred at first for further staggered surgery [35]. Even today, the Hartmann procedure has still been the most frequently performed method in obstructing tumors of the left colon, which involves the resection of the segment with tumor and making an end colostomy [34]. However, being relatively easier and having a better anastomotic safety, the surgery of right colon tumors is less difficult compared to the left ones [34].

Another option in the patients admitted with tumoral colonic obstruction is the stenting of the obstructed segment. It can be performed successfully in properly selected patients by an experienced endoscopist. Following the stenting, the patients can be prepared for elective surgery. Another benefit of the stenting is the prevention of extensive resections in the patients with metastasis or with a short life expectancy. A prospective randomized study comparing the elective surgery after stenting and emergency colon resection reported a decreased number of permanent ostomies and surgical area infections and an increased rate of primary anastomosis in the stent-performed patients [34, 36, 37].

Surgery in Metastatic Colon Tumors

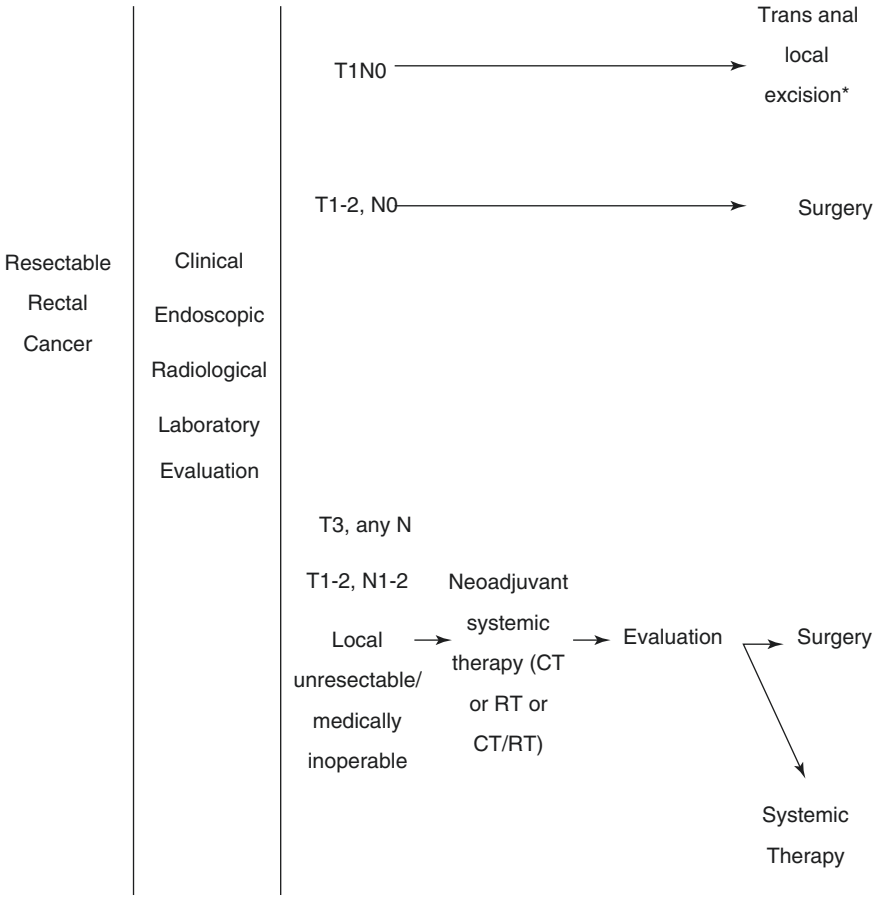
The patients with operable pulmonary or liver metastases might benefit curative resections. The resection of the primary tumor in the patients with operable metastases must be in accordance with the oncological principles. There is no consensus on the timing of resection of the primary tumor, resection of the metastases, and oncological treatment. The priority order of these treatments must be decided individually for each patient by a multidisciplinary team approach [38, 39]. Recently, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in properly selected patients with intraperitoneal metastases have been suggested and taken its place in guidelines [13, 40–42].

Surgical Treatment Approaches to the Rectum Cancers

The rectum cancer was first identified in the nineteenth century, and the treatment principles are well-described. The advances in surgical, anesthesiological, radiologic, oncologic, and postoperative patient care techniques have provided better prognosis in its treatment. Especially, following the developments in radiologic imaging, preoperative staging has become to be done more correctly, and the effective use of preoperative chemoradiotherapy has increased the success of oncologic results. Treatment algorithm for resectable rectal tumors and pathological staging-based treatment approaches were given in Tables 13.5 and 13.6, respectively. Detailed patient history and a careful rectal digital examination have a very important role in treatment planning. Questioning the individual cancer history can help in researching the main tumor and metastatic disease. Family history can help to determine the possible hereditary cancer syndromes and syndrome-related pathologies [43]. Preoperative basal level of carcinoembryonic antigen must be measured so that it can be used as a marker for recurrence during postoperative follow-up period [44, 45]. The distance of the tumor to the anal verge, its relationship with anal sphincters, its mobility, and the presence of synchronized colon tumors can be found using rectal digital examination and colonoscopy [45, 46]. Preoperative radiological staging must be performed for metastatic disease in all the rectal cancer patients. Liver and lungs are the most common metastatic sites for the rectal cancer [12, 47, 48]. Along with the systemic staging, local staging using rectal magnetic resonance imaging (MRI) or endorectal ultrasonography (EUS) should be done to determine the need for neoadjuvant therapy [49–51]. In locally advanced rectum cancers (T3, T4/Nx or Tx/N+), multidisciplinary treatment has been a standard approach. Preoperative use of chemoradiotherapy has been shown to be effective with its high effectiveness, low toxicity, and better long-term results [52].

In rectum cancer surgery, total mesorectal excision (TME) is performed to achieve better curative results. TME aims to achieve a cancer-free radial margin and to remove tumoral seedings within the mesorectum and perirectal lymph nodes within an intact fascial sheath [53–55]. For rectosigmoid junction and upper rectal cancers, resection of the mesorectum with a 5 cm tumor-free distal margin is

Table 13.5 Treatment algorithm in non-metastatic rectal cancers



CT chemotherapy, *RT* radiotherapy
[a]Stage should be based on pelvic magnetic imaging (IMR) or endorectal ultrasound

sufficient. However, a complete mesorectum excision and 2 cm disease-free distal surgical margin must be achieved in the middle and low rectal cancers [43].

For the tumors located at the mesorectal margin or below the mesorectal margin, 1 cm distal mural margin is acceptable [43]. The TME has decreased local recurrence rates from 30% to 40% to 5–15% [56, 57]. Moreover, TME provides protection of pelvic autonomous nerves and prevents urogenital function disturbances as well as decreasing intraoperative bleeding. The supporters of lateral lymph node dissection (LLD), which involves all lymph nodes around the internal iliac arteries, have reported a better local disease control and increased survival rates. However, a meta-analysis comparing the LLD and conventional surgery reported that LLD does

Table 13.6 Pathological staging-based treatment approach following surgery in rectal cancers

Stage	T	N	M	Treatment
Stage 0	Tis	N0	M0	Observe
Stage 1	T1	N0	M0	Observe
	T2	N0	M0	Observe
Stage 2A	T3	N0	M0	Systemic therapy or Observe[a]
Stage 2B	T4a	N0	M0	Systemic therapy
Stage 2C	T4b	N0	M0	Systemic therapy
Stage 3A	T1, T2	N1/N1c	M0	Systemic therapy
	T1	N2a	M0	Systemic therapy
Stage 3B	T3-T4a	N1/N1c	M0	Systemic therapy
	T2, T3	N2a	M0	Systemic therapy
	T1-T2	N2b	M0	Systemic therapy
Stage 3C	T4a	N2a	M0	Systemic therapy
	T3-T4a	N2b	M0	Systemic therapy
	T4b	N1-N2	M0	Systemic therapy
Stage 4A	Any T	Any N	M1a	Systemic therapy
Stage 4B	Any T	Any N	M1b	Systemic therapy
Stage 4C	Any T	Any N	M1c	Systemic therapy

[a]Well-differentiated or moderately differentiated tumor, less than 2 mm mesorectum invasion, no lymphatic or vascular invasion and upper rectum tumor

not provide further oncological benefit. If there is not any lymph node invasion clinically, performing LLD is not necessary in addition to the TME [58–61].

Surgical Techniques in Rectal Cancer Operations

Local Transanal Excision

Local transanal excision (TAE) is used for selected cases, and its use is not proper in every patients. By using MRI or EUS or both, it is important to confirm that it is not advanced cancer, and the lymph node invasion is absent, preoperatively. Being well-differentiated and smaller than 3 cm in diameter, T1 (SM1, SM2) tumors of which the lymph node invasion and tumor budding are absent, form the ideal patient population. Both transanal excision and transanal endoscopic microsurgery (TEM) can be performed with minor postoperative complications. The recurrence rates for T1 lesions following local excision vary between 7% and 21%. Local excision after neoadjuvant treatment might be considered in well-selected and high-risk patients [62–64].

Abdominoperineal Resection (APR)

It includes en bloc resection of sigmoid colon and mesentery, rectum and mesorectum, anal channel, anus and surrounding skin with subcutaneous tissue, some part of the levator ani muscle, and the anal sphincters. In the end, a permanent stoma is

created. It is the operation which is generally used for the distally located rectal tumors with anal sphincter invasion and anal cancers [27].

Anterior/Low Anterior Resection

While the resection performed for the tumors located at rectosigmoid junction and upper 1/3 of the rectum is called anterior resection, the one performed for the middle 1/3 and distal rectal tumors with the anastomosis at the anorectal region is called low anterior resection. The descending colon is anastomosed with the remained rectum. Some surgeons perform a diverting colostomy to decrease operative complications and enhance anastomotic healing [27].

Sphincter Sparing Surgery-Coloanal Anastomosis

It is a technically difficult, experience necessitating procedure. In this kind of patients, a rectal segment has not remained following the resection. The anastomosis is performed by hand-sewn technique at the dentate line level, and always a diverting stoma is performed [27].

Minimally Invasive Surgery

The data shows that, in experienced hands, laparoscopic TME can be performed with similar oncological results compared to the conventional TME. Randomized controlled studies reported no significant difference in terms of 5-year local recurrence rate, disease-free, and absolute survivals [65–67]. COLOR II study reported that there is no difference in terms of distal or circumferential radial margins, and the number of the lymph nodes excised [68]. The surgeons planning to perform minimally invasive surgery in rectal cancers must have the sufficient experience and knowledge.

Tumor-Related Emergencies

Approximately, 20% of the colorectal cancer patients have emergency admission. In obstructing or bleeding rectal cancers, provided that a perforation or life-threatening bleeding is absent, stenting or ablation procedures can be considered in experienced centers. In selected patients, expandable stents might decompress the colon and serve a bridge to surgery, thus allowing to make primary anastomosis or contribute to the palliation in metastatic disease [69, 70]. In inappropriate patients for stenting or in the centers without stenting facility, proximal diverting loop colostomies are beneficial in overcoming the rectal tumor-related obstructions.

Surgical Treatment of the Unresectable Rectal Cancers

Total pelvic exenteration can be considered in the selected patients with locally advanced rectal cancers. Its adverse effect on life quality should be considered. In total pelvic exenteration-considered patients, multidisciplinary treatment principles are valid, and radiotherapy and chemotherapy are also performed. The studies reported significantly increased survival rates with a tolerable morbidity [71–73].

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Appendix Tumors

14

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Neuroendocrine Tumors of the Appendix

Neuroendocrine tumors (NETs), previously known as carcinoid tumors, are most frequently seen in the gastrointestinal tract (54.5%) [1]. The estimated prevalence of gastrointestinal neuroendocrine tumors is 2–5/100,000 per year [2]. 0.2–0.7% of all appendectomy materials reveal NET findings upon histological examination [3]. Most appendiceal NETs are seen in the second or third decade of life, and the prognosis largely depends on the histological type, stage, and malignancy of the tumor. NETs of the appendix are associated with better survival outcomes compared to other neuroendocrine tumors [4].

World Health Organization [5] divides NETs of the appendix into four:

1. Well-differentiated NENs (neuroendocrine neoplasias)/G1 (NET-G1)
2. Intermediately differentiated NENs/G2 (NET-G2)
3. Poorly differentiated neuroendocrine carcinomas (NEC-G3)
4. Mixed adenoneuroendocrine carcinomas (MANECs)

NETs of the appendix originate from neuroendocrine cells which are found in the submucosal layer of the appendix wall and the lamina propria of the subepithelial layer [6, 7]. Tumors originating from neuroendocrine cells of the subepithelial plate were first defined by Masson 1928 [8]. Chromogranin A (CgA), synaptophysin, and Ki-67 proliferation index are used for the histopathological diagnosis of NETs. CgA and synaptophysin are the most commonly used indicators of endocrine

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properties of neoplastic cells. WHO and ENETS rating system defines NETs with less than 2 mitotic cells per 10 high-power fields (HPFs) and a Ki-67 index lower than 2% as grade 1 NETs (NET-G1). Grade 2 NETs have 2–20 mitotic cells per 10 HPFs and a Hi-67 index between 3% and 20%. Grade 3 NETs have more than 20 mitotic cells per 10 HFPs or a Ki-67 index above 20% [1].

Neuroendocrine carcinomas are poorly differentiated malignant neoplasms and have immunohistochemical staining properties that are similar to neuroendocrine tumors. They are particularly associated with increased synaptophysin and mild or focal chromogranin A expression, obvious nuclear atypia, multifocal necrosis, and a high mitotic count [9, 10]. Neuroendocrine carcinomas and high-grade poorly differentiated neuroendocrine tumors are the most aggressive subgroup [11].

Clinical Overview

NETs of the appendix do not have specific clinical findings. Their most common clinical manifestation is acute appendicitis (54%) [12, 13]. Advanced or metastasized tumors can also present as abdominal pain or compression [14, 15]. Carcinoid syndrome rarely presents with NETs of the appendix and only after metastasis [16]. Carcinoid syndrome is all the signs and symptoms caused by secretions of carcinoid tumors (such as serotonin and other vasoactive amines). The symptoms of carcinoid syndrome include diarrhea, redness of the face, palpitations, high blood pressure, skin lesions, and shortness of breath. These symptoms are present especially when carcinoid tumors spread to the liver [14, 15].

Diagnosis

Appendiceal neuroendocrine tumors are mostly incidentally diagnosed during the examination of appendectomy material. There are not any specific preoperative diagnostic methods. Endoscopy can successfully diagnose appendiceal NETs only if the tumor becomes too large and invades the cecum [17].

Patients with NETs smaller than 1 cm that are treated with R0 resection do not require post-appendectomy CT or MRI examinations. For NETs between 1 and 2 cm, the patients are recommended at least one follow-up CT or MRI exam to determine any lymph node or distant metastasis. If the tumor is larger than 2 cm, or invades into the mesoappendix or the surrounding vasculature, the patient should be followed up with abdominal CT or MRI examinations and somatostatin receptor scintigraphy (or SR-PET/CT). CgA (cromogranin) is a potential diagnostic marker for advanced neuroendocrine tumors. However, there is not a clear correlation between CgA and tumor size; hence, it cannot be used alone for diagnosis or follow-up. Urine 5-HIAA (5-hydroxyindoleacetic acid) level is an indicator that can be used to evaluate carcinoid syndrome [17].

Main Prognostic Features of NETs of the Appendix

Size

A simple appendectomy is sufficient to treat tumors smaller than 1 cm. The survival rate is 100% for both children and adults. However, it becomes difficult to decide for the optimal treatment if tumor size larger than 1 cm but smaller than 2 cm. Even though metastasis is rare in this subgroup, they constitute 5–25% of all appendix neuroendocrine tumors, and metastasis becomes a significant risk if tumor size is over 1.5 cm. NETs of the appendix are very rarely larger than 2 cm. However, these NETs are associated with a metastasis rate of 40% and require radical oncologic surgery [17, 18].

Location

Sixty percent to 70% of appendiceal NETs are located at the tip of the appendix, while 5–20% are located in the body and less than 10% are located in the base of the appendix. In the latter case, the patient will probably require R1 or R2 resection [18].

Mesoappendix

Since tumors that invade the mesoappendix pose a higher risk of vascular (V1) or lymphatic (L1) metastasis, the prognosis can be more aggressive especially if the invasion is deeper than 3 mm. These patients should be monitored longer and more frequently, even if tumor size is less than 2 cm (20% adults, 40% children) [18, 19].

Surgery

There are two surgical techniques described for local and locoregional appendiceal neuroendocrine tumors: simple appendectomy and right hemicolectomy (as per oncological principles).

- In T1 (ENETS) (European Neuroendocrine Tumor Society) and T1a (UICC/AJCC) (American Joint Committee on Cancer) NET (i.e., <1 cm) tumors, simple appendectomy is usually sufficient with R0 resection. However, in certain cases, if the tumor is at the base of the appendix or invades more than 3 mm into the mesoappendix, right hemicolectomy is recommended [19–21].
- In T2 (ENETS) and T1b (UICC/AJCC) NET (i.e., >1 cm but <2 cm) tumors, lymph node and distant metastasis are rare. However, some studies report cases of metastasis in these patients. Hemicolectomy can be preferred to achieve long-term survival. The physician should compare the peri- and postoperative morbidities of right hemicolectomy against the possibility of late recurrence associated with simple appendectomy. This condition is particularly significant for younger patients [21].

  Risk factors that contribute to decision-making are as follows:

- WHO grade 2 tumors (2–20 mitotic cells per 10 HPFs (high power field), 3–20% Ki-67 index)
- Vascular or lymphovascular invasion
- Mesoappendix invasion >3 mm

Hemicolectomy is required if one or more of the abovementioned conditions are present.

- In T3 (ENETS), T2 (UICC/AJCC) or more advanced NET (i.e., >2 cm) tumors, right hemicolectomy should be performed to prevent the risk of distant or lymph node metastasis. Right hemicolectomy can be performed during or after an appendectomy [21].
- Right hemicolectomy is necessary for every case of appendiceal neuroendocrine carcinoma (e.g., adenocarcinoma) regardless of tumor size [22].

Follow-Up

There is no specific appendectomy follow-up protocol for neuroendocrine tumors smaller than 1 cm [23]. This is also the case for NETs larger than 1 cm treated with right hemicolectomy with a R0-resection if there is no lymph node metastasis [24]. Long-term follow-up is recommended for patients with distant metastasis resection or lymph node metastasis.

CgA can be used as a biochemical marker in appendiceal neuroendocrine tumors; therefore, these patients should be followed up with an annual CgA evaluation. However, the diagnostic value of CgA levels in predicting recurrence has not yet been proven. Patients that present with carcinoid syndrome symptoms can be evaluated using urine 5-HIAA levels [25].

Epithelial Neoplasms of the Appendix

Introduction

One of the most commonly performed surgeries today is appendectomy. Appendix-related diseases can occur as a result of inflammatory or neoplastic processes and often result in appendectomy. The most common pathological diagnosis of appendectomy specimens is related to inflammatory diseases of the appendix. Although the incidence of neoplastic pathologies of the appendix is low, a better understanding of neoplastic processes is needed as even benign pathologies require long follow-up and serious treatments.

Appendectomy neoplasms are reported in approximately 0.9–1.4% of all appendectomy specimens. Although it is possible to diagnose patients during the application, they are largely diagnosed during or after surgery [26]. This is because the findings are not specific to the disease and may mimic acute appendicitis symptoms. Another reason is that the diagnosis of the appendix with colonoscopy is rarely possible.

We can classify epithelial appendix neoplasms shortly as a mucinous and non-mucinous neoplasm [26]. Mucinous type neoplasms account for 70%. They are

diagnosed especially in the middle and advanced age group and can be detected by nonspecific signs and symptoms and sometimes by chance with abdominal pain and distension. Mucinous neoplasms are the most common cause of pseudomyxoma peritonei (PMP) [27]. An article of Peritoneal Surface Oncology Group International (PSOGI) on the terminology and classification of epithelial appendix neoplasms and PMP was published in 2016 [28]. Confusion about this issue was resolved with this publication, and appendix epithelial neoplasms were terminologically clarified. This terminology is the basis of the subject of this section.

Adenoma

They are rare non-mucinous epithelial neoplasm. Predictably, it is difficult to diagnose, but it is detected during surgery or by pathological examination [29]. They resemble colorectal adenomas and show pathologically tubular, tubulovillous, and villous dysplastic polyploid structure [30]. Their treatment is controversial. Although appendectomy is considered sufficient with a general evaluation, right hemicolectomy is recommended in case of tumor size greater than 2 cm, invasion of Meso-appendix, nodal spread, and lymphatic or vascular embolism [31].

Serrated Polyps

PSOGI's article clarified that the definition of cystadenoma has long been not sufficient as a diagnostic term, and a consensus was reached to use the term serrated polyp for all lesions that show serrations similar to the sessile serrated adenomas in the colon [28]. Hyperplastic polyps can be shortly described as focal mucosal hyperplasia, while differently from this, serrated polyps can be described as diffuse mucosal hyperplasia [32]. Serrated polyps are restricted to the mucosa and do not progress to the muscularis mucosa. They do not genetically resemble colon serrated lesions due to the frequent occurrence of KRAS mutation and less frequent occurrence of BRAF mutation [33]. They may be dysplastic, and when diagnosed, colonoscopy examination should be done to detect simultaneous colonic serrated polyps. If invasive adenocarcinoma is pathologically excluded and a negative resection margin is available, there is no need for additional treatment, and there is no risk of disseminated disease [34].

Low-Grade Appendiceal Mucinous Neoplasm (LAMN)

It is detected in 0.3% of all appendix pathologies. These tumors, consisting of a single row of the tall mucus-secreting adenomatous epithelium, secrete a large amount of mucin into the lumen [35]. According to WHO classification, LAMN and mucinous adenoma and mucinous adenocarcinoma are classified within mucinous

appendiceal neoplasms. Although the LAMN is in benign morphology unlike mucinous neoplasm, it holds the appendix wall and can cause peritoneal spread. Its hematogenous and lymphatic spread is unknown [36, 37]. Appendectomy alone is sufficient if no mucin or mucinous epithelium is detected outside the appendix serosa and the resection margin is intact. In this case, it was concluded that the disease had no recurrence and no peritoneal spread [38]. In the case of periappendicular spread, cecum resection or right hemicolectomy may be recommended. In case of rupture, the clinical picture can progress to PMP state. In patients with this condition, cytoreductive surgery and hyperthermic intraperitoneal chemotherapy are the standard treatment [39, 40]. Zauber P. et al. found 100% positivity of the KRAS gene mutation in the appendix LAMN and in turn revealed that it was 41% in low-grade mucinous neoplasm of the ovarium [35]. Images of our patient are available in Fig. 14.1a, b.

High-Grade Appendiceal Mucinous Neoplasms (HAMN)

They are mucinous epithelial lesions that are structurally similar to LAMN, with no infiltrative invasion, but with high-grade dysplasia. They could be more aggressive than LAMN [28]. Mucin accumulation and PMP risk are similar to LAMN. Pathologically, it shows increased nuclear alignment along the entire thickness of the epithelium, cribriform growth, loss of polarity, hyperchromatic and vesicular growth of the nucleus, and frequent or atypical mitosis features [28]. If a negative margin can be provided, appendectomy is sufficient, and additional surgery is not required. If the surgical margin is positive, right hemicolectomy and lymph node dissection are recommended [34, 37]. If mucinous deposits are found on the peritoneal surface together with high-grade dysplasia, it would be more accurate to identify them as mucinous adenocarcinoma instead of HAMN [34].

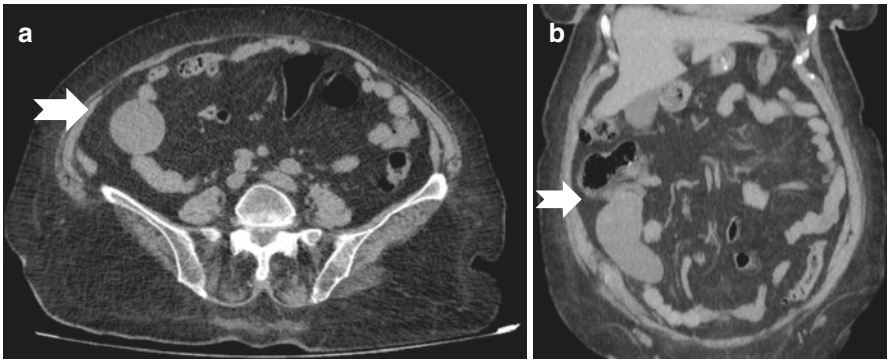


Fig. 14.1 (**a**) Preoperative image of appendiceal mucocele in a patient with postoperative LAMN histopathology, Abdominal CT, axial section. (**b**) Preoperative image of appendiceal mucocele in a patient with postoperative LAMN histopathology, Abdominal CT, coronal section

Adenocarcinoma of the Appendix

Mucinous Adenocarcinoma

More than 50% of appendix adenocarcinoma must contain a mucin component. They differ biologically and histologically from colorectal cancers. Patients are often diagnosed with the rupture of the primary tumor and the spread to the peritoneal cavity [41]. Those with more than 50% signet ring cells are called "signet ring cell carcinoma," and those with less than 50% signet ring cells are called "poorly differentiated adenocarcinoma with signet ring cells" [28]. The presence of signet ring cells is indicative of bad prognosis. In the treatment of mucinous carcinomas, right hemicolectomy and lymph node dissection are performed. Well-differentiated mucinous adenocarcinomas tend to spread to peritoneum rather than distant metastases [42]. Peritonectomy and hyperthermic intraperitoneal chemotherapy are performed due to the resectability of the tumor in case of peritoneal spread.

Colonic-Type Adenocarcinoma

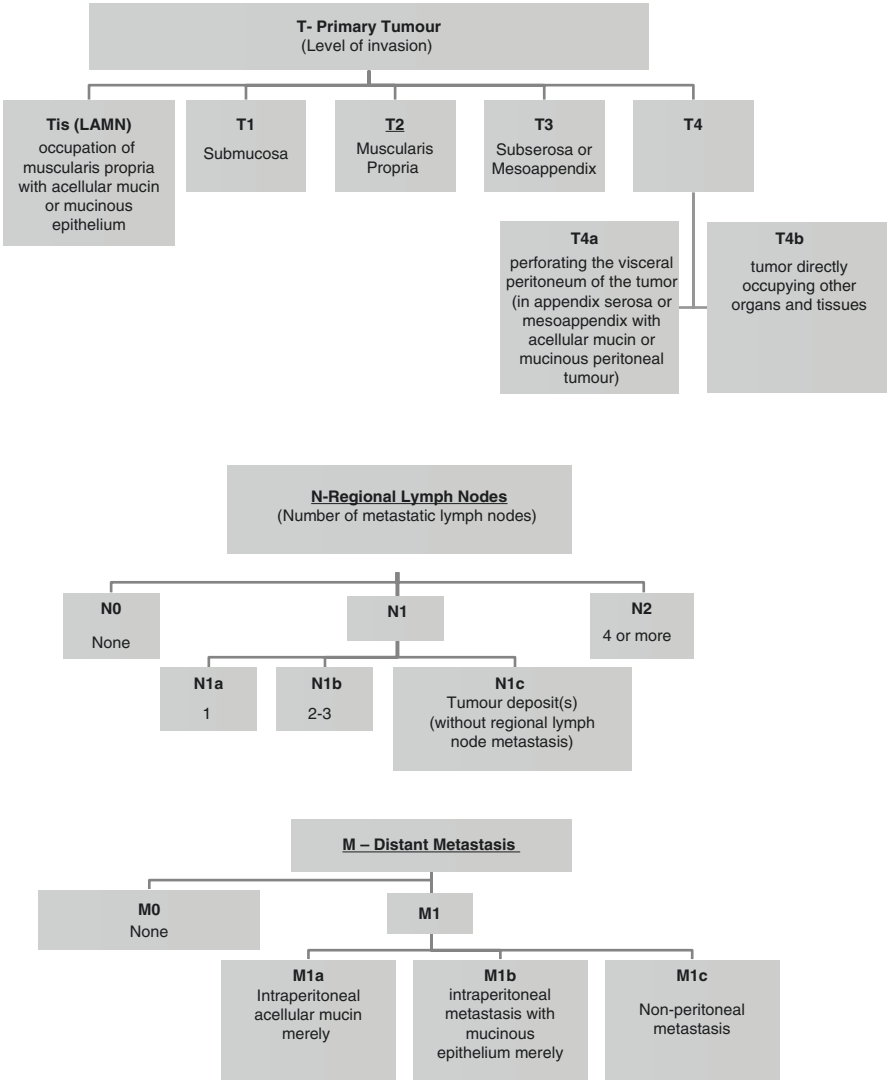
Colonic-type adenocarcinomas, also called non-mucinous, account for 60% of primary appendix cancers. However, it is 0.5% of all lower gastrointestinal cancers. It is often coincidentally shown in appendectomy specimens. In the grade 1 or 2 T1 tumors, if there is no lymphovascular invasion and the resection border is clear, appendectomy may be sufficient. However, right hemicolectomy and lymph node dissection are recommended in patients with high grade or positive resection border or lymphovascular invasion, even if it is T1 [41].

Goblet Cell Adenocarcinoma

They are very rare and have a hybrid structure consisting of both epithelial and neuroendocrine elements. It is more aggressive than neuroendocrine tumors of the appendix and has a greater risk of metastasis. The majority of patients are admitted with appendicitis symptoms. Right hemicolectomy should be performed when it is detected within 3 months after the appendectomy. Prophylactic oophorectomy is controversial [43].

AJCC (American Joint Committee on Cancer) 8th Edition is used to classify appendix adenocarcinomas. LAMN was included in the classification for the first time. The T4 definition changed and was added to N category as the free tumor deposit N1c, and category M was redefined. The following diagram shows the classification of TNM and staging by the Table 14.1 [44].

Table 14.1 TNM system



STAGE	T	N	M
Stage 0	Tis Tis(LAMN)	N_0	M_0
Stage I	T_1, T_2	N_0	M_0
Stage IIA	T_3	N_0	M_0
IIB	T_{4a}	N_0	M_0
IIC	T_{4b}	N_0	M_0
Stage IIIA	T_1, T_2	N_1	M_0
IIIB	T_3, T_4	N_1	M_0
IIIC	Any T	N_2	M_0
Stage IVA	Any T	N_0	M_{1a} M_{1b}, G_1
IVB	Any T	Any N	M_{1b}, G_2, G_3, GX
IVC	Any T	Any n	M_{1C}, Any G

Pseudomyxoma Peritonei

Appendiceal mucinous neoplasms are the most commonly encountered tumors of appendix. These tumors contain mucin secreting cells and can be classified as benign or malignant according to their histopathological features. Even though they are defined benign due to the limited invasion to the appendix wall, their most important clinical feature is that they can cause pseudomyxoma peritonei (PMP). PMP is a clinical syndrome characterized by progressive accumulation of mucinous acid and peritoneal implants due to rupture of mucin secreting tumor into the peritoneal cavity. It is a macroscopic image of mucinous acid with gelatinous consistency in the peritoneal cavity rather than a histopathological diagnosis. The most common cause of PMP is mucinous appendiceal neoplasms. Rarely, colonic, ovarian, urachal, and pancreatic mucinous neoplasms can cause development of PMP. Ovarian neoplasms that can cause PMP are typically mature teratomas. The primary mucinous tumors of ovaries do not cause PMP. If ovarian and appendiceal mucinous tumors exist together, appendix should be considered as the primary focus [42].

Tumor originating from appendix blocks its lumen as it enlarges, thus causes appendiceal rupture due to mucus accumulation. Then tumor cells seeded in the abdomen and free mucin are dispersed throughout the peritoneal cavity and lead to peritoneal implants. The tumor cells progressively secrete mucin and cause typical "jelly-belly" appearance of PMP. The distinctive feature of PMP is the redistribution phenomenon. Freely moving tumor cells track the route of normal peritoneal fluid flow and are relocated on the places, where peritoneal fluid is absorbed. Thus, tumor cells deposit on the greater and lesser omentum, in sub-diaphragmatic area, pelvis and paracolic areas. The mobile organs such as small intestines are usually avoided early on in the disease process [45].

The prevalence of PMP is 2 in every 10,000 laparotomies, and it is more common among females. The most common primary symptoms are abdominal discomfort, distention, and pain due to accumulated mucin. Newly developed inguinal hernia is an important symptom in males (%14). On the other hand, detection of ovarian mass in routine pelvic examination is another important sign (%39). In time, intra-abdominal palpable masses (omental cake) develop. In the later stages, malnutrition, intestinal obstruction, and respiratory problems may be observed, and they lead to fatal outcomes [46].

In computerized tomography, the hallmark sign of early-stage disease is localization of tumor mainly in the abdomen and peripheral part of the pelvis without involvement of small intestines and mesentery (termed the "redistribution phenomenon"). Intensive liver and spleen capsule involvement by tumor deposits leads to scalloping of liver surface and diffuse calcification. It is observed that subdiaphragmatic spaces are thickened especially due to cystic masses caused by the mucinous tumor. If implants larger than 5 cm are encountered on the jejunum, proximal ileum, and the adjacent mesentery, then peritoneal mucinous carcinomatosis (PMCA) should be considered rather than disseminated peritoneal adenomucinosis (DPAM). Segmental obstructions in the small intestines are the evidence of PMCA [47].

In 2016, PMP was divided into four categories according to the histological features by Peritoneal Surface Oncology Group International (PSOGI) [28]. Categorization of PMP as acellular, low grade, high grade, and high grade with signet ring cells provides better prognostic evaluation and setting up a standard treatment protocol. Acellular PMP is characterized by the loss of epithelial cell in the mucin of peritoneal cavity. The most common cause is low grade appendiceal mucinous neoplasms (LAMN), and less commonly it results from ruptured benign appendiceal mucocele. Due to the slow progression rate, the clinical outcome is quite good. The 5-year survival rate is 95.2% [48, 49]. Important prognostic parameter is whether epithelial cells are present in the peritoneal mucin. If the mucin is acellular, then the prognosis is better. In the 8th edition of TNM (Appendix carcinoma TNM staging 8th edition), if the mucin in the abdominal cavity is acellular, the stage is defined as pM1a. If it contains cells, then the stage is defined as pM1b. Low grade PMP is the most commonly encountered variant. It is also referred as "low grade mucinous carcinoma peritonei" or DPAM. Cytological atypia and mitotic activity are low among the neoplastic cells that form mucin lakes in small groups. The most common cause is LAMN. High grade PMP is also referred as "high grade mucinous carcinoma peritonei" or PMCA. It consists of high grade nuclear atypical neoplastic cells that present with cribriform structures in desmoplastic stroma. There is an invasion of underlying organs. Signet ring cells are observed. In this condition, it is defined as high grade mucinous carcinoma peritonei with signet ring cells or peritoneal mucinous carcinomatosis with signet ring cells (PMCA-S) [28, 42].

For many years, debulking surgery has been the main treatment for PMP. Due to the common recurrences, reoperations are usually necessary. Recently, cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS + HIPEC) has been performed. Peritoneal cancer index (PCI) is used in all the peritoneal malignancies in order to determine disease load. The abdomen is divided into 13, and each part is graded for tumor load between 1 and 3. According to this grading, total PCI is calculated between 1 and 39. CRS + HIPEC should be performed in low grade PMP without PMI score consideration. Despite high PMI score, there is still a chance for cure. The 5-year survival rate is 83% [48, 49]. In high grade PMP with high PCI score, the survival rate is low although CRS + HIPEC is performed. Considering the selection of patients with low PCI index, better survival is achieved. The 5-year survival rate is 47% [48, 49]. In high grade PMP with signet ring cells, CRS + HIPEC has minimal effect on survival rate, but can still be performed in selected cases. The 5-year survival rate ranges between 0% and 22% [48, 49]. In PMP, there is no indication for standard neoadjuvant or systemic adjuvant chemotherapy. However, CRS + HIPEC can be performed subsequently to neoadjuvant chemotherapy in high grade PMP cases with high PCI scores, which have low prediction of resectability. Palliative systemic chemotherapy may be considered in irresectable or recurrent PMP, especially in patients with high grade PMP [48].

Rare Neoplasms of Appendix

Lymphomas
Metastases
Mesenchymal tumors
GIST
Desmoid
Leiomyoma
Leiomyosarcoma
Noncarcinoid NETs
Ganglioneuroma
Pheochromocytoma
Paraganglioma
Sarcomas
HIV-associated Kaposi sarcoma
Desmoplastic small round cell tumor
Neuroectodermal and nerve sheat tumors
Schwannoma
Neurofibroma

Appendiceal Lymphoma

Appendiceal lymphomas are extremely rare clinical condition [50]. Primary appendiceal lymphoma accounts for 0.015% of all gastrointestinal lymphomas [50–52]. The definitive diagnosis of appendiceal lymphoma is mostly made by postoperative histopathological examination. These patients mostly presented with symptoms of acute appendicitis followed by symptoms of bowel obstruction, intussusception, palpable mass, gastrointestinal bleeding, and ureteral obstruction [53]. Although the preoperative diagnosis of appendix lymphomas is very difficult, CT provides more than 90% sensitivity and specificity for acute appendicitis and helps other differential diagnoses [51, 54]. A presumptive diagnosis of appendiceal neoplasms can be made based on >3 cm diameter of the appendix with heterogeneity in surrounding tissues being one of the nonspecific findings suggesting appendiceal lymphoma on CT [54, 55]. Specific views such as intra-abdominal lymphadenopathy and aneurysmal dilatation of the appendix lumen detected on CT increase the probability of appendiceal lymphoma [55]. Appendectomy is sufficient for the treatment of localized lymphomas. Postoperative adjuvant treatment is not necessary and not recommended limited tumors in appendix [56]. However, if the tumor spreads from the root of the appendix to the cecum or mesentery, right hemicolectomy is necessary. For these patients, staging must be performed before starting adjuvant therapy. There is insufficient data to suggest whether an aggressive surgical approach provides greater survival benefit than a more conservative approach. Ayup et al. [56] reported that the mean survival difference was not observed between patients who underwent appendectomy and/or partial colectomy for appendiceal lymphoma and those who underwent right hemicolectomy or larger resection. Also, Cirocchi et al. [57] reported that there was no difference in overall survival between the patient

group operated and the patient group followed by medical treatment. In the light of this information, surgery should be performed for cases with an emerging character such as acute abdomen or perforation, and medical treatment should be considered as a priority for other cases. For patients with emergency operation, staging should be done after surgery and before starting adjuvant treatment.

Metastases

The probability and rate of different primary tumors to metastasize to the appendix are lower than the rate of metastasis to the surrounding tissues and organs of the appendix [58]. Although it is a rare condition, metastasis can be seen in the appendix secondary to breast, lung, gastrointestinal, and urogenital system cancers [58]. The mechanism of metastases from other organs to the appendix remains uncertain, but the appendix is estimated to spread by the peritoneal route [59]. Appendiceal metastasis can remain asymptomatic and could be diagnosed incidentally. In the majority of cases reported as appendiceal metastasis of primary tumors, metastatic cancer cells are implanted into appendiceal serosa. This implantation can infiltrate all layers up to the mucosa of the appendix, leading to the development of obstruction and even perforation in the lumen [60]. Almost half of these metastatic cases in the appendix are obstructed in the appendix and secondary perforation, and patients often present with perforation and acute appendicitis. The underlying reasons for detecting such late clinical findings in patients may be due to steroids and chemotherapy, mostly due to primary tumor [60]. Although exclusion of a metastatic lesion is thought to increase survival, Yoon et al. [60] reported that appendectomy does not increase survival when there is a metastasized tumor in the appendix.

Mesenchymal Tumors (GISTs, Desmoid, Leiomyoma, Leiomyosarcoma)

Gastrointestinal Stromal Tumors (GISTs)

Gastrointestinal stromal tumors (GISTs) are the primary mesenchymal tumor of the gastrointestinal tract, usually developing from Cajal's cells [61, 62]. GISTs are mostly seen in the stomach (%55.6), followed by the small bowel (%31.8), colorectal system (%6), and other areas (%5.5) [62]. Appendiceal GISTs are a rare type of neoplasia, and primary appendix GISTs have been reported in the literature with cases or case series [61–63]. Although most of them are benign, appendiceal GIST cases with malignant character are also available in the literature [61]. According to literature reports, appendiceal GISTs have no specific clinical symptoms [61–63]. Appendiceal GIST often presents with symptoms such as abdominal pain, abdominal distention, abdominal palpable mass, nausea, vomiting, and hematochezia [61, 62]. It is very difficult to determine preoperative appendix GISTs. The diagnosis is made mainly after the surgery, during the pathological examination of the specimen. Immunohistochemical staining is useful to confirm the diagnosis of stromal tumors.

In appendiceal GISTs, CD117 (80–100%) and CD34 (50–80%) positivity was found; besides, it was reported in studies that the DOG-1 protein showed high sensitivity and specificity [63, 64]. In addition to CD117, CD34, and DOG-1 protein, KIT gene mutations were analyzed in 78.5% of GISTs [64, 65]. The basis of therapy in GISTs is surgical resection with microscopic tumor-free margins. Vasos et al. [57] reported that appendectomy is that the standard treatment for many cases within the appendix body or tail. Zhang et al. [62] reported that more than half of appendiceal GISTs (54.2%) are located in the body or tail; therefore, laparoscopic appendectomy is possible. However, since tumor rupture is an independent negative prognostic factor, relevant prospective large clinical studies are needed to confirm the safety of laparoscopic surgery [62]. Endoscopic application of the "endo-bag" should be used to prevent tumor perforation and seeding [62]. In some cases, resection of adjacent tissues and organs or the bottom of the cecum could also be required to en bloc resection of the tumor to minimize the risk of local recurrence. Although it has been reported that there are prognostic indicators such as tumor size, mitotic index, and tumor placement in determining the malignancy potential of GISTs, no factors have been identified in the prognosis of the appendiceal GISTs [62, 63]. In the treatment of locally advanced and metastatic appendiceal GISTs, imatinib mesylate, a tyrosine kinase inhibitor, can be used [63, 64].

Desmoid

Desmoid tumors are extremely rare. These tumors arising from musculoaponeurotic structures are also called aggressive fibromatosis [66]. Although these tumors are benign neoplasms without metastatic potential, they are mostly locally aggressive and have a high recurrence rate. Desmoid tumors can affect every part of the extra-abdominal and intra-abdominal body and can occur sporadically or as part of congenital syndromes (Gardner's syndrome, familial adenomatous polyposis—FAP and bilateral ovarian fibromatosis) [67, 68]. Appendix is a rare location for desmoid tumor. The most known risk factors for desmoid tumors are female gender, estrogens, pregnancy, trauma, trisomy 20 and 8, and APC germline mutation [67]. A multidisciplinary approach involving surgery, chemotherapy, and radiation therapy is applied in the treatment of desmoid tumor. Although the main treatment for desmoid tumors is surgery, antihormonal therapies, indomethacin, sulindac, tyrosine kinase inhibitors, chemotherapy, and radiotherapy can be used for treatment of inoperable desmoid tumors [67, 68].

Leiomyoma

Leiomyoma is a benign type of tumor originating from smooth muscles and can be seen in any part of the gastrointestinal tract, from the esophagus to the rectum [69]. While the most common part of the gastrointestinal tract is the stomach, appendix leiomyomas are rarely reported in the literature with cases [70]. Appendicular leiomyomas mostly present with symptoms and clinics of acute appendicitis such as abdominal pain, weight loss, hemorrhage, palpable mass, constipation, nausea, and vomiting. Patients can also apply with abdominal distention and ascites secondary to rupture of appendiceal leiomyoma [71]. There is no specific imaging methods or

imaging appearance for diagnosing preoperative appendicular leiomyomas. The definitive diagnosis is mostly based on postoperative histopathological examination. It is important to make differentiation between leiomyoma and leiomyosarcoma with histopathological examination. The number of mitotic figures per high power area (HPF) is the most important criterion of malignancy [70]. Most researchers state that the prognosis is good if less than 2 mitosis per 10 HPF are found. A tumor showing 2 or more mitotic figures per 10 HPF is generally considered malignant. Surgical resection is the most effective treatment for both benign and malignant tumors [70].

Leiomyosarcoma

Appendiceal leiomyosarcoma is a rare tumor type; what is known in the literature is limited to a few case reports [70–73]. Therefore, in the treatment of appendicular leiomyosarcoma, colon sarcoma and other sarcoma types are used. Hatch et al. [70] reported that the leiomyosarcoma of the appendix and colon often occurs between the second and seventh decades. They reported that most patients presented with symptomatic, pain, acute or chronic gastrointestinal hemorrhage, weight loss, or constipation [70]. Gastrointestinal hemorrhage, weight loss, and pain are more common in leiomyosarcoma than leiomyomas [70]. The appendix leiomyosarcoma is difficult to diagnose preoperatively, and the final diagnosis can often be made by postoperative examination of all surgical resection material [70, 73]. Surgical excision with the en bloc excision of the affected viscera adjacent to the surgical treatment of appendiceal leiomyosarcoma is the main point of treatment and is the only option that offers a chance of recovery [74]. During surgical treatment of leiomyosarcoma, performing lymphadenectomy is not significant in the prognosis and treatment of the disease as in adenocarcinomas [73]. Adjuvant radiotherapy and chemotherapy have been shown to have little effect on disease progression and outcome [73, 74]. Tumor size does not matter in prognosis; often prognosis is determined by the number of mitosis and the rate of spread at the time of initial diagnosis [70, 73]. More data and research are needed to better understand and manage the treatment of this rare tumor.

Noncarcinoid NETs (Ganglioneuroma, Pheochromocytoma, Paraganglioma)

Ganglioneuroma

Appendiceal ganglioneuroma (AG) is a very rare seen tumor with benign character [75]. Ganglioneuromas are not premalignant; they are generally detected in older men and women with lesions that do not have a risk of developing carcinoma [76, 77]. Most AGs are asymptomatic and can be presented with symptoms of acute appendicitis such as abdominal pain, nausea, vomiting, and constipation when they reach larger sizes [75, 77]. Surgical excision of the tumor is adequate in the treatment of AG. AG had a good prognosis and recurrences are rarely seen in AG [75, 76].

Pheochromocytoma

Pheochromocytoma is a hormone-active tumor that can exhibit benign and malignant character which is frequently observed in patients with neurofibromatosis type 1, multiple endocrine neoplasia (MEN) syndrome, and von Hippel-Lindau (VHL) syndrome [76, 78]. Pheochromocytoma as the primary tumor of the appendix can be seen very rarely [78–80].

Paraganglioma

Paragangliomas (PG) are rarely seen types of neuroendocrine tumors which are mostly seen in the upper gastrointestinal system especially in the second part of duodenum [81, 82]. Due to similarity of pheochromocytoma, mostly PG presented with symptoms of catecholamine discharge such as high blood pressure, tachycardia, palpitations, and perspiration [81, 83]. Appendix PG is an extremely rare clinical condition with few cases reported in the literature. Appendiceal PG presented with symptoms of acute appendicitis in two cases, in one case the patient had with right upper quadrant pain as a symptom of cholelithiasis, appendiceal mass was found incidentally with help of CT, and in one case without symptom, PG was detected in the mesoappendix incidentally [81–83]. AP (appendiceal paraganglioma) shows staining with various markers such as synaptophysin, chromogranin, and S100, and immunohistochemical examination has an important role in the differential diagnosis of this tumor [81]. Abdelbaqi et al. [81] supported that surgical treatment of AP should not be limited to local resection. They stated that due to the deficiency of prognostic markers of the disease in the literature, the disease may occur with recurrence or distant metastasis. Therefore, they suggested performing surgical resection with lymph node dissection [81].

It has been reported that appendectomy is adequate for tumors smaller than 2 cm in surgical treatment [83]. Due to the absence of markers that can assist in differentiating the benign or malignant disease and there are insufficient cases and data in the literature, like any patient with a chromaffin cell tumor, these patients should be followed-up for whole life [81, 83]. The metastatic diseases should be excluded with PET/CT in the patients with definitive pathology of AP [83].

Sarcomas (HIV-Associated Kaposi Sarcoma, Desmoplastic Small Round Cell Tumor)

HIV-Associated Kaposi Sarcoma

Kaposi sarcoma is a vascular tumor generally caused by human herpesvirus-8 (HHV-8) infection [84]. Kaposi's sarcoma had four subtypes: classic, endemic, organ transplant-related, and related to acquired immune deficiency syndrome (AIDS) [84, 85]. Although AIDS-related Kaposi's sarcoma is frequently reported in patients with HIV infection, it can be seen in patients with normal CD4 levels [85]. Gastrointestinal (GI) involvement in KS can occur with or without cutaneous disease and may be asymptomatic or cause abdominal pain, GI bleeding, or diarrhea [85]. Various gastrointestinal sites affected by Kaposi sarcoma have been

documented, including the oropharynx, esophagus, stomach, liver, and small and large bowel [85, 86]. Appendiceal Kaposi sarcoma with appendicitis, a critical manifestation of GI Kaposi, is extremely uncommon, and a review of the literature revealed a few published case reports [85, 86]. AIDS-related Kaposi sarcoma subtype has the most common appendix involvement among the four subtypes of Kaposi's sarcoma [85]. In the reported cases, it was observed that appendiceal Kaposi sarcoma was frequently presented with symptoms of acute appendicitis such as fever, nausea, vomiting, anorexia, right lower quadrant pain, or tenderness. In the laboratory findings of the patients, leukopenia, normal white cell count, and polymorphonuclear leukocytosis have been reported [84–86]. Acute appendicitis cases caused by appendiceal Kaposi sarcoma are treated by conventional or laparoscopic surgical resection [84–86].

Desmoplastic Small Round Cell Tumor

Desmoplastic small round cell tumor (DSRCT) is a very rare aggressive soft tissue sarcoma in the abdominopelvic cavity [87]. The disease contains translocation t (11; 22) (p13; q12), and microscopically, DSRCT is similar to mesothelioma, small cell carcinoma, Wilms tumor, and sarcoma/peripheral neuroectodermal tumors of Ewing and is characterized by small round blue cells [88, 89]. Histopathological examination and cytogenetic results play an important role in the diagnosis of DSRCT. The disease often occurs in men in adolescence and early adulthood [88]. Thomas et al. [88] reported that most common clinical presentations were abdominal mass (75%), abdominal pain (50%), and weight loss (15%). Also DSRCT could be found incidentally during surgery [88]. CT is the most useful imaging method for diagnose and staging of DSRCT. Chemotherapy, radiotherapy, and hyperthermic intraperitoneal chemotherapy (HIPEC) are used in the treatment of DSCRT [89].

Neuroectodermal and Nerve Sheath Tumors (Schwannoma, Neurofibroma)

Schwannoma

Schwannomas are mostly benign neurogenic tumors, caused by Schwann cells in the Auerbach plexus [90]. Most of the schwannomas occur in the head, neck, cranial nerves, and upper and lower extremities [90, 91]. Schwannoma is very rare in the gastrointestinal tract; most schwannomas are observed in the stomach with 83%, followed by the small intestine with 12% [90]. Schwannomas are much rarer in the colon, rectum, and appendix than in the stomach and small intestine. Schwannomas have an equal incidence in males and females, and the average age of occurrence is sixth decade [92]. Immunohistochemical staining plays an important role in the diagnosis of schwannoma and in differential diagnosis from other gastrointestinal stromal tumors. Although most schwannomas are sporadic lesions, some of them are associated with neurofibromatosis type 2 (NF2) syndrome or hereditary NF2 gene mutations [93]. Appendiceal schwannoma is generally asymptomatic and does not usually give clinical symptoms due to their slow growth. It is important to recognize and diagnose these tumors, which can cause malignant degeneration if

untreated. Complete surgical excision with conventional or laparoscopic appendectomy with tumor-free margins is the preferred treatment for appendiceal schwannomas [91, 92]. These tumors have a low rate of recurrence and an affirmative prognosis.

Neurofibroma

Neurofibromas are often seen in neurofibromatosis type 1 (NF1), an autosomal dominant hereditary tumor syndrome [94]. Although 10–25% gastrointestinal involvement can be observed in NF1, appendiceal involvement is very rare [94, 95]. Appendiceal neurofibromatosis is a rare seen clinical condition. No gender difference was observed in a very few appendiceal neurofibroma cases reported in the literature [94–96]. Although gastrointestinal neurofibromas are usually asymptomatic, patients can apply with constipation, abdominal pain, palpable abdominal masses, and symptoms of obstruction as the size of the lesions grows [95, 96]. A large-sized neurofibroma of the appendix can cause complications such as the development of perforation secondary to obstruction [94, 96]. The treatment of appendix neurofibromas is conventional or laparoscopic surgery. Surgical resection has been proposed to get ahead of the risk of complications and malignant transformation potential secondary to neurofibromas. The optimal surgical procedure remains still controversial for patients with appendiceal neurofibroma. Although a wide range of surgical treatment methods has been reported in the literature, from appendectomy to regional lymph node dissection and right hemicolectomy, a clear treatment method to be followed in terms of surgical management of neurofibromas has not been clarified in the guidelines [96].

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Surgical Treatment of Colon Cancer (Open and Laparoscopic Surgery)

15

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Preoperative Assessment

A patient with a colon cancer diagnosis is a candidate for major abdominal surgery. Since it is frequently seen in the population older than 50 years of age, it is necessary to evaluate the cardiovascular and pulmonary functions of patients for potentially present comorbid diseases. It is critical to perform surgery under optimal conditions, particularly for ensuring anastomosis safety and a smooth postoperative period. Furthermore, the nutritional status of patients should be assessed to take precautions or initiate treatment in compliance with the guidelines developed by the European Society for Clinical Nutrition and Metabolism (ESPEN) and American Society for Parenteral and Enteral Nutrition (ASPEN) [1, 2]. Detailed anamnesis should be obtained from patients, and a thorough physical examination should be performed in the preoperative period. It is necessary to investigate the signs of obstruction so that patients in need of emergency surgery are not overlooked. Although colorectal cancer is sporadic in most of the patients, genetic infrastructure and familial risks are identified in 3% and almost 30% of the patients, respectively, in this patient population [3]. Questioning patients for hereditary colorectal cancer is necessary, and genetic counseling should be obtained when indicated. Since one of the most critical prognostic factors is the disease stage, a thorough staging should be performed preoperatively. Carcinoembryonic antigen (CEA) levels are examined at regular intervals in the postoperative follow-up period. Moreover, preoperative CEA levels may be informative. Although CEA levels are elevated in the disseminated disease, it has been demonstrated that preoperative CEA levels at early stages (stage I–III) are associated with overall survival as an independent predictor [4].

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The diagnosis of colon cancer is usually made based on findings obtained from colonoscopy and biopsy. Tumor location described in colonoscopy should be verified by radiological methods that will provide more precise descriptions. It is important to examine other segments of the colon beyond the tumor location during colonoscopy to investigate synchronous cancers or polyps. It should be considered that even in sporadic colorectal cancers, the odds of identifying synchronous tumors and adenomatous polyps accompanying the tumor are 4% and about 30–50%, respectively [5, 6]. In the preoperative period, computed tomography (CT) scans of the chest, abdomen, and pelvis are adequate to screen a metastatic disease in patients scheduled for elective surgery. Sometimes a multidisciplinary approach is needed with the contributions of a hepatobiliary surgeon and a urologist or gynecologist to perform R0 resection when preoperative staging studies reveal neighboring organ invasion or liver metastasis. En bloc resection should be preferred particularly in adjacent organ invasions [7, 8]. Regardless of the selected method to provide access to the surgical site, our main goal should be to perform the resection adequately without compromising oncological principles.

Bowel Preparation

Bowel preparation before elective colorectal surgery is recommended and performed by many centers today. Bowel preparation is performed for various reasons. Having an empty colon during the operation facilitates surgical manipulations and allows for the use of colonoscopy when necessary. Especially during laparoscopic surgery, grasping and traction of the stool-filled colon with hand-held surgical instruments may cause tears. The efficacy of mechanical bowel preparation in reducing the rates of surgical site infections has been studied extensively in the literature. As it is known, the rate of surgical site infections after elective colon resection ranges from 5% to 23% [9]. Mechanical bowel preparation involves the use of orally administered solutions and antibiotics. Antibiotics such as neomycin, erythromycin, and metronidazole can be administered orally on the day before surgery. Over the last decade, some randomized controlled studies have reported that bowel preparation is not necessary for colon surgery [10–12]. Preoperative bowel preparation may cause fluid and electrolyte disorders due to vomiting and diarrhea, especially in old-age patients. Therefore, hospital admissions may be needed in the geriatric patient population so that intravenous fluid therapy can be supplied on the day before surgery when necessary. Although some major studies and groups state that bowel preparation is not necessary, several other studies are available in the literature, reporting contradicting results. Using the National Surgical Quality Improvement Program's colectomy database, a case series study included 45,724 patients, who underwent a colon resection. These patients underwent elective colectomy in the years between 2012 and 2015. Approximately 70% of the patients underwent bowel preparation, whereas 25% did not. The results revealed that oral antibiotic administration along with mechanical bowel preparation provided advantages to avoid surgical site infections, anastomosis leakage risks, and complications in the early postoperative period [13]. A meta-analysis of seven randomized studies compared

patients receiving mechanical bowel preparation and oral antibiotics to those receiving only bowel preparation, demonstrating better outcomes for surgical site infections in the group of patients receiving the combination of mechanical bowel preparation and oral antibiotics (7% versus 16%) [14]. Many studies emphasize the importance of additive oral antibiotics administered with mechanical bowel preparation. It is reported that this combined approach is associated with the most favorable outcomes. The World Health Organization's surgical site infection prevention guidelines state the necessity of the use of the combined approach [15]. Another meta-analysis investigating the same subject included 38 randomized studies. The meta-analysis reported that the combination of mechanical bowel preparation with additive oral antibiotics is the best option and that oral antibiotic therapy alone holds the second rank. No differences have been reported in the literature between the administration of mechanical preparation alone and performing no bowel preparation at all [16]. The clinical practice guideline for the bowel preparation developed by the American Society of Colon and Rectal Surgeons was published in 2019. The guideline recommends mechanical bowel preparation combined with additive oral antibiotics typically before elective colorectal resections. This statement has been made under the strong recommendations category. Enema alone, with no bowel preparation and additive oral antibiotics, has been addressed under the weak recommendations category [17]. In conclusion, despite several studies and discussions, it appears that a common consensus has currently been achieved to administer mechanical cleansing with the use of additive oral antibiotics before elective colon surgery.

Thromboprophylaxis

Prophylaxis against deep vein thrombosis (DVT) and, consequently, pulmonary embolism are major components of colorectal surgical treatments. Risky patients should be identified in advance. The age and weight of the patient and the type of surgery to be performed are the criteria that we usually use to identify patients at risk for deep vein thrombosis. Several large-scale patient series studied risk determination to start prophylaxis. General classifications include "very low risk," "low risk," "moderate risk," "high risk," and "very high risk" categories [18]. We can argue that the majority of patients undergoing colorectal surgery are in the high-risk group. The use of intermittent pneumatic compression (IPC) devices in the operating room and early mobilization of the patient are significantly important for prophylaxis. Furthermore, we should minimize the risk of deep vein thrombosis by giving the patient medical treatment that is called chemical prophylaxis. For this purpose, the most commonly used medication is the low molecular weight heparin administered subcutaneously. Studies have shown that the rate of DVT is reduced by 65% when necessary precautions are taken in the scope of DVT prophylaxis [19, 20]. Although these studies report an increased incidence of complications including wound hematoma, it is known that these complications do not pose a major risk. Chemical prophylaxis can be started before or immediately after surgery. It is necessary to continue prophylaxis for up to 4 weeks, especially in high-risk patients.

Main Principles

We know that the surgeon is a prognostic factor in primary colon cancer surgery. There is a chance of complete cure with surgical treatment, particularly in early-stage colon cancer; however, inadequacies in the use of oncological methods adversely affect outcomes. An adequate surgical technique can be applied during open surgery or laparoscopy. Basically, the tumor segment should be resected, and adequate lymphadenectomy should be performed.

Resection Margins

In colon cancer surgery, a certain distance should be kept to the distal and proximal tumor margins to reduce the likelihood of local recurrences. Studies have investigated the optimal length from the line of transection in the colon lumen to the tumor. Several series suggest that the proximal and distal margins should be at least 7 cm [21–23]. Unlike rectum resection, radial margin positivity is not a common problem in resection of colon tumors. However, positive radial margins are associated with distant metastases and recurrences. A retrospective case series of 984 patients reported unfavorable rates of overall survival and disease-specific survival in patients with radial margin positivity [7]. If radial margin positivity is estimated, en bloc resection should be performed including adjacent organs.

Lymphadenectomy

Along with the resection of the colon segment with the tumor, it is necessary to remove the lymph nodes around the blood vessels supplying the tumor segment. Lymphadenectomy is important both for determining the disease stage and resection of metastatic lymph nodes. At least 12 lymph nodes must be removed in colon cancer surgery [24]. The American Society of Colon and Rectal Surgeons guidelines state that the surgeon should count the lymph nodes once more if the number of lymph nodes is not found adequate in the pathology report [25]. Inadequacies in lymphadenectomy constitute an indication for adjuvant chemotherapy, particularly in patients with stage 2 cancer. This means unnecessary chemotherapy administration to some patients. When performing lymphadenectomy, vascular ligation should be performed at an adequate proximal distance. Also, the mesentery to be exposed must be excised without tearing and puncturing. The level of vascular ligation remains to be controversial. A standard vascular ligation method should include epicolic, paracolic, intermediate, and central lymph nodes. Some surgeons prefer to perform lymphadenectomy covering a wider area. The method, called high ligation, central vascular ligation, complete mesocolic excision, or D3 dissection, provides a wider area for lymphadenectomy.

Open vs. Laparoscopic Colectomy

The history of colon cancer surgery goes back 150 years. Advances in technology and surgical techniques developing over the past 150 years contributed to both oncological and functional improvements in patient outcomes. Laparoscopic colon surgery was performed for the first time in 1991 by Jacobs, and it is still popular today [26]. Due to problems such as port-site recurrence, some concerns about oncological outcomes arose in the first years of laparoscopy; however, these concerns disappeared in the following years. Nevertheless, the common use of laparoscopy in the world has been delayed since it is a difficult technique, requiring a certain period of experience and advanced laparoscopy skills of the surgeon. Laparoscopic colon surgery started to be commonly used after the completion of randomized studies comparing open and closed surgery and reporting their results by the 2000s. There are many advantages to the patient with laparoscopic surgery. Postoperative pain occurs in less severity, bowel movements return faster, and the length of hospitalization is short after laparoscopic resections. Despite its several advantages, laparoscopy has not yet been defined as the gold standard method in contrast to cholecystectomy since it requires advanced laparoscopy skills and experience of the surgeon, and it takes longer to perform laparoscopy compared to open surgery. As the team members in our clinic with a high volume of patients, we prefer laparoscopic methods that allow us to perform minimally invasive colon resection in clinically non-complicated tumors with no adjacent organ or tissue invasions and in patients having no severe cardiopulmonary problems or intestinal obstruction.

Surgical Technique

Regardless of the surgical technique used in colon cancer surgery, the main issue that we should not compromise at all is not to violate the oncological principles we defined above. The studies by Heald established the steps of resection, particularly in rectal cancer surgery [27]. In colon cancer surgery, the surgical technique is more flexible to some extent with no clear cut established steps. However, we know that we need to proceed along embryological planes in colon cancer surgery and ligate the vascular structures providing blood supply to the tumor as much proximally as possible. Hohenberger from Erlangen described the concept of complete mesocolic excision in 2009. This technique has been described for colon cancer resections, stressing the importance of removing the tumor segment and the mesocolon together. Furthermore, it is emphasized that the mesocolon should be excised with no perforations and disruptions in its integrity. It is reported that vascular ligation should be performed at the closest point to the superior mesenteric artery and the vein. Then, the outer lining of the superior mesenteric vein (SMV) should be cleaned to ensure a favorable lymphadenectomy (Fig. 15.1) [28]. Hohenberger reported that the 5-year local recurrence rate for colon cancer was reduced from 6.5% to 3.6% and the cancer-related survival rate was increased from 82.1% to 89.1% with the use of

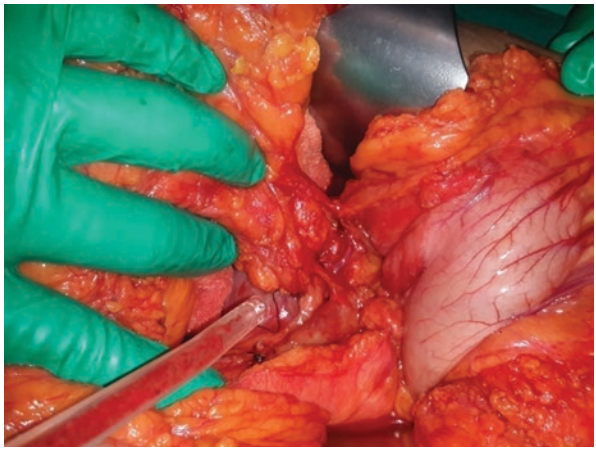

Fig. 15.1 The outer lining of the superior mesenteric vein (SMV) should be cleaned to ensure a favorable lymphadenectomy

this technique. Although this technique of Hohenberger attracts attention all over the world, it has not been performed commonly in daily practice because it is found too radical and risky by some centers. In the next sections, the stages of both open and laparoscopic techniques will be discussed.

Right Hemicolectomy

We can categorize right colon tumors based on their location as the tumors located in the cecum, ascending colon, and the right half of the transverse colon. The ascending colon, including the hepatic flexure, is covered with peritoneum. Its posterior part is retroperitoneal and neighbors the retroperitoneal structures. The arteries that we will encounter during the right colon surgery are the ileocolic artery, the right colic artery, and the middle colic artery. Also, some veins accompany these arteries. The gastrocolic trunk of Henle that is formed by three tributaries including the right gastroepiploic vein, the anterior superior pancreaticoduodenal vein, and the superior right colic vein should receive particular attention during right hemicolectomy [29] (Fig. 15.2). This venous structure can be torn during the mobilization of hepatic flexure, particularly with excessive traction on the colon. Tears in the gastrocolic trunk of Henle may result in profuse bleeding. Controlled manipulation of Henle's trunk is considerably difficult and associated with risks because it lies adjacent to the pancreas and SMV. Therefore, the ideal approach is to know the anatomy of this region very well in order not to allow any injuries to happen. During right hemicolectomy, the duodenum and the head of the pancreas are observed adjacent to the mesocolon retroperitoneally. The right ureter runs closely to the mesocolon at the level of the iliac bifurcation. It is adequate to ligate the ileocolic artery, the ileocolic vein, the right colic artery, and the right colic vein in tumors of the ascending colon and the cecum, whereas the middle colic artery should be ligated and divided additionally in tumors of the hepatic flexure and the proximal transverse colon. This way, we have performed an extended right hemicolectomy [30, 31].

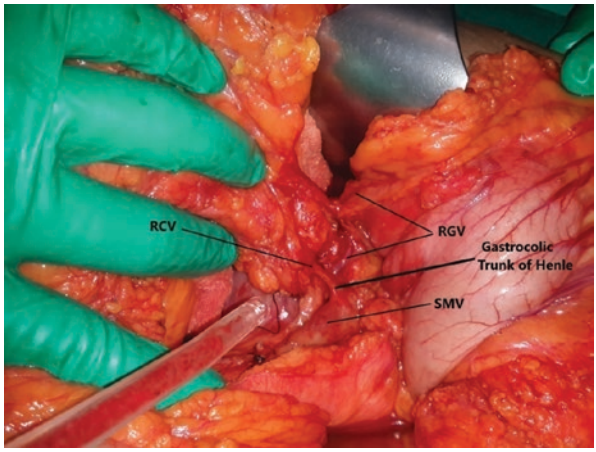

Fig. 15.2 Right colic vein (RCV), right gastroepiploic vein (RGV), superior mesenteric vein (SMV)

Fig. 15.3 Lloyd Davies position

Surgical Technique

Like many other colorectal surgery centers, we perform right hemicolectomy while the patient is in Lloyd Davies position with the legs separated wide (Fig. 15.3), although it is not necessary. The patient should receive two-drug antibiotic prophylaxis comprising a second-generation cephalosporin and metronidazole half an hour before the incision. If surgery lasts longer than 4 h, the second dose should be administered to the patient. During open surgery, the intraperitoneal cavity is entered after a median incision is made. Before starting the surgery, the abdominal cavity should be explored via inspection and palpation. Particularly, the liver should be palpated to detect any metastasis, and the pelvic peritoneum should be inspected

to identify any sites of tumor implantation. Extensive much manipulation of the tumor segment should be avoided both during the exploration process and the surgical procedure [30, 31].

Open Right Hemicolectomy

Open surgery starts with mobilization of the lateral ligaments of the ascending colon. The cecum, the ascending colon, hepatic flexure, and the mesocolon are separated from the retroperitoneum with sharp dissection. Sharp dissection of avascular planes with cautery will minimize bleeding and enable removing oncological planes as a whole with no tears. During the separation of the right colon from the retroperitoneum, the dissection should proceed by leaving Gerota's fascia, the right gonadal vein, and the ureter in the retroperitoneum. The dissection should further proceed, leaving the retroperitoneal part of the duodenum and the pancreatic head in the retroperitoneum. This way, the right colon should be mobilized to the level proximal to the vascular pedicle. After mobilizing the colon and cecum, the gastrocolic ligament should be dissected and separated from the omentum. At least the right half of the omentum can be included in the specimen. When the lateral dissection is completed in open surgery, the right colon can be easily taken out of the abdomen, allowing for starting dissection from the medial (Fig. 15.4a). We can utilize transillumination to decide where to divide the ileum before proceeding to dissection from the medial (Fig. 15.4b). With medial dissection, vascular ligation is completed after ligating the right colic vein and the ileocolic artery and vein from a proximal point. If we plan to perform extended right hemicolectomy, we need to connect the middle colic artery at this stage. After completing the vascular ligation, we determine where we will transect the colon and ileum to complete the resection. After taking the specimen out of the surgical site, we need to proceed to the anastomosis stage. After performing the right hemicolectomy, we can perform an end-to-end, end-to-side, or side-to-side ileocolic anastomosis. We can use linear staples with appropriate punch length to make anastomosis. We need to ensure that the blood supply is maintained while performing an anastomosis [30, 31].

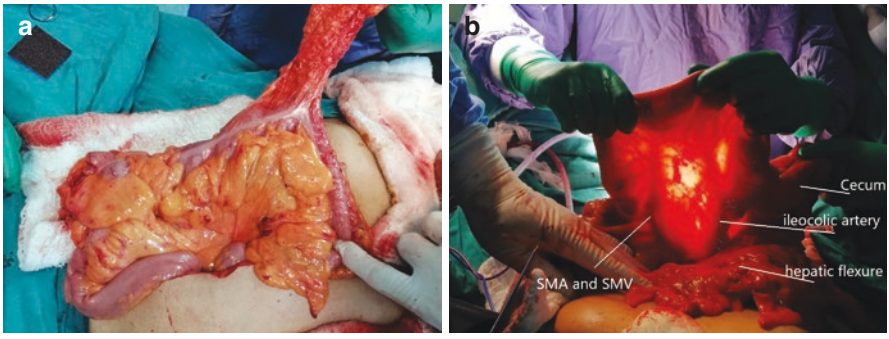

Fig. 15.4 (**a**) Right colon. (**b**) superior mesenteric artery (SMA), superior mesenteric vein (SMV)

Laparoscopic Right Hemicolectomy

The preparation phase of laparoscopic cases takes a little longer than that of open surgery. After preparing the laparoscopy device and establishing the connections, the abdomen is insufflated with CO_2. The intra-abdominal pressure is usually set at 12 mmHg. Sometimes, in patients with respiratory or cardiac risks, the intra-abdominal pressure may be set at lower pressures after consulting with the anesthesiology team. The operation can be completed with the use of four ports, comprising one camera port and three handpieces; however, one should not avoid using additional ports if necessary. When the surgeon stands on the left side or between the legs of the patient, the camera is placed on the left side of the surgeon. The first assistant can stand on the right next to the assistant holding the camera. As with all laparoscopic colorectal surgeries, a 30-degree angle optic camera is used. It is necessary to position the patient during the laparoscopic right hemicolectomy after the general exploration of the abdomen. Generally, the technique is performed from medial to lateral. For this reason, the patient is brought to the mild Trendelenburg position and is laid down on the left so that the small intestines are removed from the surgical site. Primarily, the pedicle comprising the ileocolic artery and vein is elevated to expose the mesocolon and enter the retroperitoneum. After entering the retroperitoneum, avascular planes will be visualized with the use of CO_2, facilitating dissection. In this area, dissection is performed with the use of a vessel sealer, hooks, or scissors. During the dissection, the third portion of the duodenum will be exposed. The third portion of the duodenum should be left under our dissection plane, and the ileocolic artery and vein should be ligated at a proximal point as much as possible (Fig. 15.5a). After this stage, the right

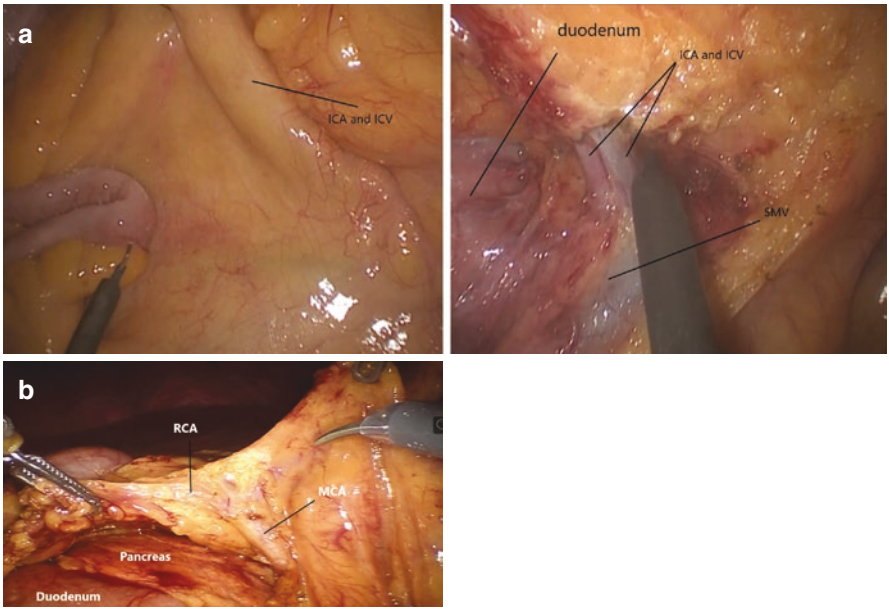

Fig. 15.5 (**a**) Ileocolic artery (ICA) and vein (ICV). (**b**) Middle colic artery (MCA)

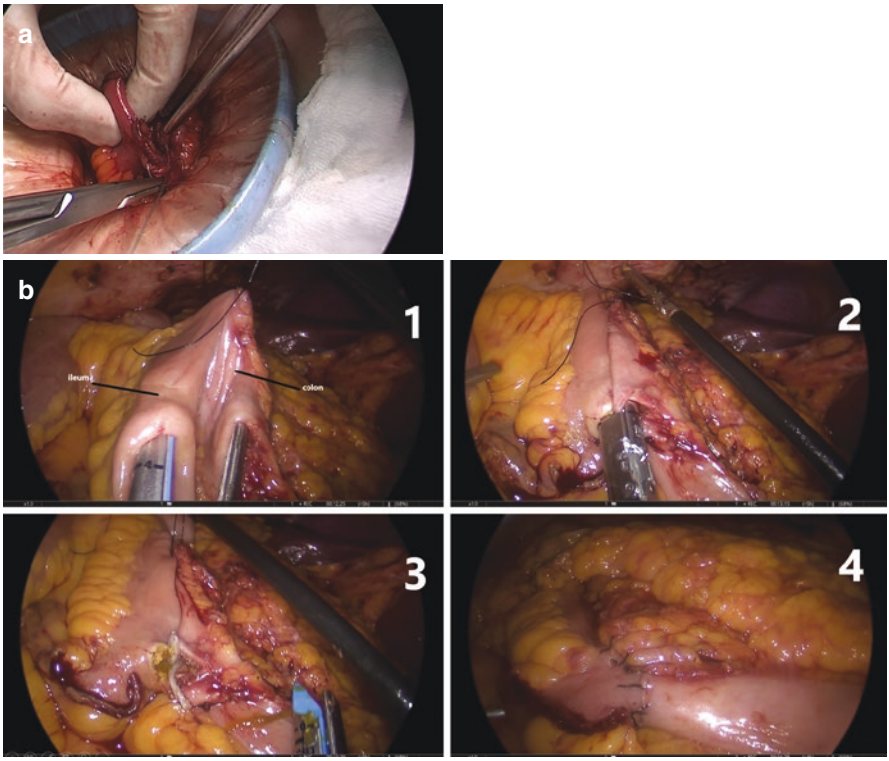

Fig. 15.6 (**a**) Extracorporeal anastomosis. (**b**) intracorporeal anastomosis

colic artery and the vein should be ligated and cut. If extended right hemicolectomy is to be performed, the middle colic artery and vein should be ligated and cut, too (Fig. 15.5b). Perhaps, the most demanding part of the operation is mobilizing the gastrocolic ligament to separate the omentum. At this stage, dissection should be performed with vessel sealers. After completely mobilizing the colon segment containing the tumor and dividing the lumen by using a stapler, we can proceed to the anastomosis stage. After removing the specimen from the operative field through wound protectors in a median incision of 4–5 cm, we can proceed to perform the anastomosis using the same incision (Fig. 15.6a) or we can insufflate the abdomen again to perform an intracorporeal anastomosis (Fig. 15.6b) [30–33].

Transverse Colectomy

For the surgical treatment of transverse colon tumors, some centers prefer extended right hemicolectomy or extended left hemicolectomy to transverse colectomy. Particularly for the tumors located on the right half of the transverse colon, it may be adequate to ligate the middle colic artery along with the right colic artery to

complete the resection with an extended right hemicolectomy. For tumors on the left half of the transverse colon, it is again possible to perform resection by ligating the middle colic artery along with the ligation of the left colic artery or inferior mesenteric artery [34–36]. Especially for the surgical treatment of tumors located in the middle of the transverse colon, transverse colon resection and a colon-to-colon anastomosis can be performed. In transverse colectomy, the aim is to remove the tumor along with the lymphatics surrounding the transverse colon, omentum majus, and the middle colic artery. Firstly, the omentum majus is separated from the large curvature of the stomach along a line passing over or underneath the gastroepiploic arch. Then, the dissection proceeds until reaching both of the two flexures. Meanwhile, care should be exercised not to injure the stomach. In order to make a tension-free anastomosis, both flexures of the colon should be adequately mobilized. End-to-end anastomoses can be performed manually in open surgery. In laparoscopic surgery, the anastomosis can be made manually after removing the specimen through wound protectors inserted via a small umbilical incision [30, 31].

Left Hemicolectomy

Open Surgery Technique

Left hemicolectomy is usually performed for the surgical treatment of tumors located at the level of the splenic flexure or in the descending colon. First, the patient is brought to Lloyd Davies position. The surgeon stands on the right side of the patient during the surgery. The assistant, who will retract the abdominal wall, stands on the left side of the patient. The first assistant stands between the patient's legs. Although some surgeons prefer to perform a left paramedian incision, many surgeons prefer working through a median incision today. After making a median incision, the abdominal cavity is entered. Then, the liver and peritoneal surfaces are explored to detect any metastatic diseases. After completing the exploration, the lateral ligament of the colon, which is called Toldt's fascia, is incised from lateral to medial. The sigmoid colon and the descending colon are separated from the retroperitoneal structures with sharp dissection. The ureter and the gonadal vein should be left in the retroperitoneal area, and the procedure should proceed along avascular embryonal planes. To minimize the spread during the dissection, manipulation of the tumor should be avoided as much as possible. It is absolutely necessary to mobilize the splenic flexure during left hemicolectomy. The splenocolic ligament is cut to mobilize the splenic flexure. Meanwhile, it is necessary to be attentive and exercise care to avoid splenic injuries. The gastrocolic ligament is dissected; the omental bursa (lesser sac) is entered, and the left half of the omentum is partially included in the specimen. After mobilizing the left colon by dissecting it from the retroperitoneum and the splenic flexure, the surgeon can proceed to ligate the vessels. In descending colon tumors, the inferior mesenteric artery is dissected after it is ligated at the level of the root of the aorta. Then, the inferior mesenteric vein is cut after ligating it at a level close to its entry point to the pancreas. The middle colic artery

is preserved. The colon is transected distally from the upper rectum and proximally from the distal transverse colon. Then, a colorectal anastomosis is performed using circular staples. If the tumor is in the splenic flexure, the middle and left colic arteries are cut after being ligated. Then resection can be performed, preserving the inferior mesenteric artery; or extended left hemicolectomy can be performed by anastomosing the right half of the transverse colon to the rectum after ligating and cutting both the middle colic artery and the IMA (inferior mesenteric artery). The second method is usually employed less commonly [30, 31].

Laparoscopic Left Hemicolectomy

Contrary to the open surgical technique, the laparoscopic one involves the use of the medial to lateral dissection method as performed by several other centers. After the patient is brought to Lloyd Davies position, the abdomen is insufflated. After the intra-abdominal exploration, the patient is brought to the Trendelenburg position, slightly facing the right side. The small intestines and the omentum are removed from the dissection area in the midline. In descending colon tumors, firstly, the peritoneum on the promontorium is exposed to enter the avascular, fatty, and porous area under the inferior mesenteric artery. Meanwhile, an assistant surgeon must pull the sigmoid colon toward the lower left quadrant to stretch the mesocolon. Dissection should continue by proceeding superiorly and laterally to the left along the exposed plane. The ureter and the gonadal vein should remain below this plane. Furthermore, we should avoid cleaning the outer lining of the aorta extensively to prevent hypogastric plexus injuries. It was established years ago that anatomical features of the area and dissection characteristics should be well known. Harry Bacon's studies are of historical importance, determining the location of vascular ligations for distal colon and rectal resection [37]. The angle between the aorta and IMA, formed during vascular dissection, is called the axilla abdominis of Bacon [38]. During the dissection of the inferior mesenteric artery in a laparoscopic intervention, it is important to observe the formation of this angle for the preservation of the hypogastric nerves. After revealing this anatomical structure, IMA is released and clipped and cut 1–2 cm distally to its origin from the aorta. Then, lateral dissection is continued (Fig. 15.7a). The inferior mesenteric vein is clipped and cut just next to the duodenum (Fig. 15.7b). These ligations can be performed by using hem-o-lok plastic clips or vascular sealing devices, depending on the surgeon's discretion. We prefer the clipping method. After adequately releasing the mesocolon medially from the retroperitoneal space, we can proceed to release the splenic flexure. It is useful to be patient at this stage. During splenic flexure dissection, surgical procedures can be performed by using a second monitor placed at the level of the left shoulder of the patient or the procedure can be continued after bringing the laparoscopy tower closer to the left shoulder of the patient. The assistance provided by the assisting surgeon is important during the mobilization of the flexure. As the assistant surgeon pulls the transverse colon downward, the instrument in the surgeon's left hand pulls the omentum upward. This way and by using a vessel sealing device or cautery, the

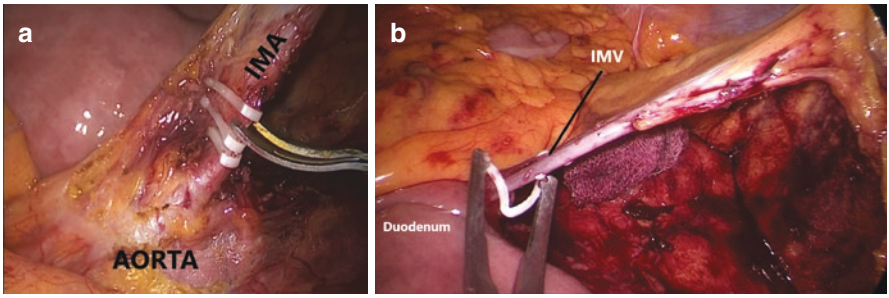

Fig. 15.7 (**a**) Inferior mesenteric artery (IMA). (**b**) inferior mesenteric vein (IMV)

splenic flexure is mobilized. "Melani technique" has been described for splenic flexure mobilization. In the classical method, it is attempted to enter the lesser sac by proceeding between the omentum and the left half of the transverse colon. With Melani technique, the medial to lateral approach is used, and the left mesocolon is mobilized laterally and superiorly as much as possible. The dissection is continued along the avascular planes until reaching the inferior border of the pancreas superiorly and beneath the descending colon laterally. The transverse mesocolon is exposed by approaching just superiorly to the inferior mesenteric vein and over the pancreas. This way, the lesser sac is entered. Then, IMV is ligated and cut. Following this step, the mesocolon is divided along the lower edge of the pancreas. These procedures mobilize the splenic flexure (Fig. 15.8) [39].

It will be easier and more enjoyable to separate the left lateral ligaments of the colon after this stage. After completely releasing the sigmoid colon, descending colon, and the splenic flexure, the time comes to divide the colon. After performing the transection at the level of the upper rectum distally by using endoscopic linear staples, the specimen is taken out of the surgical field with an accompanying wound protector through a small Pfannenstiel incision. Then, proximal colon transection is performed through this incision. Simultaneously, the circular stapler anvil is placed, and the colon is returned to the abdominal cavity. Then, the abdomen is insufflated again. Either the surgeon or the first assisting surgeon proceeds the circular staples transrectally while standing between the legs of the patient. In the meantime, the loop of the proximal colon is checked to detect whether it has revolved. Then, the colorectal anastomosis is performed by using staples. Some factors need further attention during the anastomosis procedure. Achieving a tension-free anastomosis with a favorable blood supply will minimize the risk of leakage. A laparoscopic resection can be performed by ligating the middle and left colic arteries and preserving IMA to treat tumors located close to the splenic flexure. To perform this procedure, the medial to lateral dissection should be used starting under the inferior mesenteric vein. Then, the left colic artery should be found and ligated (Fig. 15.9). Following that, IMV (inferior mesenteric vein) should be ligated, and the dissection should proceed toward the middle colic artery. After the middle colic artery is ligated, the splenic flexure should be mobilized, and the colon loop to be resected should be separated with the omentum around it from the stomach. The adequately mobilized

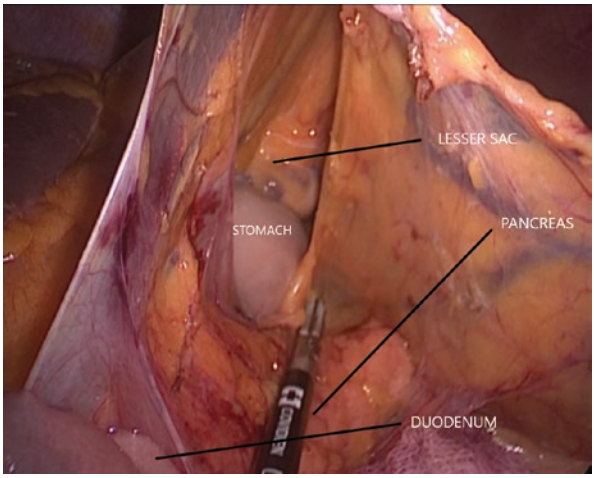

Fig. 15.8 Mobilization of splenic flexura with Melani Tecnique

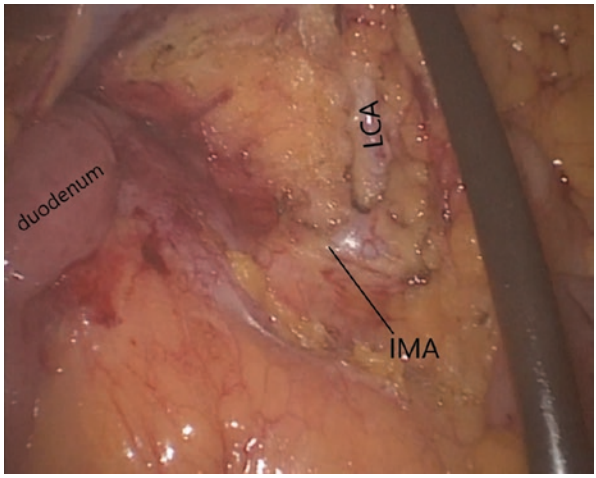

Fig. 15.9 Inferior mesenteric artery (IMA), left colic artery (LCA)

colon should be transected at the level of the transverse and sigmoid colons proximally by using endoscopic linear staplers. Because the distal transection line is at the sigmoid colon level, it will not be possible to perform the anastomosis by using circular staples. In this case, just like we did during the right hemicolectomy, the anastomosis can be performed manually through the incision we removed the specimen. Also, a side-to-side intracorporeal anastomosis can be performed [30, 31, 37–39].

Sigmoid Resection

The resection performed to surgically treat a sigmoid colon tumor is called sigmoid resection or anterior resection. It is technically easier to perform compared to resection of other segments of the colon. Especially, at the start of the learning curve of laparoscopic surgery, patients with sigmoid colon cancer should be selected as initial cases.

Open Sigmoid Resection

Median incisions should be preferred in open surgery. The lower end of the incision should extend to the symphysis pubis, especially in obese patients. A mild Trendelenburg position will move the small intestines superiorly and away from our surgical field. Small intestines until the sigmoid mesocolon should be moved away from the pelvis by using wet compresses. After general exploration, the sigmoid colon is mobilized, starting from the left lateral ligaments. After the retroperitoneum is entered from the left side, a sharp dissection proceeds along avascular embryonal planes, leaving the ureter and the gonadal vein in the retroperitoneum. The dissection starts from medial, and it proceeds beneath the region where the inferior mesenteric artery continues as the superior hemorrhoidal artery, reaching the lateral opening. Meanwhile, avascular planes should not be violated to prevent injuries to the hypogastric plexus. If the patient's sigmoid colon is not too short, splenic flexure mobilization is usually not necessary. IMA is found medially and ligated and cut at a point 2 cm distal to the point of its origin from the aorta. During the ligation procedure, it is necessary to be attentive to the hypogastric plexus, which extends on both sides of the aorta. The risk of injuring the hypogastric plexus is high at this point of ligation. After IMA is ligated, it is beneficial to ligate IMV under the pancreas. However, IMV can be ligated at a more distal level if it is foreseen that it will be a tension-free anastomosis. In sigmoid colon tumors, we need to achieve a surgical margin of at least 5–7 cm distally. Observing these limits, transection starts distally. Then, the mesocolon containing an adequate quantity of lymphatics is divided proximally. Following these steps, the specimen is taken out of the surgical field. Distal transection is usually performed with a green roticulator or TA, having a punch length of 55 mm. The anvil is inserted into the proximal end and fixed with purse-string sutures. The anastomosis is performed by using a circular stapler, which is proceeded transanally. While some surgeons close the mesocolon opening, some prefer not to close it [30, 31].

Laparoscopic Sigmoid Resection

Laparoscopic sigmoid resection is a type of intervention that should be preferred especially by surgeons, who have just started to specialize in laparoscopic colon surgery. In laparoscopic sigmoid resection, when the splenic flexure will not be mobilized, the study area will be smaller, and the number of vessels to be ligated will not be more than two. These features will allow the procedure to be performed easily. In general, surgery can be completed with four trocars. The camera is inserted after the insufflation performed through the edge of the navel. Then, the other trocars are inserted using the camera. After a general exploration performed initially, surgery starts with a medial to lateral dissection technique. Firstly, the first assistant stretches the sigmoid mesocolon. Then, after exposing the rectosigmoid mesocolon at the promontorium level, the retroperitoneal avascular porous fat tissue is entered. The more precisely the dissection proceeds from the starting point, the easier will be the surgery. Dissection is performed from medial toward lateral and cranial

directions. There is no need to spend special efforts to locate the ureter when proceeding from the right plane. The surroundings of IMA are cleaned by exercising extra care to stay away from the hypogastric nerves. After completing the ligation with plastic clips, the blood vessel is divided. Meanwhile, the mesocolon is released from the medial to the descending colon. Then, IMV is ligated at a level close to the ligament of Treitz of the duodenum. If the bodyweight of the patient is not much to hinder laparoscopic interventions, ligation and cutting of IMV proximally will allow the mesocolon to be tension-free, further allowing for achieving a tension-free anastomosis. After the vascular ligation, transection is performed from a distal level, using an Endo GIA™ stapler. The part to be cut proximally should be determined after removing the specimen through a wound protector from a small Pfannenstiel incision. After performing the transection at a suitable level, the anvil is inserted into the proximal end. The abdominal wall is closed with a wound protector, and insufflation is performed. The assistant surgeon will stand between the legs of the patient and perform the anastomosis by advancing the circular staples transanally [30, 31].

Total Colectomy

Total colectomy is usually necessary for the treatment of synchronous cancers or polyposis coli. Also, total colectomy may be necessary for the treatment of benign pathologies such as ulcerative colitis, diverticulosis coli, and constipation. The term total colectomy refers to resections from cecum to the upper rectum or sigmoid. Generally, the steps of the procedure before the surgery are the same as those described above for segmental resections. A long median incision is necessary to perform the open technique. It may be necessary to extend the incision upward, especially when mobilizing the splenic flexure. The resection usually starts with a right colon resection, continuing with resections of the transverse colon, the ascending colon, and the sigmoid colon, respectively. The technical details described above for segmental resections are valid for total colectomy, too.

Laparoscopic total colectomy is very advantageous because it will be completed only with a much smaller incision compared to the open technique. To complete the surgery with a laparoscopic method, it is necessary to perform dissections almost in all abdominal quadrants and to know the anatomical planes very well. During the operation, surgeons and assistant surgeons will need to change their positions several times. Also, the place of the laparoscopy device should be changed several times from the patient's feet to the shoulder level. Therefore, it is a longer procedure compared to the open technique. No matter how long it takes, the surgeon should choose the laparoscopic method if he is experienced enough. Advantages of laparoscopic methods, including the lower intensity of pain, faster return of bowel movements, and a faster recovery, are evident in patients undergoing total colectomy [30, 31].

Comparison of Short-Term Results

Laparoscopic surgery and open surgery have been compared in many randomized controlled trials [40–42]. The studies demonstrate that patients undergoing laparoscopy benefited more advantages to some extent in the early period, that is, in the first 30 postoperative days, including surgical site infections and anastomosis leaks, compared to those undergoing open surgery. Also, compared to the open surgery group, the rate of complications is reported to be lower in the laparoscopy group owing to low rates of bowel adhesion [43]. In one large case series, 872 patients were included in the study. Patients with colon adenocarcinoma are divided into open surgery and laparoscopy groups. The length of operation was longer, but the length of hospital stay was shorter in the laparoscopy group compared to the open surgery group. The rates of early postoperative complications and readmissions were found equal in these two groups [40, 44]. In another case series performed quite recently, 425 patients were included. The patients were divided into open surgery and laparoscopy groups, and these two groups were compared. The results of the study show that the quality of life scores were better in the laparoscopy group in the early postoperative period [45].

Comparison of Long-Term Results

The outcomes of laparoscopy, especially oncologic outcomes, arouse curiosity. In the series published by the COST study group in 2007, it was reported that the disease-free 5-year survival (68.4% in the open surgery group and 69.2% in the laparoscopy group, $p = 0.94$) and the overall 5-year survival (74.6% in the open surgery group and 76.4% in the laparoscopy group, $p = 0.93$) were similar for the two groups. The recurrence and distant metastasis rates were found to be similar in the follow-up period [44]. As it is known, at least 12 lymph nodes should be excised in colon cancer resections. A meta-analysis of several randomized controlled trials, comparing the number of lymph nodes removed in laparoscopic interventions versus open surgery, demonstrated that 11.8 lymph nodes were removed in open surgery and 12.2 were removed in patients undergoing laparoscopy [46]. Today, the total number of patients that were included in trials with high evidence levels is expressed in thousands in meta-analysis studies. The comparison of the number of lymph nodes, results of survival analyses, and recurrence rates in many meta-analysis studies showed that the long-term oncological outcomes were equal in the open surgery and laparoscopy groups [46, 47].

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Open and Laparoscopic Surgery in Rectal Cancers

16

Eyup Murat Yilmaz, Erkan Karacan, and Tayfun Yoldas

Today, rectal surgery is performed in the presence of polyp that cannot be removed endoscopically, solitary rectal ulcer, diverticular diseases, and rectal carcinomas. Currently, the laparoscopic technique has gained popularity in the diseases of rectal surgery, while this procedure is not recommended in emergencies such as perforation, obstructive ileus, and bleeding [1].

The primary goal of the surgery to be performed in rectal cancer is to remove the segment where the tumor is located along with the lymphatics it is drained through safe surgical margins. While determining the resection margins in the surgery to be performed for this purpose, the localization of the tumor, regional lymph node drainage, and vascular structures that supply the relevant segment should be taken into consideration. The preference of anastomosis after resection may vary depending on the conditions of the resection and the surgeon's preference [1].

The surgical treatment of rectal cancer shows significant differences from colon surgeries since the rectum is limited to the osseous structures within the pelvic structure and is closely adjacent to the pelvic autonomic nerves and urogenital organs. Today, great progress has been made in rectal surgery after the development of circular staplers [2].

Anatomy

The rectum is about 12–15 cm long. It is the last portion of the gastrointestinal tract that extends from the promontorium level to the anal canal [3].

While the rectum is adjacent to the third, fourth, and fifth sacral vertebrae and coccyx, presacral plexus, superior rectal artery/vein, and the levator anus muscle at

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the posterior, it is adjacent to the bladder fundus and prostate in males and the proximal part of the uterus and vagina in females on the anterior side. Arterial blood supply of the rectum is mainly provided by the superior rectal artery originating from the inferior mesenteric artery and the middle and inferior rectal artery originating from the internal iliac artery. In the venous circulation of the rectum, the upper rectal vein drains into the portal system through the inferior mesenteric vein. The middle and lower rectal veins drain into the inferior vena cava through the internal iliac vein. Therefore, tumors located in the lower 2/3 of the rectum are likely to metastasize to the lung without liver metastasis [3].

The mesorectum is surrounded by the visceral fascia and contains vascular structures, lymphatic ducts, and lymph nodes. Rectal blood flow was mainly supplied by the superior rectal artery (branch of the inferior mesenteric artery) and the middle and inferior rectal artery (branch of the internal iliac artery). Pelvic sympathetic hypogastric nerves travel laterally and caudally preaortically parallel to the plexus and ureters of hypogastric origin above the aorta. Pelvic parasympathetic nerves (nn.splanchnici-nn.erigentes), fibers stemming from the sacral segments, participate in the formation of plexus pelvinus. The parasympathetic fibers stemming from here innervate the vesica urinaria, rectum, male sex accessory glands, uterus, vagina, and penis/clitoris in the pelvic cavity and cause vasodilator effect on the vessels in this region [4].

Preoperative Staging

Total mesorectal excision (TME) is absolutely necessary in the surgery of rectal cancer. Preoperative staging and tumor localization are important. Preoperative localization is determined by colonoscopy; staging is performed with the help of transrectal ultrasound, MR (magnetic resonance), and tomography. The resectability rates increase with neoadjuvant therapy in patients with mesorectal lymph node involvement and T3 and T4 tumors [5].

Oncologic Resection Principles

There are three critical surgical margins for the surgery to be successful in rectal cancer surgery. The proximal surgical margin generally does not cause any problem since the proximal rectum and sigmoid colon are resected along with the rectum. Although the generally accepted proximal and distal surgical margin is at least 2 cm, there are studies showing that excellent results can be achieved with less surgical margins in early-stage cases today. A minimum of 2 mm is required for a sufficient circumferential margin, and this margin can be obtained with a good TME. Although the ligation of the inferior mesenteric artery from its base is the generally accepted technique in rectal cancer surgery and this technique provides sufficient oncologic resection, it may cause insufficient blood supply to the distal portion of the left colon in patients with inadequate blood circulation and

vascular diseases, which may endanger the anastomosis safety. In such cases, it may make sense to ligate the inferior mesenteric artery just distal to the left colic artery [5–8].

Preoperative Preparation

Bowel preparation is recommended to the patient 1 day before the surgery. A single-dose broad-spectrum antibiotic is administered preoperatively. The location of a potential stoma of the patient should be determined preoperatively in advance. After general anesthesia, the patient is prepared in the lithotomy (in open surgery) or Lloyd-Davies (in laparoscopic surgery) position. Depending on the preference of the anesthesiologist, a urinary catheter is inserted for the purpose of urine follow-up throughout the surgery after the arterial and venous catheters are inserted. In addition to preoperative low molecular weight heparin, antiembolic socks or pneumatic compression devices are preferred for deep vein thrombosis prophylaxis. The surgeon should definitely examine the patient before the surgery. Because the examination to be performed while the patient is awake can give surprising information since the patient can contract himself/herself, the examination performed under anesthesia can provide more enlightening information since the patient will be more relaxed [9].

Low Anterior Resection (Open)

The abdominal cavity is entered using a midline incision of about 6 cm extending from the symphysis pubis to the umbilicus, and a systematic exploration is performed to investigate the presence of metastasis in the liver and peritoneum. The patient is placed in the Trendelenburg position, and the small intestines are collected to the upper right side in the abdominal cavity and exposure is obtained [10].

For the mobilization of the sigmoid colon, the sigmoid colon is pulled medially and the white line of the Toldt's fascia is opened with the help of cautery. The parietal peritoneum is opened reaching up to the left colon proximal and the rectum proximal, and the sigmoid colon is mobilized. Meanwhile, the ureter, gonadal vessels, and hypogastric nerve should be identified and not damaged. The mobilization of the left colon and splenic flexure after the mobilization of meso contributes to a tension-free anastomosis [10].

The sigmoid colon is pulled to the left, and the mesocolon is opened from the right side of the sigmoid mesocolon over the aorta bifurcation; the incision is extended caudally to the right lateral presacral peritoneum. In this line, the inferior mesenteric artery is identified over the aorta and cut by ligating with 2/0 vicryl (polyglycolic acid) material from the aortic output or the distal of the left colic artery. At this level, the inferior mesenteric vein is also identified and cut by ligating. After the right ureter is identified and preserved, the presacral space is entered by dividing the loose areolar tissue at the promontorium level. The presacral space is enlarged caudally, and it is advanced up to the level of the levator ani muscles. The

rectovaginal septum or rectovesical space is opened, and the rectum is mobilized ventrally. In anterior tumors of the rectum, dissection should be in front of the Denonvilliers' fascia. While it is advanced in front of the Denonvilliers' fascia in more distally located tumors, the Denonvilliers' fascia is opened after the prostate is passed, and the dissection plane is continued behind this fascial plane. Otherwise, the cavernous nerves in this region may be injured. Meanwhile, care should be exerted in terms of hypogastric nerve injury. The distal rectum is closed up with stapler by descending at least 2 cm below the tumor. Angled staplers may contribute to resection in low rectal tumors [11].

After the completion of mesorectal dissection (Fig. 16.1) and transection, the piece is removed. The anastomosis technique may vary depending on the surgeon's preference. Circular staplers provide great convenience in terms of anastomosis, especially in low rectal tumors. The proximal colon stump is created with the end-to-end anastomosis technique using a circular stapler, and after the stapler's anvil is placed, it is pursed with 2/0 prolene. Then, at the rectal stump, the circular stapler is inserted and the distal rectum is perforated with the pointed guide at the end of the stapler, and the tip of the stapler is taken out in the abdomen. Meanwhile, care should be exerted not to injure the surrounding organs with the sharp guide at the end of the stapler. In females, care should be exerted to take out the circular stapler tip at the posterior of the staple line in the distal rectum. Otherwise, the vagina may

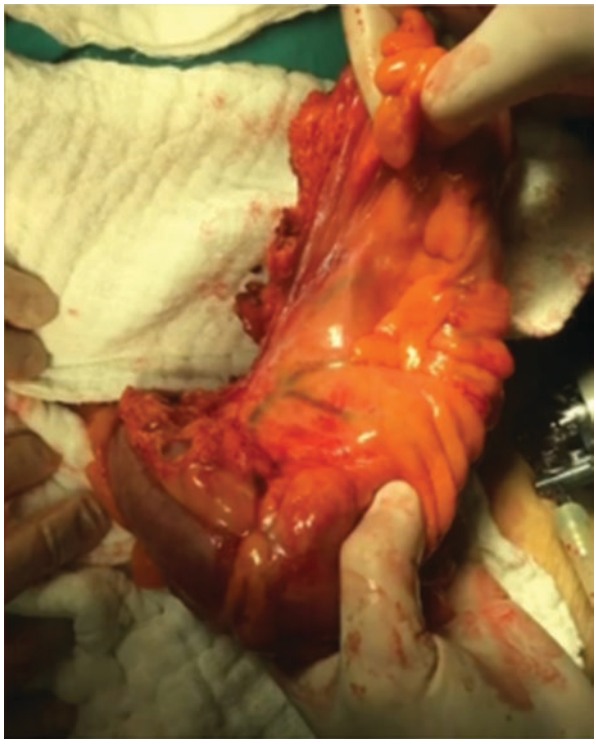

Fig. 16.1 Total mesorectal excision

be injured. Then, the circular stapler opening is coupled to the anvil in the proximal colon stump, and anastomosis is completed. Information about anastomosis safety can be obtained by checking the presence of ring integrity remaining in the circular stapler after anastomosis. Early leaks can be prevented by performing an air-fluid test with the air delivered from the rectum after anastomosis. If the test is positive, the defect should be repaired if the anastomosis line can be reached, and a protective ileostomy creation should be considered [12].

Diverting colostomy or ileostomy should be performed on very low rectal tumors, patients who received neoadjuvant therapy, patients who underwent coloanal anastomosis, and patients with obstruction or perforation [12].

Anastomosis should not be tight when doing an anastomosis. A drain should then be placed in the pelvis, and the closure should be done properly.

Postoperative Care

The patient should be mobilized as early as possible postoperatively. Early oral nutrition should be initiated. Although it is reported that bladder catheterization with foley should be performed at around 5–7 days since bladder functions will recover late after lower rectal tumor surgery, this period has been rather shortened according to the ERAS (enhanced recovery after surgery) protocols. Postoperative anastomosis leaks usually manifest themselves with fever, leukocytosis, and ileus symptoms after the postoperative fifth day. Physical examination and abdominal tomography can be utilized in the diagnosis. If a leak cannot be controlled with percutaneous interventions, a diverting ileostomy or colostomy creation should be considered [12, 13].

Sphincter-Preserving Resections

While the conventional surgical technique for low rectal cancer is abdominoperineal resection, it has become possible to perform resection by preserving the sphincter functions and anal sphincters without compromising oncological principles due to the development of various facilities. Therefore, the routine abdominoperineal resection (APR) procedure has currently been abandoned in rectal tumors at a distance of 0–5 cm from the anal verge, and sphincters are attempted to be preserved in eligible patients [14].

In some studies, when preoperative neoadjuvant therapy is administered in low rectal tumors, intersphincteric resection and coloanal anastomosis can be performed. The oncological results of this type of surgeries are equivalent to abdominoperineal resection [15].

In tumors 3 cm proximal to the dentate line, anastomosis is possible with stapler after resection, while sphincter-preserving techniques can be used in tumors with lower localization. It has been reported that intersphincteric resection can usually be performed on tumors above 0.5–1.5 cm above the dentate line [16].

Although it is controversial when the tumor involves the sphincteric muscles and pelvic floor muscles, it is generally considered contraindicated in terms of intersphincteric resection. Before performing intersphincteric resection, the patient should undergo a detailed physical examination and should be evaluated using endoanal ultrasonography and pelvic MR techniques. In local, advanced-stage tumors, tumor size can be reduced by neoadjuvant chemoradiotherapy, thereby increasing the rate of intersphincteric resectability. The continence status of the patient should be evaluated well before the surgery. While some surgeons evaluate continence with a physical examination, some refer to anorectal physiology studies [17]. In short, intersphincteric resection should not be performed in patients with preoperative incontinence that will not allow a clean surgical margin after resection and with T3–T4 tumors involving pelvic and external sphincteric muscles.

Surgical Technique

The goal is to remove the lower rectum totally by dissection from the perineum from the intersphincteric region after the rectum is mobilized using the open or closed technique. After the perianal Lone Star Retractor is installed, the intersphincteric area is entered through an incision made on the mucosa from the dentate line or the anoderm below the dentate line. The lower rectum is mobilized circumferentially with intersphincteric dissection performed with cautery or scissors and combined with the pelvic dissection plane prepared according to the oncologic principles. For a tension-free anastomosis, the proximal colon should reach the perineum. For this, it should be mobilized up to the middle of the transverse colon. Ligating the inferior mesenteric vein below the pancreas significantly contributes to mobilization. Colonal anastomosis can be performed manually or with the help of a stapler. However, diverting ileostomy or colostomy is routinely recommended after coloanal anastomosis [18, 19].

There are studies showing no difference between intersphincteric resection (Fig. 16.2) and abdominoperineal resection (Fig. 16.3) in terms of local recurrence and survival.

Laparoscopic Low Anterior Resection

After the first laparoscopic cholecystectomy surgery in the 1980s, minimally invasive surgery has rapidly developed today. Less postoperative pain in laparoscopic surgeries and shorter length of hospital stay are the reasons that make laparoscopic surgery popular. Thus, surgeries such as Nissen fundoplication and cholecystectomy have been routinely performed using the closed technique. The first laparoscopic colon resection was performed by Jacob in 1991. Since then, laparoscopic colon resections have become increasingly popular, and the frequency of performing them has increased. However, they are still not the gold standard treatment in rectal cancers [20].

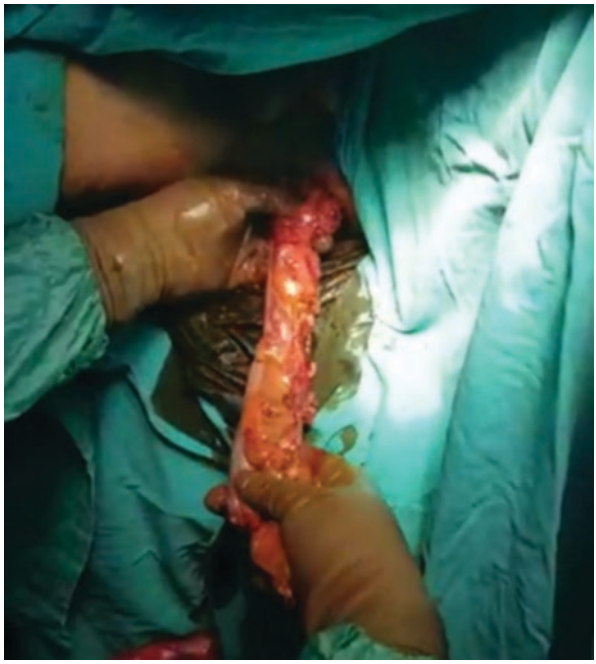

Fig. 16.2 Intersphincteric resection

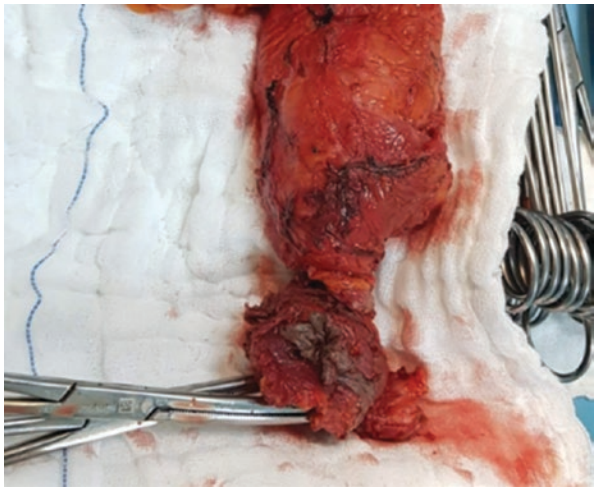

Fig. 16.3 Abdominoperineal resection piece (hourglass appearance)

Nevertheless, due to the fact that the learning curve of laparoscopic colon surgery is long and the surgeon should be able to use both hands with the same skill in order to perform laparoscopic surgeries and the surgeon needs to command laparoscopic instruments caused the colorectal surgeons not to lean toward the technique at the beginning [20].

Table 16.1 Indications and contraindications for laparoscopic colorectal surgery

Indications	Contraindications	
Cancer	**Absolute**	**Relative**
Diverticular disease	T4 tumor	Obese patient
Inflammatory bowel diseases	Large mass	History of laparotomy
Volvulus	Ileus, perforation	Peritoneal carcinomatosis
Rectal prolapse		Resectable liver metastasis
Stoma creation		

Recent studies have found no difference between rectal resections performed laparoscopically or using the robotic technique and open surgery. Due to technological developments, the frequency of using laparoscopic colorectal surgery in current surgery has gradually increased. The increasing interest in laparoscopic colorectal surgery has resulted in the recognition of various problems. Complications that may develop during the surgery and secondary mortality and morbidity are the most significant of these problems. The most important principles to prevent these are the surgeon's learning curve and experience. Various indications and contraindications for laparoscopic colorectal surgery are given in Table 16.1 [21].

Preoperative Preparation

The preoperative preparation is the same as in open surgery. The patient is placed in the Lloyd-Davies position. Antiembolic socks and preoperative low molecular weight heparins are used for deep vein thrombosis prophylaxis.

Patient Position and Trocar Insertion Sites

After the patient is prepared in the Lloyd-Davies position and fixed to the table, the surgeon and assistant operate on the patient's right side. The monitor should be on the left side of the patient at the level of the left hip. The trocar insertion sites are shown in Fig. 16.4.

Then, inside the abdomen is visualized by a 10-mm trocar after creating pneumoperitoneum through the incision made above the umbilicus. The inside of the abdomen is explored. The presence of metastasis in the liver is checked. The intra-abdominal pressure is adjusted to be 12–14 mmHg. The patient is positioned on about a 15–30° incline. The patient is rotated at about 15° so as to turn to the surgeon (right shoulder down). This position contributes to move away the small intestines from the surgical site. After placing the omentum between the transverse colon and the stomach, the small intestines remaining in the surgical site are collected in the right quadrant of the abdomen. Thus, the surgical site is emptied. Mesorectal dissection can be started by inserting other trocars [22–24].

The sigmoid colon meso is retracted upward and caudally, and deperitonizing the sigmoid colon meso over the promontorium, it is opened reaching up to the area

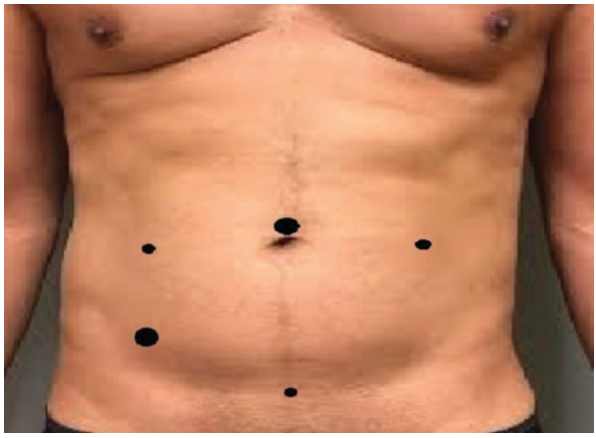

Fig. 16.4 Trocar insertion sites

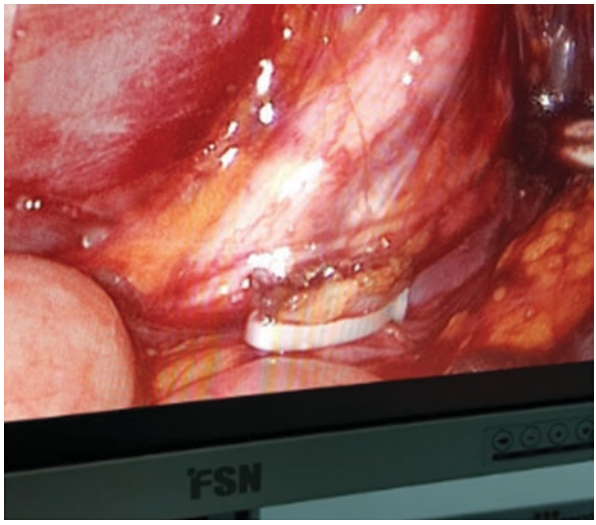

Fig. 16.5 Visualization of the ureter

where the inferior mesenteric vein enters in the lower part of the pancreas. The inferior mesenteric artery (IMA) is exposed. By preserving the hypogastric nerve structures under the IMA, the Toldt's fascia is dissected medially to reach up to the Whiteline. Meanwhile, the left ureter and left gonadal veins should be visualized and preserved. Figure 16.5 shows the visualized ureter [22–24].

Controversies about from where to ligate the inferior mesenteric artery in the ligation of vascular structures are ongoing, and it has not yet been clarified from where it should be ligated. While some surgeons suggest that the autonomic nerves will be less damaged by recommending to ligate it from the distal of the left colic artery, a group of surgeons prefer to ligate the IMA from its origin by stating that the ligation of the inferior mesenteric artery from the distal of the left colic artery will not provide sufficient oncological resection. Recent studies have shown that ligation

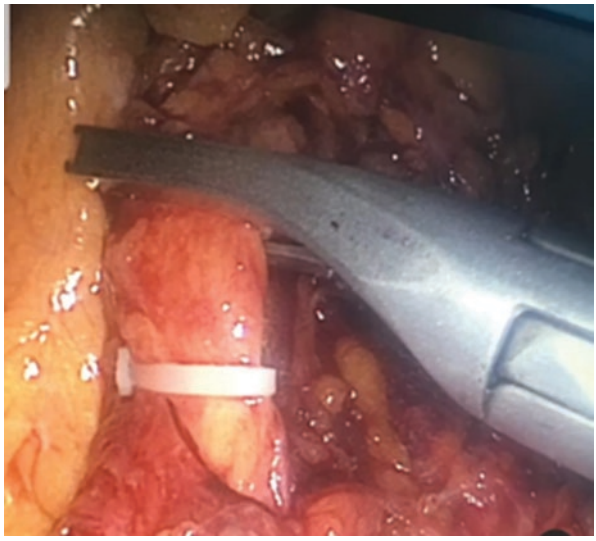

Fig. 16.6 Clipping of the IMA (high ligation)

of the IMA from its origin does not damage autonomic nerves. By ligating the IMA from its origin, the colon can also be mobilized better, thereby providing a tension-free anastomosis. The IMA is then clipped from where it originates from the aorta (Fig. 16.6) or cut using vascular sealing instruments. Subsequently, the inferior mesenteric vein is clipped under the pancreas and cut [22–25].

Then, the colon meso is mobilized from medial to lateral. Meanwhile, caution should be exercised in terms of autonomic nerve injuries. The mobilization is performed by advancing through the avascular area over the Toldt's fascia. It should be mobilized reaching up to the Whiteline and splenic flexure at the lateral side. With the aim of mobilizing the rectum, the distal sigmoid colon is gripped and pulled toward the abdominal wall. Thus, the rectum meso becomes tense. The avascular reticular structure appears right in front of the sacral promontorium. Expanding this area makes it easier to identify the hypogastric nerves with the traction applied. At this stage, it is important to go through the presacral avascular area. Meanwhile, we can encounter presacral arterial and venous structures. Excessive traction during this time can lead to rupture in the presacral plexuses. The hypogastric nerves are located under and in the medial of both ureters. At this stage, it is important to remain in the right plane in order to provide oncologically adequate resection and not to damage the presacral vascular structures and the hypogastric nerves. After the posterior rectum is mobilized, the rectum is mobilized from the medial of the right ureter. After obtaining mobilization in this way, the sigmoid colon is suspended on the right medial side, and the rectum is started to be mobilized from the left side. The lateral peritoneum is mobilized beginning from the Whiteline of the sigmoid colon and advancing up to the distal of the rectum. Thus, the rectum is mobilized from both sides and posteriorly. The rectovaginal septum or rectovesical space is opened, and the rectum is mobilized ventrally. In anterior tumors of the rectum, dissection should be in front of the Denonvilliers' fascia. While it is advanced in front

of the Denonvilliers' fascia in more distally located tumors, the Denonvilliers' fascia is opened after the prostate is passed, and the dissection plane is continued behind this fascial plane. With the magnification provided by laparoscopy, the structures here are evaluated better. In this way, the cavernous nerves in this area are visualized better, reducing the risk of injury. Posterior dissection ends by exposing the rectal wall under the vaginal wall in females and on the prostate base in males. In this phase, whether it is reached, the prostate base and the location of the tumor are evaluated with the help of rectal examination from the bottom [4, 22, 24, 25].

It is beneficial to mobilize the splenic flexure for a tension-free anastomosis before proceeding to the transection stage. The splenic flexure is mobilized by dividing and reducing the lateral peritoneum of the left colon and the splenic flexure from the spleen. Meanwhile, care should be exerted not to injure the spleen. If the tumor can be removed by low rectal resection, the rectum is cut by descending at least 2 cm below the tumor with an endolinear stapler inserted into the pelvis (Fig. 16.7). If the under of the tumor cannot be accessed by a stapler, intersphincteric resection may then be considered. Afterwards, the abdomen is entered through a suprapubic transverse incision, and the rectum is taken out of the abdomen by laying a wound protective drape on the wound site. If APR or intersphincteric resection will be performed, this incision is not needed. The piece can be taken out of the abdomen from the perineum. After the specimen is taken out of the abdomen through the suprapubic incision, the proximal colon side is cut, and the specimen is mobilized and excised. A purse suture is made in the opening of the proximal colon loop, and an appropriate anvil is placed. The colon is delivered to the abdomen through the suprapubic incision. The suprapubic incision is closed up, and the abdomen is reinsufflated. For a tension-free anastomosis, it is checked whether the proximal colon loop is easily aligned with the rectal stump. For anastomosis safety, it is checked whether there are ischemic changes in the proximal colon. The circular

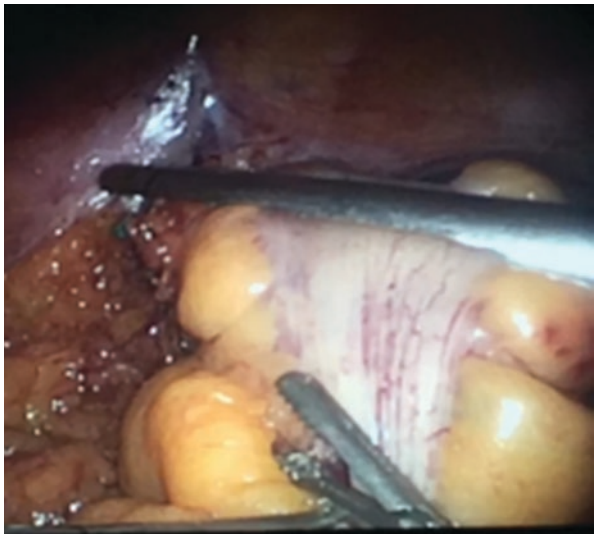

Fig. 16.7 Cutting the sigmoid colon with endostapler

stapler is removed from the distal rectal stump posterior under the camera vision (Fig. 16.8). In the meantime, applying too much force to the circular stapler may result in dehiscence in the distal stump. Afterwards, continuity is provided by circular stapler coupled to the anvil (Fig. 16.9). In the meantime, care should be exerted for the colon not to rotate by being torsioned. The integrity of the rings is checked. The integrity of the rings is important for anastomosis safety. The pelvis is then filled with water to carry out an air-fluid test. It is checked whether the air delivered from the rectum goes into the abdomen. If there is a leak in terms of anastomosis

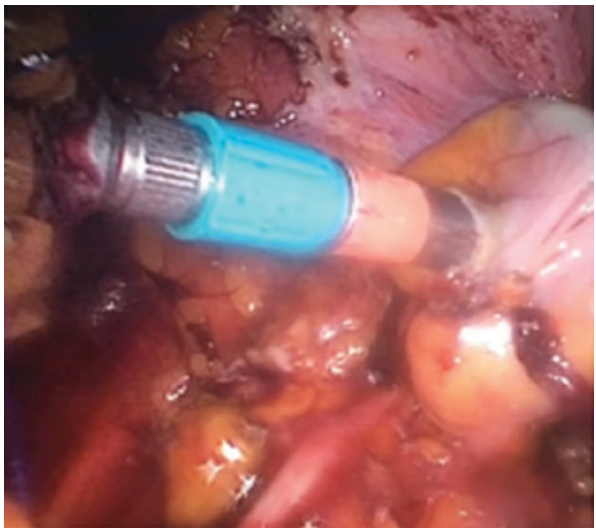

Fig. 16.8 Removal of circular stapler from the rectum

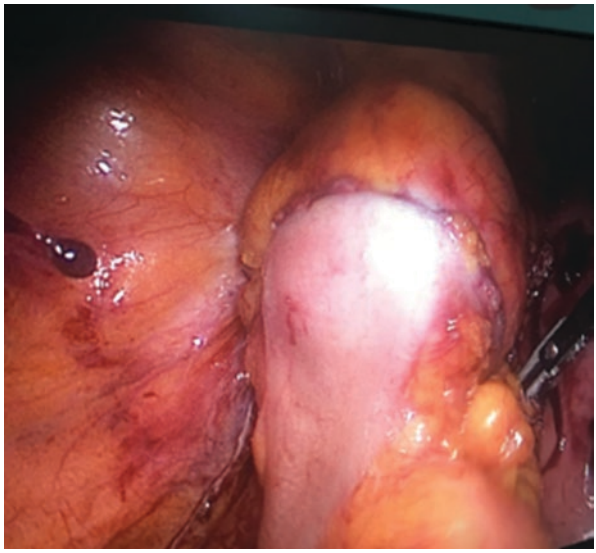

Fig. 16.9 Completion of anastomosis with circular stapler

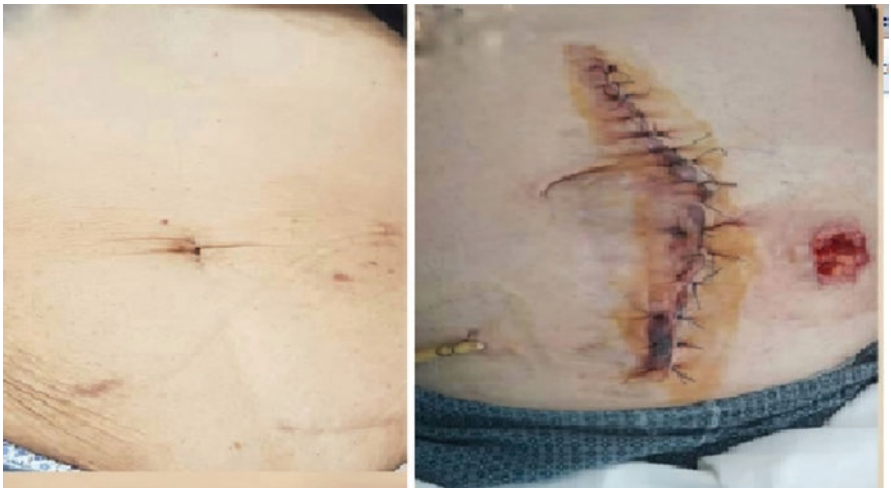

Fig. 16.10 Comparison of laparoscopic–open surgeries

safety and it is visible, it should be repaired, and if it is not visible to the naked eye, a diverting ileostomy should be opened [12]. For tumors 5 cm below the dentate line, a diverting stoma is required. Figure 16.10 shows the postoperative image of patients who underwent open and laparoscopic rectal surgery.

Postoperative Care

After the patient recovers postoperatively, the nasogastric tube is pulled out. Clear watery foods are started at the 12th hour postoperatively. Following the operation of preserving ileostomy, soft watery foods can be started. Deep vein thrombosis prophylaxis is continued for 1 month.

Complications

While the complications may be Veress needle- and trocar-related intestinal vascular injuries generally seen in laparoscopic surgery, the surgery-related complications are the same as in open surgery.

Local Excision

While local excisions, which were the procedure used for T1 and T2 tumors, were previously performed by cutting the anal sphincter (transsphincteric) or using the posterior parasacral approach, these techniques have currently been replaced by transanal endoscopic microsurgery.

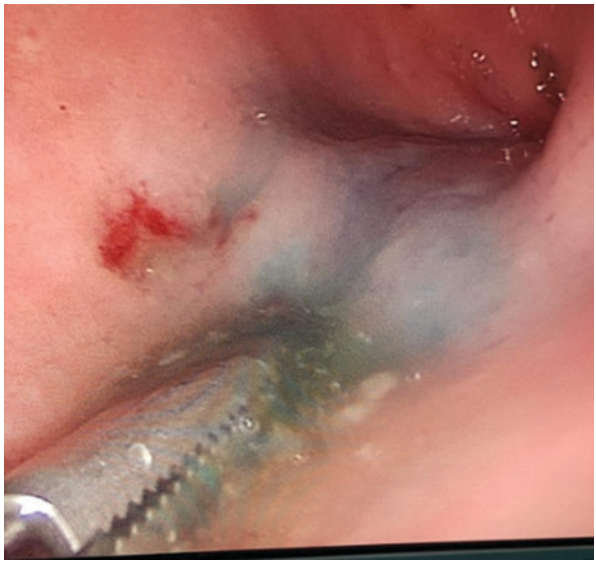

Fig. 16.11 Excision of the tubulovillous adenoma that is swollen and is not clearly distinguished from the mucosa using TAMIS (transanal minimally invasive surgery) after being marked with methylene blue

Table 16.2 Indications for local excision are explained in this table

Indications for local excision
Tumors smaller than 4 cm
Tumors maximum 8 cm proximal to the anal verge
Well or moderately differentiated tumors
Mobile and non-ulcerated tumors
Absence of perirectal and presacral lymph node involvement on ERUS and MR
Tumor less than 1/3 of the circumference of the rectal wall
T1 and T2 tumors

With the transanal minimally invasive surgery (Fig. 16.11), lesions about 18 cm proximal to the dentate line can be removed by local excision. While TEM is as successful as radical surgery in T1 tumors, the local recurrence rate in T2 tumors is high in many series. The indications for local excision are given in Table 16.2 [26].

Who Requires a Diverting Stoma in Rectal Cancer Surgery?

Anastomotic leak is the most feared complication in low anterior resection surgery. Considering the literature, the rate of anastomotic leak varies between 3% and 20%, while the associated mortality rate varies between 2.1% and 22%. Anastomotic leaks in patients increase the length of hospital stay, cost, morbidity rate, as well as recurrence rate since it delays the time to start adjuvant chemoradiotherapy. Therefore, opening a diverting stoma has frequently become a current issue in patients at high risk of anastomotic leak (Table 16.3) [27].

Table 16.3 Risk factors for anastomotic leak

Risk factors
Malnutrition
Receiving steroid
Obesity
Intraoperative hemorrhage
Male sex
Anastomosis close to the anal canal
Preoperative/intraoperative radiotherapy
Emergency surgery (obstruction, perforation)

Minor or major complications may occur in patients in whom we created a diverting stoma to prevent anastomotic leak. The most common stoma complication is peristomal skin irritation. It may cause distress to impair the patient's quality of life. In addition, many complications such as kidney failure due to dehydration, wound site infections, collapsed stoma, and parastomal hernia at a rate of 15–40% can be encountered [28].

Do Diverting Stomas Reduce the Rate of Anastomotic Leak?

To date, there are many retrospective studies conducted on anastomotic leaks and diverting stomata. These studies are thought to be subjective as they are retrospective. The most effective studies on these are the Cochrane analyses. When the 2010 Cochrane study that analyzed anastomotic leaks, 30-day mortality, long-term mortality, major/minor complications, and length of hospital stay by including six studies is examined, it was found that diverting stomas reduced the risk of anastomotic leak, but did not have an effect on reoperation and mortality [29–31].

Which Type of Diversion Should We Use?

The most common types of diversion used in diverting stomas are loop ileostomy and loop colostomy. There are many studies on their advantages and disadvantages over each other. In the study by Rondelli et al. on 1529 rectal cancer patients, it was found that loop ileostomy had a lower risk than loop colostomy in terms of prolapsus and sepsis, while other complications were equal in both groups. In the meta-analysis of ten studies by Paschalis et al. investigating loop colostomy and loop ileostomy, the rates of wound site infection, skin irritation, prolapsus, anastomotic leak, fistula, high flow, sepsis, and incisional hernia were compared. As a result of the study, the rates of wound site infection and incisional hernia were higher in patients with colostomy, while high-flow fluid loss was higher in patients with ileostomy, and there was no significant difference between the two groups in other parameters [29–31].

In conclusion, given the previous studies in the literature, there are different results on prolapsus and infections, whereas current studies have not found

superiority between ileostomy and colostomy. If an ileostomy is to be chosen, the patient's general condition, age, and flow rate to be lost should absolutely be taken into account. Besides, the practice and experience of the surgeon is of great importance.

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Robotic Surgery in Colorectal Cancers

17

Gokhan Akbulut

Robotic Surgery in Colorectal Cancer from Past to Future

History of Robotic Surgery

In 1982, the first surgical robot was developed in Canada, and a year later it performed its first surgery [1, 2]. There have been rapid developments in this field, since the 1990s. Robotic surgery has undergone a major evolution. PROBOT was used in the UK to assist prostate surgery in 1992. ROBODOC was used in 1992 to assist in orthopedic surgery. AESOP and ZEUS robotic surgical systems have been developed for gynecological and cardiac surgeries (Computer Motion Inc., Santa Barbara, CA). The da Vinci system (Intuitive Surgical Inc., Mountain View, CA) (Fig. 17.1) that we use today is based on telesurgery and intended for use in battlefields or long distances and was developed in 1999 and approved by the Food and Drug Agency (FDA) in 2000. Robotic operations routinely popularized and spread in the 2000s through a console [1–3].

Advantages of Robotic Surgery

The first laparoscopic surgery in 1988 marked a technical revolution in surgery [4–6]. This revolution resulted in better postoperative cosmetic results and less postoperative pain, shorter hospital stay, and lower incisional hernia risk. Laparoscopic surgery became widespread. It was performed in many areas of surgery. However, the inability to open arms created problems in narrow and deep places. In laparoscopic operations such as left colectomy, there were about 180 learning curves. Likewise, anastomosis and microsurgical procedures were extremely difficult. Robotic surgery has reduced this problem, especially with its small arms opening up

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Fig. 17.1 da Vinci Robotic System (**a**) the console, (**b**) video processor, (**c**) robotic arms

to 270°. It prevented the reflection of fine tremor in the hands to the image and activity. The surgeon can sit in the master console and perform surgery in a less stressful and ergonomic environment, even sipping coffee, within surgical slave system. The image gives a better sense of depth compared to laparoscopy with dual-3 chip camera, magnified 10–12 times, and is three dimensional. The robotic arms are made by simulating the wrist joint, but can be opened more than that. It can reach all directions precisely. This gives very good dissection and suturing possibilities in deep and narrow areas. It allows micromovements and microsurgery. Most of these features are almost impossible in conventional laparoscopy [7]. Adequate removal of mesorectal incision is the same as open surgery and laparoscopic surgery. Complication rates are acceptable [8, 9]. Apart from all these, it gives the chance to perform telesurgery (e.g., between different continents).

Disadvantages of Robotic Surgery

Despite all these developments, robotic surgery has its own disadvantages as in every new system. The future of robotic surgery will provide improvements to eliminate these disadvantages.

Robotic surgery is used safely all over the world and has been shown to be used in all areas of surgery. However, the device is too large; the need for specially trained personnel for the use of the device, the tactile, and haptic responses (sense of touch by the surgeon) cannot be as clear as laparoscopy or open surgery, positioning and re-docking for each different anatomical regions, docking of the operation times, and prolongation due to patient position placement and cost more than laparoscopic surgery. da Vinci Robotics systems (Intuitive Surgical Inc., Sunnyvale, CA, USA) cost approximately US$ 0.5 million, with an average case cost of US$ 850–1500 [9]. Another important issue is the learning curve. Although different for each surgery, there is a shorter learning curve than conventional laparoscopy. According to different studies, it varies between 8 and 150 cases [7]. On the other hand, the costs of robotic surgery prevents it from taking part in assistantship training.

Robotic Surgery Technique

In colorectal robotic surgery, from medial to lateral dissection is preferable. This method, which is widely used in laparoscopy, is also used in robotic surgery. In contrast, it is easier to work from lateral to medial in robotic surgery than laparoscopic surgery.

Right Hemicolectomy

The robot is located on the right side, and half-moon-shaped ports are placed (Fig. 17.2). The distance between the port catheters is as large as a hand palm (5–6 cm).

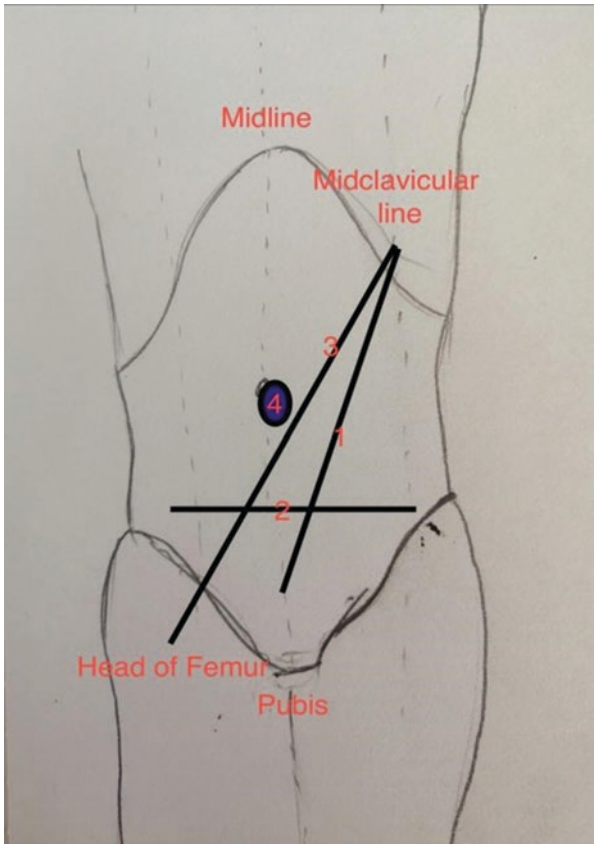

Fig. 17.2 Right hemicolectomy port locations

The right colon is suspended, and its mesentery is stretched so that the right colic artery becomes visible. After opening the peritoneum, the artery is dissected. Hook cautery or scissors can be used when opening the peritoneum. The third arm suspends the colon; then proximally from the opened window, dissecting over the pancreas over the duodenum, after the liver relief becomes visible, the hepatic flexure is reduced by sharp dissection and is descended distally to release the right colon and terminal ileum. If necessary, the omentum minus is opened and proceeded to the middle of the transverse colon. Cattell Braasch maneuver, following the tipping of the right colon and the vein of the terminal ileum, without interrupting the veins leading to the tissues. The dissection includes cutting the mesenteric structures up to the junction of second and third part of duodenum. In this way the right colon will be fully mobilized. The duodenum will be clearly visible through the pancreas. Under normal conditions, it is sufficient to free the right colon up to the common bile duct. The artery can be held twice using either long clips or locked clips. It can only be sufficient if it is sealed proximally twice distal once by sealing. It should be considered that there may be ureteral tissue at the level of the iliaca communis and the dissection plan should be carried out over the endopelvic fascia and the ureter should be searched if necessary.

If the right colon is devascularized at a distance of 5 cm from the terminal ileum, the area of the onset third of the transverse colon and the head of the pancreas should be fully visible.

Anastomosis and resection can be performed in the abdomen or with a small incision outside the abdomen. Robotic surgery technically makes it easier to perform anastomosis intracorporeally [10, 11].

Should İntracorporeal or Extracorporeal Anastomosis Be Performed?

It is thought that intracorporeal anastomosis is better in terms of the amount of bleeding, return of bowel movements, narcotic need, duration of hospital stay, and perioperative morbidity performed in right hemicolectomy [11].

Transverse Colectomy

When performing a transverse colectomy, the robot approaches the patient's head, and the port locations are placed upward from the lower part of the abdomen. Retractor port and assistant port can be entered more lateral and more forward when needed. The distance between the ports is planned to prevent the arms from overlapping. The omentum is pushed proximally, the patient's head is raised, and the middle colic artery is clipped away from the proximal part of the SMA. Hepatic flexure and splenic flexure should be released. A window should be opened from the edge of the middle colic artery, and the superior border of the pancreas should be used and the omentum majus and minus should be entered. The blunt dissection should be performed over the pancreas to the right and left side, followed by a sharp separation of the colon meso at the level of the tail and head of the pancreas. Extracorporeal anastomosis can be performed after the ascending and descending colon is released enough to be anastomosed, and surgical margin is obtained and taken out of the abdomen with intracorporeal or small incision. In anastomoses in the abdomen, anastomosis can be performed with the help of sutures with stapler or robot arms [12, 13].

Left Hemicolectomy and Rectal Resection

It is preferable to start left hemicolectomy by releasing splenic flexure in robotic surgery. Conventional laparoscopically, the splenic flexure can be dropped or the robot can be placed in the lower right region approaching the ports to cross the abdomen. In this case, it may be possible to complete the operation with a single docking in cases where the splenic flexure is not very proximal. Otherwise **two** second **docks** docking will be required.

When the splenic flexure is released, the transverse colon is removed and a window opens to the left of the middle colic artery. The pancreas is found and the omentum majus is entered. Pancreas is sealed over the tail and proceeded with sharp dissection. Section 4 of the duodenum is dissected, the inferior mesenteric vein is

clipped and cut from the edge of the treitz. The lower end of the spleen will be reached when blunt dissection is advanced from this area. Subsequently, the omentum is sealed under the great curvature of stomach by preserving the gastroepiploic vessels, and the splenocolic ligament is separated from the lateral by medial sharp dissection while preserving the splenic artery [13]. Afterwards, the left colon is released from the endopelvic fascia plan down to the pelvis by blunt dissection; if necessary, the inferior mesenteric artery is ligated and passed into the pelvis.

In women, the uterus is sutured to the abdominal wall. It should be monitored and maintained along the traction of the ureters on both sides. Tissue dissection in the pelvis should be inserted through the posterior and progressed through blunt dissection to the end of the coccyx. Avascular **plan area** should be used just in front of the Waldeyer fascia. In some cases, it may be necessary to seal the superior rectal artery. Subsequently, lateral ligaments are cut by sealing the right and left sides near the **mesorectal plan mesorectum** and in males dissection by protecting the avascular **plan area** in front of the seminal vesicles, but sometimes by staying closer to the mesorectum (beside the risk of bleeding) in order to reduce nerve injury [14].

Robotic surgery has the advantage of less bleeding and a more comfortable surgical dissection because of the arms opened in the distal rectal dissection. As with any surgical type, dissection of male (narrow pelvis), obese patients and bulky tumors is difficult.

The ligament between the coccyx and anus is lowered posteriorly before entering distal rectum, the rectum is pulled proximally through the assistant port, and the bladder should be ruled out. The anus is then **advanced** dissected to the dentate line and controlled with anal digital examination.

The rectum is seperated and taken out of the abdomen with a small pelvic incision. It is then anastomosed inside the abdomen with staples or robotic sutures [14].

Taking the Specimen Out of the Abdomen

The specimen is separated by steples if an intracorporeal anastomosis is to be performed and can be removed from the vagina, from the rectum, or by a small incision in the abdomen. To prevent the spread of tumor cells, the specimen should be placed in the endobag. Dressings, covering the abdominal wall, such as wound-protective retractors, should be used.

Anastomosis can be performed outside the abdomen in the right and transverse colon. In this case, the specimen is taken out of the abdomen by a small incision from the area closest to the anastomosis line, where anastomosis can be performed by **hand** extracorporeally **or with or without** stapler. The abdominal wall should be protected with plastic covers.

In left hemicolectomy and rectum resections, the specimen taken into the endobag can be removed from the rectum, vagina or abdomen; anastomosis can be done with the help of robotic arms or staples [13, 14].

Which İncision Should Be Performed to Minimize the Risk of Hernia?

Midline incisions can be performed by separating the pararectal muscle, Pfannenstiel incision, ostomy area, and NOSE (natural orifice subtract extraction such as vagina or rectum). In these cases, midline incision has the highest incidence of hernia (8.9%). Fifty-five percent of these cases required surgery, and these complications were seen more frequently in patients with high body mass index [15].

Anastomosis

If anastomosis is to be performed with robotic arms, interrupted sutures or continuous sutures may be used. There are not enough studies on the differences between these methods in robotic surgery. However, there was no difference in open surgical methods and experimentally. Stapler anastomosis is similar to laparoscopic anastomosis.

The same materials for suturing used in open surgery can be used. In addition, barbed V-Loc sutures (Med-Tronic, USA) are generally preferred in minimally invasive surgery. Such sutures reduce the need for knotting.

Does İndocyanine Green (Firefly) İncrease Anastomosis Safety?

Indocyanine green (ISG) is a chemical substance that instantly shows intestinal circulation in fluorescent light after intravenous injection. Areas with good perfusion appear green because blood circulation is present. Tissue perfusion of unstained areas is considered to be poor. It is a cheap method. The rate of leakage in ISG-treated anastomoses is found three times less [16].

Is Laparoscopic Surgical Experience Necessary?

Laparoscopic colon surgery has the longest learning curve among surgical techniques. Approximately 180 cases are required. This number is recommended for the reduction of splenic flexure and for distal rectal surgery. However, this requirement for robotic surgery is controversial. It is thought to be a shorter learning curve, but there is not enough research on this subject [17–19].

Does Robotic Surgery Süperior to Effect Voiding and Sexual Function?

In robotic surgery, the return of urinary and sexual functions takes less time than laparoscopic surgery [20, 21].

Kim et al conducted laparoscopic total mesorectal excision in a prospective study of 39 patients by robotic surgery. Urogenital functions were assessed by uroflowmetry, a standard questionnaire of the international prostate symptom score (IPSS) and international erectile function index (IIEF), before and 1, 3, 6 and 12 months after surgery. Robotic TME for rectal cancer was associated with normal voiding and earlier recovery of sexual function compared to patients treated with laparoscopic TME. However, the authors reported that this result should be confirmed by larger prospective comparative studies [20].

In a meta-analysis, Broholm et al. evaluated four non-heterogeneous studies involving 152 patients in the robotic group and 161 patients in the laparoscopic group. At 3-month and 6-month follow-up, IIEF scores were better in robot-assisted surgery than in laparoscopic surgery [21].

Complications of Robotic Surgery

Complications specific to robotic surgery have not yet been described in the literature. Complications seen in open and laparoscopic surgery, i.e., anastomotic leakage, voiding, sexual dysfunction, and incontinence robotic surgery, are also present. However, the return time seems to be shorter [14–21].

Although there is no complication in the literature yet, strong robotic arms have necessitated careful use. For this reason, it is necessary to receive training in robotic surgery until it gains competence in both dry and wet laboratories.

Although there are no definite contraindications of robotic surgery, it is necessary to be careful in cases where increase in intra-abdominal pressure is harmful, in severe heart and lung diseases which may be damaged in Trendelenburg, borderline hepatic insufficiency, and high intracranial pressure. This situation is valid for all minimally invasive surgical conditions with pneumoperitoneum [22–24].

Conclusion

Robotic surgery provides long and thin arms, angular structure, and surgical technique advantage in deep places in narrow areas. The learning curve is claimed to be shorter than laparoscopic colectomy. It provides ease of operation especially in pelvic surgery involving the rectum. The development of the device seems to compensate for its shortcomings such as docking time, change of position, development of haptic sensations, and cost.

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Management of Colorectal Surgery Complications

18

Ramazan Serdar Arslan, Lutfi Mutlu, and Omer Engin

Colon and rectum make up the last part of the gastrointestinal system. Although its average length varies, it is about 1.5 m. Colon and rectal diseases constitute an important part of gastrointestinal system surgery. Hemorrhage, perforation, obstruction, and malignancy constitute a big part of surgical etiology. Colorectal cancers are the third most common type of cancer diagnosed in women and men in the United States [1]. In general, the risk of progressing colorectal cancer is 4.49% for men and 4.15% for women during life. This risk is slightly lower among women than men [1, 2]. Regardless of gender, colorectal cancer ranks fourth among newly diagnosed cancer types and second in cancer-related deaths [2]. Complications after colon and rectal surgery have a special importance in gastrointestinal system surgery due to high morbidity and mortality [3]. Complications seen in laparoscopic or open surgeries are similar. Complications after colorectal cancer are more common than operation complications due to benign etiologies [3]. Due to the anatomy of the rectum and the characteristics of the surgical technique, the complication and mortality rates are higher than the colon [3–5]. There are different classifications for complications in colorectal surgery [4]. Intraoperative complications, postoperative complications, early complications (postoperative first week), late complications (complications after 1 month), surgical and nonsurgical complications, etc.

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Complications Due to Anastomosis

Anastomotic Leakage

The main cause of anastomosis-related complications is leaks in the anastomosis line. The definition of anastomotic leakage (AL) varies from a puncture hole to complete separation. It is frequently seen in postoperative 4–6 days. The major cause of large splits and full-thickness separation is ischemia in the bowel wall [6]. The rates of anastomotic leakage after emergency surgery are higher than elective surgery. Systemic (malnutrition, diabetes, hypoalbuminemia) and local (foreign body in the anastomosis line, insufficient bowel cleansing) factors are effective on anastomosis healing. Another important factor in AL is the anastomosis technique. Stretching of the anastomosis tips, impaired feeding of the anastomosis tips, foreign bodies in the anastomosis line, and poor anastomosis technique increase the possibility of leakage. In a good anastomosis line, the fat tissues in the bowel ends should not be dissected more than 4–5 mm, and it should be seen that the cut ends have bleeding in leakage style. Inadequate rectal stump feeding after rectal resection may result in AL as well [6–8]. Rectum leaks often occur in the middle back line [8]. AL has been reported to be caused by external compression of the fluid leaking into the pelvis. There are also reports of leakage in cases where negative pressure drains are placed in the pelvis [9]. Fecal fistulas after AL close spontaneously in 4–6 weeks if there is no underlying systemic problem [10]. There was no difference between the surgical techniques: hand-sew, stapler, single-double layer sutures, interrupted-continuous sutures [7–10]. Mc Dermott et al. [10] reported that AL rates were most frequently seen in coloanal and colorectal anastomosis (5–19%) and at least in ileocolic and enteroenteric anastomosis (1–4%). Clinical, physical examination, laboratory tests, and imaging methods are used in the diagnosis of AL. In stapler anastomosis separations, stapler rings are seen as discrete in X-ray radiography. Water soluble contrast enema (WSE) can be used to detect extraluminal discharge. The presence of anastomosis line on the X-ray after rectal contrast does not mean that there is no leakage. After anterior resection (AR), AL can be detected in 18–43% radiographically by using enema with gastrografin [9–11]. Anastomotic leaks can be classified as dendritic, horny, saccular, and serpentine according to their morphological features in the radiographs taken using WSE [11, 12]. Also, anastomotic leaks, pelvic hematoma, fistula, stricture, and intra-abdominal collections can be detected with abdominal tomography using WSE [13–15]. Based on a literature review, it is found out that there are reports showing procalcitonin and C-reactive protein (CRP) can be used in early AL in inflammatory and biochemical tests [16, 17]. CRP is an acute phase reactant synthesized in the liver [16]. It increases in infectious complications and inflammatory events after abdominal surgery. A normal or low measurement result indicates a low probability of AL [16]. Therefore, serum CRP value between 3 and 5 days postoperative is helpful as a negative predictive test [16]. Sua et al. [17] reported that procalcitonin level after elective colorectal surgery could be used as a negative predictor in anastomotic leakage, such as CRP. They found out that procalcitonin level on postoperative fifth day was significant [17]. Anastomotic leakage

may be asymptomatic or life-threatening. The treatment algorithm changes according to the patient's examination findings and laboratory values [5–10]. After the operation, tachycardia, fever, tachypnea, oliguria, changes in consciousness, abdominal distention, leukocytosis, and CRP elevation in laboratory tests are indicative of AL [5–10]. In the treatment of AL, treatment algorithm changes according to factors such as location of leakage, patient's clinic, and degree of leakage. The patient underwent exploratory laparotomy in the presence of diffuse intestinal content in the abdomen and signs of sepsis and peritonitis. In exploration, primary repair, drainage, and proximal diversion can be performed if the anastomosis defect is <1 cm and the anastomosis supply is good. If the defect is <1 cm but anastomotic feeding is poor, anastomotic resection, reanastomosis + proximal diversion, or anastomosis resection may be performed followed by end stoma.

In cases with defects >1 cm, anastomosis resection, reanastomosis, proximal diversion, or resection of anastomosis and end stoma may be performed. If anastomosis cannot be reached due to perioperative severe inflammation and intestinal adhesion, drainage and proximal diversion may performed. If the intestinal leakage is minimal and if there is no deterioration in the clinic, conservative treatment can be performed by frequent examination with antibiotherapy. If the patient's examination deteriorates during conservative treatment, percutaneous drainage procedures or laparotomy can be performed. In case of minimal leakage and radiological abscess <3 cm, broad-spectrum antibiotic and bowel rest are applied. Percutaneous drainage or laparotomy can be performed if there is no improvement according to clinical follow-up. If the abscess is >3 cm, broad-spectrum antibiotherapy is initiated with percutaneous drainage (Fig. 18.1). If no clinical improvement is detected, laparotomy is performed [18–20].

An enterocutaneous fistula (ECF) is an aberrant connection between the intra-abdominal gastrointestinal (GI) tract and skin/wound [21]. ECF can be classified as high, moderate, and low-output fistula based on the 24-h output rate [21]: high

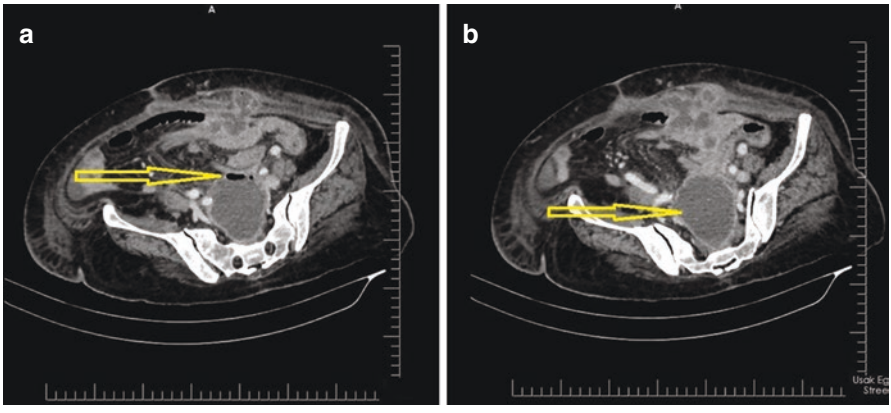

Fig. 18.1 Pelvic abscess in total proctocolectomy and ileoanal j pouch operation. (**a**) Air in the abscess pouch. (**b**) Abscess

output >500 mL/24 h, moderate 200–500 mL/24 h, and low output <200 mL/24 h [21]. Great part of ECFs is iatrogenic (75–85%); between 15 and 25% occurred spontaneously. AL, adhesiolysis, and inflammatory bowel disease (IBD) are the other important in etiology [21, 22]. In the etiology of spontaneous fistulas, malignancy, appendicitis, diverticulitis, radiation, actinomycosis, and ischemia are prominent [21, 22].

There have been reports in the literature that fistulas were closed in 19–92% without surgical intervention with good wound care and parenteral nutrition [23, 24]. Predictive factors for spontaneous fistula closure are 24-h flow rate less than 200 mL, fistula length > 2 cm or end fistula, no sepsis and no electrolyte imbalance, serum transferrin level > 200 mg/dL, and absence of intestinal obstruction [24]. Ileal, jejunal nonsurgical causes, inflammatory bowel diseases, history of radiation, fistula tract less than 2 cm, flow rate more than 500 mL in 24 h, multiple fistula, intestinal obstruction sepsis, fluid electrolyte disorder, and serum transferrin level < 200 mg/dL has a negative effect on fistula closure [24] (Figs. 18.2 and 18.3).

Bleeding in the Anastomosis Line

Bleeding in the colorectal, colocolonic, or ileocolic anastomosis line is rare. Surgeons want to see bleeding in the anastomosis line for good perfusion of the anastomosis. Mostly, these bleedings stop at the end of the anastomosis. The incidence of bleeding in the anastomosis line ranges from 0.58 to 9.6% in the literature [25–27]. Bleeding time varies in cases with stapler anastomosis. Stapler line

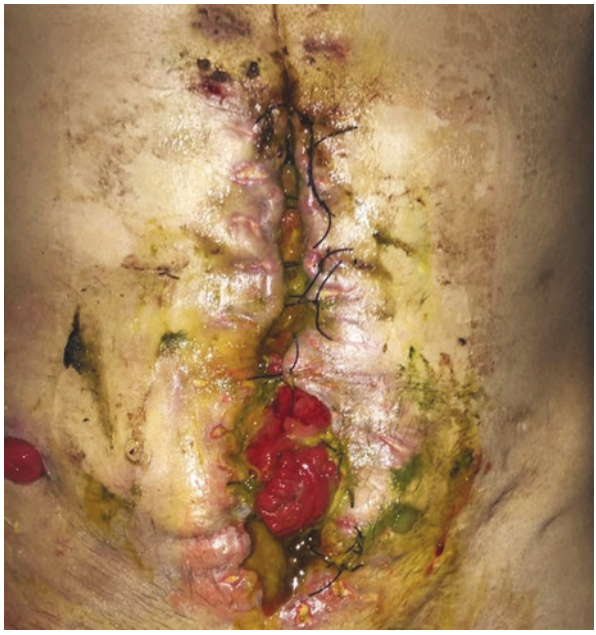

Fig. 18.2 A 46-year-old man, inflammatory bowel disease, operated for intestinal perforation and abscess. End ileostomy and enterocutaneous fistulas are seen

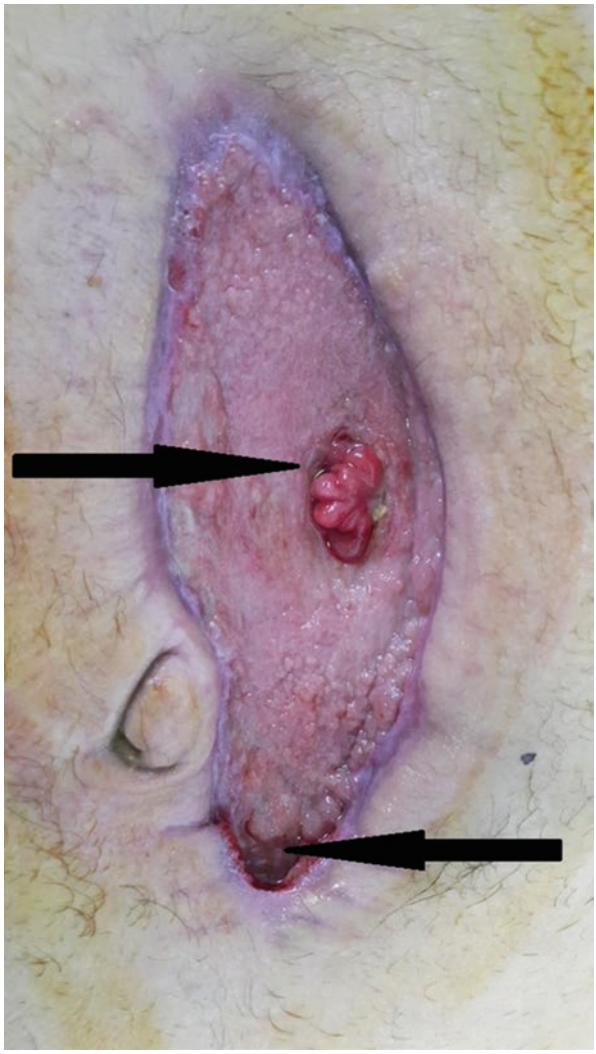

Fig. 18.3 Enterocutaneous fistulas

bleeding can start a few hours after the end of the operation or can be seen on the postoperative ninth day [28]. Bleeding in the form of leaks does not require any additional treatment. If there is an arterial bleeding in the anastomosis line, ligation and/or cauterization is necessary. Bleeding in stapler line should be controlled in stapler anastomoses and if necessary, supported with sutures. Bleeding may not be noticed in the early postoperative period. CT angiography may show the arterial bleedings. In arterial hemorrhage, computerized angiography shows contrast leakage within the lumen. In high-level anastomoses, colonoscopic examinations may disrupt anastomotic integrity. Patients without bleeding diathesis can be monitored closely and conservative treatment approach is sufficient. Colonoscopic clipping or cauterization may be used to stop bleeding in colorectal anastomoses, but

relaparotomy may be necessary if bleeding does not stop [29]. As a result of bleeding, inflammation and enterocutaneous fistula may develop in the anastomosis line [21–24].

Anastomotic Stenosis

Although the prevalence of benign anastomosis stenosis varies between 3 and 30% in the literature, its pathophysiology is still unclear [30]. Neoadjuvant chemoradiotherapy, anastomotic leaks, use of protective stomata, ischemia, and narrow stapler use are thought to be effective [30, 31]. Endoscopic balloon dilatation, digital dilatation, and hegar dilators are used in the treatment of symptomatic cases. However, surgical intervention is required in very few of them [32]. Endoscopically, balloon dilatation and stenting results are satisfactory [33] (Fig. 18.4).

Surgical Site Infection

Surgical site infections are seen at the wound postoperatively and occur in less than 2% of all operations [34, 35]. The wound infection rate after colorectal surgery varies between 2 and 45% and the mortality rate is 1–3% [35–38]. More than 50% of surgical site infections occur in abdominal surgeries. Liver transplantation and colorectal operations constitute the first two steps of the list [34–39]. As a result of the surgical site infection of the patient, the length of hospitalization and treatment costs increase [34]. Colorectal operations are considered as dirty or clear contaminated surgeries. The rate of infection is higher in such wounds [34–36]. Surgical site, wound infection, and intra-abdominal infection rates were reduced with mechanical bowel cleaning, appropriate antibiotherapy, and appropriate surgical technique. The removal of the hairs in the operation area immediately before the operation, proper prophylactic antibiotics, and normothermic retention of the patient during the operation are important in reducing surgical site infection [40]. If fever, fatigue, loss of appetite, and abdominal distension are encountered, infection and abscess should be investigated. Ultrasonography (US) and CT are commonly used imaging methods. Abscess and loculated fluid may be drained percutaneously (Fig. 18.5).

Early Small Bowel Obstruction After Surgery

Early small bowel obstruction (SBO) is defined as obstruction occurring in the first 30 days after abdominal surgery [41]. When the literature is examined, it is seen that the incidence rate is between 0.3 and 26.9% [42, 43]. Peritoneal adhesions are responsible for 56–75% of the etiology [41–44]. Abdominal surgeries, especially pelvic surgeries (colorectal, ileoanal pouch) previously experienced by the patient, are the most important reasons increasing the risk [44]. Because laparoscopic

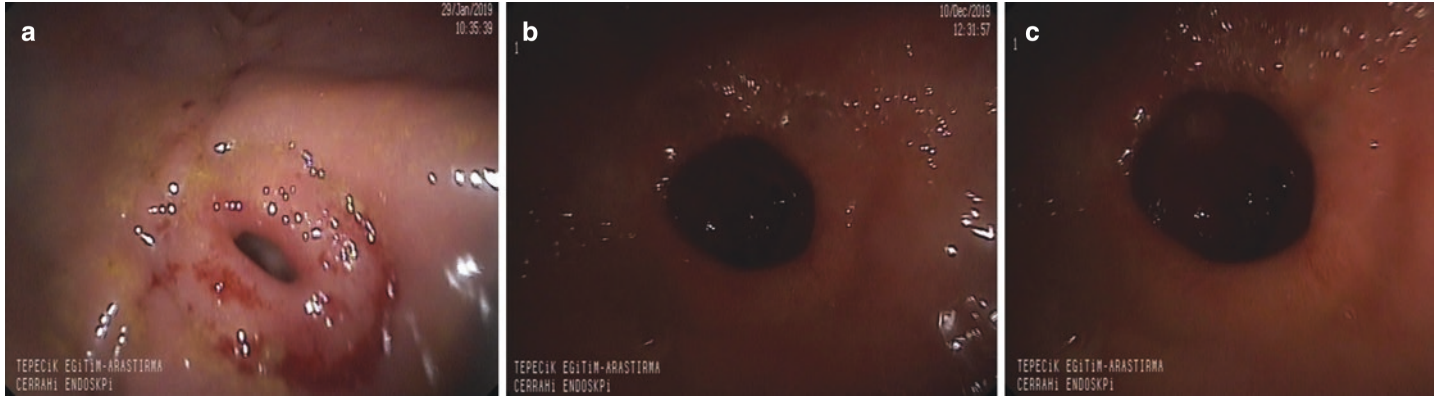

Fig. 18.4 Anastomotic stenosis. (**a**) Stapler anastomosis for rectum cancer (ca) and stenosis. (**b**) After balloon dilatation (second month). (**c**) After balloon dilatation (fourth month)

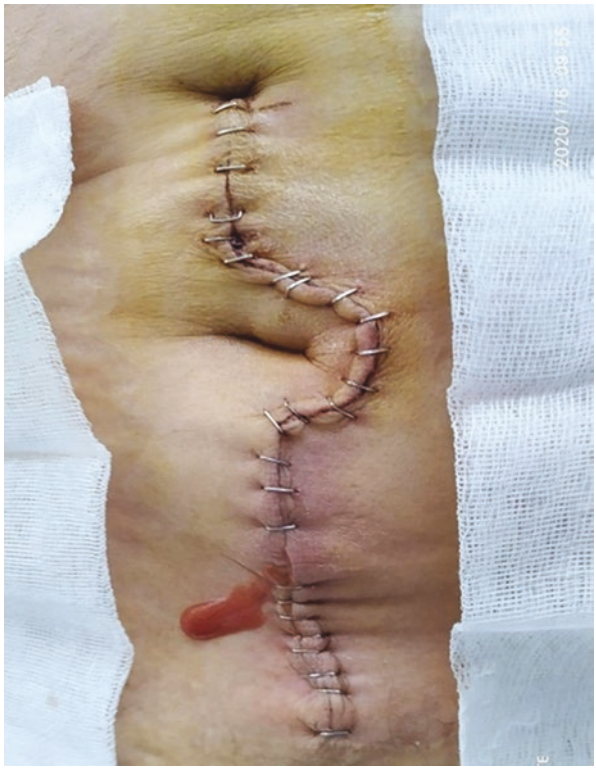

Fig. 18.5 Seropurulent discharge from the wound

surgeries reduce the risk of adhesion by 45%, postoperative SBO is less common in laparoscopic surgeries [44]. SBO increases the length of hospitalizations of patients and increases mortality and health expenses. If obstruction lasts more than 7 days postoperatively, electrolyte imbalance, intra-abdominal abscess, loculated fluid, and peritonitis should be considered. The clinical presentation of the patients was similar to mechanical bowel obstruction, with abdominal distention, colic pain, nausea, and vomiting. Radiological examination shows dilated small bowel segments. There may be minimal gas or level in the colon [42–45] (Fig. 18.6). CT is the most valuable imaging method for detecting obstruction localization, small bowel, colon separation, and intra-abdominal additional pathologies [43, 44] (Fig. 18.7). Shin et al. [45] examined the patients who underwent 504 colorectal operations and reported that there was no difference between pelvic surgery and abdominal surgery in terms of SBO. After the first attack of SBO, recurrent obstruction rates are more than 53% [46]. Colorectal cancer operations are the most common surgeries of SBO [46]. Nasogastric decompression and fluid electrolyte replacement are important in the treatment. Direct abdominal radiographs are used for follow-up. As long as the patient's clinic does not deteriorate, conservative follow-up can be continued for up to 14 days. The most important reason that increases morbidity and mortality in SBO is bowel ischemia. Therefore, mortality is reduced by early surgery in patients with small bowel strangulation [44–46].

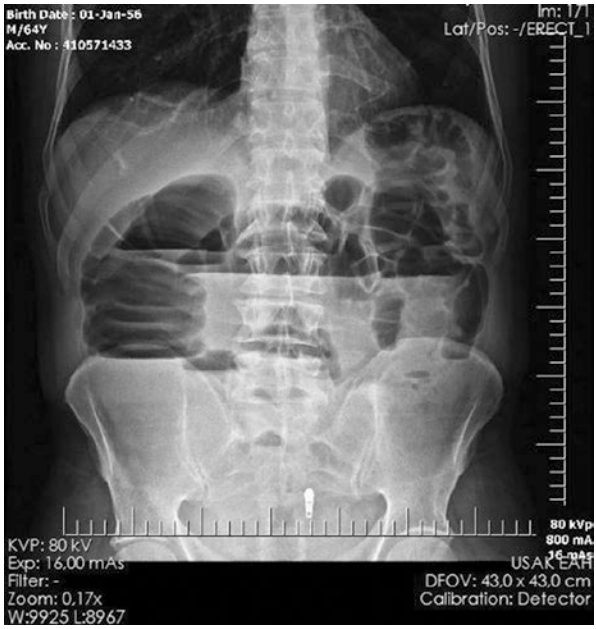

Fig. 18.6 Dilated intestinal segments

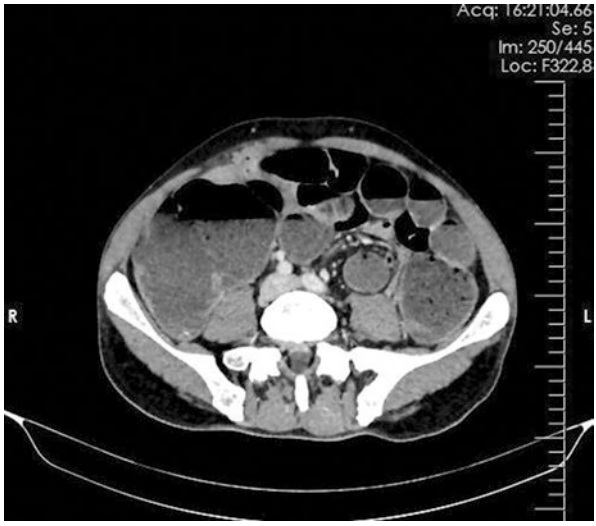

Fig. 18.7 Dilated small bowel and colon

Abdominal Wound Dehiscence

In the literature, abdominal wound dehiscence (WD) is seen between 3 and 25% after all abdominal operations, but it has high morbidity and mortality [47]. WD is defined as the separation of the sutured edges of the abdominal fascia after surgery. The underlying pathology in WD is rupture of the suture, knot failure, slack suture, or sutures cutting through the fascia [47–49]. Also intra-abdominal infection and AL facilitate WD. Abdominal wound dehiscence; 0.4–1.2% in patients undergoing elective abdominal surgery; the incidence rate can be up to 12% after emergency operations [50]. Obstructive pulmonary disease, malnutrition, emergency surgery, presence of malignancy, inflammatory disease, and abdominal distention are other factors that are effective in the separation of abdominal wound [47–50]. WD is usually seen in 3–7 days postoperatively. Serohemorrhagic discharge from the wound site can be seen as the first sign of dehiscence. There is no significant difference in WD between closing the abdominal wall in monolayer or separate layers. Söderback [47] found that the incidence of reoperations for WD in 30,050 patients undergoing colorectal surgery was 2.9%. As a risk factor for wound separation; age > 70, male gender, BMI > 30, history of pulmonary obstructive disease, history of inflammatory disease, and surgical time were important [47]. WD can only be detected radiologically in the early period, but it becomes visible with incisional hernia formation in the future [47]. Slater [50] in her study on incisional hernia and wound separation reported that hernia smaller than 3 cm can be repaired primarily. She stated that primary repair in hernias larger than 3 cm resulted in recurrence, so that the repair of hernias with prosthetic or autologous tissues should be used [50]. In large incisional hernias, if there is a strong and sufficient fascia, it is possible to repair with mesh by component fascia separation technique [50]. In cases where the fascia cannot be closed and there is no intestinal leakage, dual mesh repair or vacuum-assisted closure systems can be utilized [50].

Splenic Injury

Iatrogenic causes constitute 40% of all splenectomy operations. In colorectal surgery, iatrogenic splenic injury can be seen especially during left colon mobilization and by excessive stretching of splenocolic, splenophrenic, and gastrosplenic ligaments. Left hemicolectomy, left nephrectomy, and anti-reflux surgery are the most common operations for iatrogenic splenic injury [51–53]. In the literature, this rate is reported to be 1–8% in colorectal surgeries [51–53]. The main injury during the operation is the result of excessive stretching of the splenocolic ligament during dissection of the left colon flexure. Lolle et al. [54] examined the risk factors for splenectomy in patients operated for 23,727 colorectal cancer and reported that high age, high ASA score, surgical technique, cancer surgery, emergency surgery, and open surgical procedure are risk factors. In open surgeries, iatrogenic injury is more common [55]. The probability of iatrogenic spleen injury in laparoscopic surgeries is 3.5 times less than open surgeries [55]. Also iatrogenic splenic injury is rarely in

robotic surgeries [55]. Many factors are important in determining the treatment strategy in case of splenic injury. The general condition of the patient, the size of the injury, and the experience of the surgeon are some of them. Conservatively, topical hemostatic agents or energy-based devices, splenorrhaphy, mesh repair, or partial-segmental resection can be performed [55–59]. Total splenectomy should always be the last option. There are serious complications of total splenectomy, including immunologic, thromboembolic, transfusion requirement, and increased morbidity and mortality [56–59].

Presacral Bleeding

Presacral venous hemorrhage is one of the life-threatening complications during colorectal surgery and has an incidence of 3–9.4% [60, 61]. Injury occurs during posterior mobilization of the rectum. Bleeding in the veins begins as a result of the absence of presacral venous plexus, presacral fascia injury, or sacral periosteal injury during the operation. It may not be possible to stop this bleeding with traditional methods [62]. To prevent injury, dissection should be performed between the presacral fascia and the rectal propria [63]. Rapid bleeding control after injury is the most important step in preventing mortality [61–63]. Blunt dissection or finger dissection in the retrorectal area is the most common cause of bleeding. Rectal mobilization should be provided by sharp dissection in the presacral fascia. When bleeding occurs, the first step is to apply pressure on the bleeding area. Traditional hemostatic methods are often unsuccessful. Internal iliac artery ligation is ineffective and may result in bladder and gluteal necrosis [64]. Sterile thumbtacks and pelvis packing are widely used to stop presacral bleeding. The closure method using muscle fragment welding can also be tried [62]. Nunez et al. [62] in their study have emphasized various techniques for stopping presacral bleeding: packing techniques such as silastatic tissue expander and traditional pelvic packing; perineal expandable materials such as Sengstaken-Blakemore tube, breast implants, and saline bags; and metalic thumbtacks, topical hemostatic agents, and direct/indirect electrocoagulation [62].

Thromboembolism

Thromboembolic complications after colorectal surgery are higher than other gastrointestinal surgeries [65]. Venous thromboembolism (VTE) risk is high in colorectal diseases, especially inflammatory bowel diseases and colorectal cancers, and its incidence varies between 2.75 and 8.9% [66, 67]. Colorectal operations in non-oncology abdominal surgeries are the ones with the highest incidence of VTE (1.12%) [68]. The reason for the high incidence is thought to be due to the comorbidities of the patient, pelvic dissection, and the position of the patient during surgery [68]. Thromboembolism is the common preventable cause of perioperative mortality. Emoto et al. [65] found that the incidence of VTE in the literature research

was 1.15–2.47%. Henke et al. [69] found the incidence of symptomatic VTE in patients undergoing colectomy as 2.2% and reported age, BMI, anemia, wound contamination, surgical site infection, and sepsis as risk factors. It has been reported that there is no relationship between VTE and laparoscopic surgeries [69]. Alizadeh et al. [68] found that the incidence of VTE in 30 days was 0.32% in patients who underwent laparoscopic surgery (colorectal surgery, bariatric surgery, cholecystectomy, appendectomy, hernia repair) in their study including 750,159 patients. In the same study, they reported that the length of stay in hospital and operation time were longer in colorectal surgeries and this increased the risk of VTE [68]. Fleming et al. [70] found that the incidence of VTE in the 30-day period after colorectal surgery was 2.47%. The incidence of VTE within 30 days after discharge was found to be 0.47%. It was reported that obesity, preoperative steroid use, bleeding diathesis, ASA 3 score, and postoperative complications increase VTE before and after discharge [70]. Moghadamyeghaneh et al. [71, 72] found that the incidence of VTE was 2.1% in a study of 219,477 patients who underwent colorectal surgery and found that 33.8% of cases developed VTE after discharge. Rogers and Caprini score system can be used for venous thromboembolism [73, 74]. Early mobilization is sufficient for patients without risk factors for VTE. Compression stockings, pneumatic pumps, and low molecular weight heparins should be used as the risk factor increases [75]. Since venous thromboembolism can be seen in patients with colorectal surgery after discharge, low molecular weight heparins should be continued for 4 weeks after discharge [75]. In the postoperative period, if the patient has signs of deep vein thrombosis (DVT) (unilateral leg pain, redness, swelling, temperature, tenderness) or signs of pulmonary embolism (dyspnea, chest pain, hemoptysis, syncope, tachycardia), D-DIMER test, lower extremity color Doppler US, or pulmonary angio CT should be performed [76]. At the time of diagnosis, according to the patient's clinic, hemodynamics, DVT, and degree of pulmonary embolism, treatment may be followed by outpatient treatment with simple anticoagulant therapy. Patients with high-risk and recurrent embolism may be hospitalized for thrombolytic therapy and, if necessary, to install a filter to the inferior vena cava [76].

Ureter, Bladder, and Urethral Injury

During colorectal operations, injury to pelvic organs may occur due to anatomical proximity. Neoadjuvant radiotherapy, history of pelvic surgery, inflammatory bowel disease, pelvic inflammation, and congenital malformation increase the possibility of injury [77]. The frequency of injury of urologic organs in colorectal operations is ureter, bladder, and urethra, respectively [78]. Although ureteral injuries are rare, their incidence is 0.3–5% in the literature [79, 80]. The majority of ureteral injuries occur during gynecological operations [78]. The left ureter is often closely associated with the descending colon meso and there is a high likelihood of injury in this location. In addition, urological injuries can be occur during the inferior mesenteric artery is ligated, while the pelvic peritoneum and rectum side walls are dissected [78–80]. In colorectal operations, sigmoid resection, low anterior

resection, and abdominoperineal resection can be seen frequently [78–82]. Colorectal operations are in second place in iatrogenic ureteral injuries [82]. Ureteral injury may be of crush, shear, ligament, cauterization, or ischemic type. Early diagnosis of injury is the most important step in reducing mortality leading to renal loss.

Tom et al. [82] found that the rate of ureteral injury in patients undergoing open and laparoscopic colorectal surgery was 0.6% in open surgery and 1% in laparoscopic surgery. Anderson et al. [83] found the incidence of ureteral injury in patients undergoing 18,474 colorectal surgery to be 0.59% in laparoscopic surgery and 0.37% in open surgery. Methylene blue or indigo carmin may be given for taking control if there is suspicion of peroperative injury [82–84]. In oncologic surgery, if ureter involvement, hydronephrosis, or tumor ureter contact is seen on preoperative imaging, it would be an appropriate strategy to start surgery with ureter catheterization. Depending on the shape and location of the injury, treatment can range from primary repair to proximal diversion or nephrectomy. Contusions in the ureter can be prevented by edema and stricture by placing a ureteral double J stent. The catheter is removed within 4–6 weeks [78]. In ischemic ureter injury, dead tissues are debrided and reconstructed. In electrothermal injury, catheterization or reconstruction may be required according to the degree of effect of the ureter [78]. Surgical treatment varies according to the injury in different localization of the ureter [78]. Bladder injury occurs most frequently during gynecological operations, and the incidence of injury during colorectal operations is less than 1% [85]. As in ureteral injuries, radiotherapy, previous pelvic surgery, and tumor invasion, inflammatory-infectious process increases the likelihood of bladder injury [77]. Preoperative Foley catheter insertion and bladder emptying will reduce the risk of injury. Peroperative injury is suspected, but if serosal injury is not detected, Foley catheter and bladder filling with methylene serum will help in diagnosis [86]. Cystoscopy may be necessary in case of suspected injury to the trigone or ureter orifice. Surgical treatment varies according to the location of the injury in bladder injury [87]. Urethral injury is the least common type of urological injury. Injury can occur during Foley catheter placement or during rectal dissection. In abdominoperineal resection (APR), injury may occur during dissection of the anterior aspect of the perineum. Injuries are more common in the membranous part of the urethra [78]. Immediate recognition of urethral injury occurs when the peroperative Foley catheter becomes visible [78]. Localization of the injury can be made visible by giving methylene blue from the urethral meatus [86]. As a result of delays in diagnosis, it may present with urethrocutaneous or urethrorectal fistula. Fecaluria, pneumaturia, and recurrent urinary tract infections may be seen in patients. In delayed cases, the defect can be detected by retrograde urethrography or cystoscopy. The Foley catheter can be held for up to 4 weeks. If the injury is detected peroperatively, it can be repaired primarily with absorbable sutures and stenosis can be prevented by holding the Foley catheter for a long time. Sexual functions are controlled by sympathetic and parasympathetic nerve plexuses such as the urinary system. Sympathetic nerves are responsible for ejaculation in women and men [88]. Parasympathetic system is responsible for erection and lubrication [88]. Emotional, psychological, and

sociological factors are effective on postoperative sexual dysfunction. Sexual dysfunction in women may be related to fatigue, weight loss, and depression [89–91]. Sexual dysfunction is more common in men, especially in male patients who undergo surgery at a young age [92]. Erection, ejaculation, or retrograde ejaculation may occur. Bilateral inferior hypogastric nerve damage can lead to impotence [91–94]. Sexual dysfunction is in women dyspareunia, sexual aversion and vaginal lubrication occurs in the form of reduction [91–95]. Recent studies have shown that postoperative sexual dysfunction is the result of injury to the neurovascular network during the operation [95]. Sexual dysfunction is less common in laparoscopy and robotic surgery due to more detailed and clear vision [96–98].

Rectovaginal Fistula

A fistula is an abnormal connection between two epithelial surfaces. Enteroenteric, enterocutaneous, enterovesical, enterocolic, enteroatmospheric, rectovaginal, and rectovesical fistula are the most important ones. Rectovaginal fistula (RVF) starts from the rectum and extends to the vagina [99–102]. In the etiology, there is a history of an underlying disease or surgical operation. Diverticular disease, Crohn's disease, malignancies, and radiotherapy are examples [99–103]. There is abdominal surgery in the etiology of 75–85% of intestinal fistulas [104]. In this section, RVF after colorectal surgery will be discussed.

RVF starts from the rectal epithelium and extends to the vaginal epithelium, and obstetric injuries constitute a high proportion of the etiology [101–105]. Crohn's disease, surgical trauma, cryptoglandular abscesses, neoplasms, and radiation-related injuries are other etiological causes [105]. In colorectal operations, it can be seen as a result of anastomotic leaks, abscess, or stapler misfire. Most patients with RVF complain of uncontrolled passage of gas or stool through the vagina. Other symptoms include purulent, foul-smelling vaginal discharge, dyspareunia, perianal pain, vaginal irritation, and recurrent genitourinary tract infections [101–105]. Fistula localization, fistula width, and anal sphincter relation are important in examination. A mucosal defect can be seen in examination with anoscopic and speculum [103–105]. A tampon is placed in the vagina; the rectum is filled with methylene blue and waited for an hour. When the buffer is removed, the smudge with methylene blue shows the fistula [106]. Rectovaginal fistulas can be classified on the basis of etiology, size, and location [105, 107]. Low fistulas are placed on the dentate line and opened to the vaginal fourchette. High fistulas are used for fistulas that open to the vaginal posterior or to the edge of the cervix [105]. High fistulas are often difficult to diagnose. During the LAR, it seems due to stapler misfire. RVF incidence after LAR ranges between 0.9 and 9.9% in the literature [107, 108]. The classification is according to the fistula size: a fistula as "small" if it is less than 0.5 cm, "medium" if it is 0.5–2.5 cm, and "large" if it is over 2.5 cm in diameter [109]. It is also important that the surgery is performed at the appropriate time. Those due to obstetric trauma in the early postpartum period may close spontaneously [110]. Seton, sphincteroplasty, fibrin glue, fistula plug, and flap operations are other treatment methods [105].

Fecal Incontinence

Fecal incontinence (FI) is uncontrolled and involuntary chronic disease characterized by leakage of fecal content in solid or liquid form [111, 112]. One of the most important causes of FI is pelvic and/or anorectal surgery. FI significantly reduces the quality of life of the patient and causes biopsychosocial problems [113, 114]. The prevalence of fecal incontinence ranges from 1.4 to 19.5% [115]. The etiology of FI is multifactorial and its frequency increases after surgical operations.

In the pathophysiology of FI, the defect in anal, rectal, and pelvic floor continence mechanisms is prominent [115, 116]. Proctological examination should be performed in patients with fecal incontinence. Surgical scars, fistula, hemorrhoid, and mucosal prolapse may be seen [111–116]. Also cystocele, uterine-vaginal prolapse, and descensus can be seen. With rectal digital examination, anal canal length and sphincter tone can be felt. Inflammatory diseases and neoplastic masses can be detected by anoscopy, rectoscopy, or colonoscopy [115–117]. Anal physiology tests (anal manometry, pudendal nerve stimulation) and morphological and functional parameters are obtained objectively [117]. Internal and external sphincter anatomical structure can be evaluated with endoanal US and sphincter defects can be detected [117, 118]. Pucciani [116] investigated the postoperative FI rates. In the study, endoanal US, anal manometry, and clinical evaluation results are reviewed. The mean duration of incontinence was found to be 21.7 months. The most important problem of incontinence is loss of reservoir capacity of the rectum, pelvic nerve damage, and sphincter damage [115–118]. In the first year after the operation, incontinence can be permanent in approximately 30% of patients, even if the function improves [116, 117]. Medical treatment and supportive practices for FI include controlling symptoms and, if possible, correcting the underlying problem [116–118]. Pharmacological agents are used such as diphenoxylate/atropine, loperamide, cholestyramine, ondansetron, and amitriptyline [118]. Diphenoxylate/atropine or loperamide is often used to reduce diarrhea and may slightly increase the internal sphincter tone [118]. Amitriptyline is an alternative in the treatment of diarrhea and also reduces rectal urgency [119]. Physical exercises are aimed at strengthening the pelvic floor muscles and sphincters [117].

Surgical treatment can be categorized into procedures aimed at correcting the gross anatomical appearance, repairing sphincter and pelvic floor muscles, and neuromodulatory procedures that recruit parallel pathways to stimulate the colon and anus, procedures that create a new anal sphincter, and procedures that augment the anal sphincter [115–118].

Low Anterior Resection Syndrome

Rectal resections with anal sphincter preservation are an important milestone in the history of colorectal surgery. Coloanal anastomoses performed after ultralow and intersphincteric rectal resection up to 2 cm proximal to the dentate line using neoadjuvant chemoradiotherapy and protective stoma are a near-perfect success as an

oncologic treatment [120, 121]. Low anterior resection syndrome (LARS) is characterized by increased frequency of defecation, changes in stool form, feeling of urgent defecation, and fecal incontinence after rectal surgery [121, 122]. It can be seen in approximately 80% of patients undergoing rectal resection [121–124]. Overall, the most frequently reported symptoms were fecal incontinence (97% of studies), stool frequency (80%), flatus incontinence (70%), urgency (67%), and pad wearing (66%). In the studies, the effect of LARS on the daily life of the patients was reported as 80%. Pelvic floor rehabilitation, transanal irrigation, percutaneous tibial sinus stimulation, sacral nerve stimulation, probiotics, and 5-HT3 receptor antibodies can be used in treatment [125]. All these practices are aimed at reducing symptoms. Symptoms and daily activities of the patient may be reduced with combined treatments [123–125].

Stoma Complications

Stoma (ileostomy, colostomy) is a surgery procedure which is performed with colorectal cancer, ulcerative colitis, Crohn's disease, diverticulitis, ischemic colitis, and fecal incontinence [126]. In the USA, ileostomy and colostomy are performed to an average of 150,000 people annually [127]. Stoma affects the person's daily life in terms of biopsychosocial aspects. A well-performed colostomy or ileostomy with supportive therapies will accelerate the person's turning into his normal life and cause minimum daily life restriction [126–128]. However, as in all surgeries, there may be complications after stoma surgery. Prolapse, leakage around the stoma, parastomal hernia, infection, necrosis, skin irritation, retraction, and stenosis are the most common complications and have serious morbidity [128–131]. When the literature is examined, we see that stomal complication rates vary between 20 and 70% [128–134]. Stoma complications can be classified as early and late complications [126]. Early complications are necrosis, ischemia, retraction, parastomal infection, mucocutaneous separation, and abscess. Late complications are prolapse, parastomal hernia, retraction, and varices [126]. Malik et al. [134] found that peristomal skin complications were the most common in all stoma types and the incidence was 14% (2.5–46.2%). They reported that the second most common complication was parastomal hernia and it was found in 5.5% (0–2.88%) of the patients [134]. They found the rate of complications due to stomata as 26.5% [134]. They reported the highest incidence of complications in patients undergoing end-colostomy 62.6% (2–100%), 26.3% (13.9–100%) in loop colostomy, and loop ileostomy 14.3% (2.9–62.2%) [134].

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Intestinal Ostomies

19

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Introduction

Ostomy is derived from the Latin word "stoma" which means "mouth" [1]. Ostomy is an anastomosis between a part of the gastrointestinal system and anterior abdominal wall. The first ileostomy operation was done in 1879 by Baum to treat a patient with obstructive pathology in the right colon. Stomy is a worldwide medical and social problem. In the USA, 100000 new stomies are being constructed annually. Stomas are often constructed as ileostomy or colostomy [2].

Stoma Planning and Placement

Patient and family should be educated before elective ostomy operation. American Society of Colon and Rectal Surgeons (ASCRS) guidelines recommend that preoperative and postoperative training be performed by professional figures such as stoma nurses [3]. Patients with stoma are concerned about social acceptance, sexuality, and economic burden. To eliminate these concerns, preoperative training, counseling, and ostomy site selection should be performed with a stomatherapy nurse, if possible. Proper stoma site selection, emotional support, and patient education increase postoperative quality of life and reduce length of stay in hospital. Since the preoperative period for patient education is limited, it should be an effective education that is handled with a multidisciplinary approach, planned by expert

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educators, repeated and reinforced with written brochures, CDs, or other multimedia tools [4].

Preoperative planning of the stoma site promotes self-care in both elective and emergency surgeries, reduces stoma-related complications, and improves postoperative quality of life. ASCRS, AUA (American Association of Urology), and WOCN (Association of Wound, Ostomy and Continence Nurses) strongly recommend preoperative marking of the stoma site in both enteral and urologic stoma patients. In emergency cases, especially during out of working hours, where an enterostomal therapy nurse cannot be reached, stoma site can be selected, and patient counseling can be given by an experienced surgeon. When selecting the stoma site, factors such as abdominal wall contours, belt zone, and bone protrusions in both sitting and standing position should be considered. The patient should be able to see the stoma easily [5].

Ileostomy

Ileostomy Indications

In general, temporary or permanent ileostomy is required to protect a distal anastomosis, to bypass a distal obstruction, or to divert the feces in patients with perianal, perineal, or pelvic sepsis (Table 19.1).

Physiology of Ileostomy

The amount of outflow in an ileostomy depends on its distance from the ileum. The more proximal the ostomy is, the lesser the intestinal surface available for water and electrolytes absorption. The output on the first day of ileostomy is usually watery and bile-colored. The output thickens after oral intake has been started. The output is usually soft in consistency. Conditions such as type of food and fluid intake,

Table 19.1 Ileostomy indications

Diverting loop ileostomy	End ileostomy
Protection of low rectal/anorectal anastomosis	Total abdominal colectomy in patients with ulcerative colitis that is resistant to medical treatment
Resolve distal obstruction (malignity, diverticulitis, radiation stricture)	Familial adenomatous poliposis coli with distal rectal cancer/hereditary nonpoliposis coli
Fournier gangrene/perianal necrotizing fasciitis	Total proctocolectomy for Crohn's proctocolitis
Perianal Crohn's sepsis	
Rectal trauma/sphincter injury	
Rectovaginal/rectourethral/rectovesical fistula	
Fulminant toxic colitis	
Fecal incontinens	

medications, and active Crohn's disease may affect the consistency and amount of the output. If significant bowel resection has been performed, the output is watery and patients are prone to dehydration. In cases of short bowel syndrome, support may be requested from the intestinal rehabilitation team, and the patients may need total parenteral nutrition. Undigested foods and medicines can be encountered in the ileostomy output [6].The distally ileostomy output ranges from 500 ml to 700 ml/day. If oral intake is discontinued, the amount will be reduced. In a healthy ileostomy with normal function, a healthy, functioning ileostomy can produce up to 1000–1500 ml/day. If the output is over 1500 ml, it is considered excessive and can lead to dehydration. Reduction of oral fluid intake may help reduce ileostomy output and make it more consistent. Intake of liquid and fatty food increases the fluidity and amount of the output. Patients with ileostomy are recommended to consume a low-fiber diet because fiber absorption is reduced due to bowel edema in the first few months. Usually the ileostomy bag should be emptied daily. After proctocolectomy, small bowel passage is slowed down, possibly due to mucosal hypertrophy that develops to compensate for reduced absorption capacity. Transition time can be further delayed by drugs such as diphenoxylate-atropine (Lomotil), loperamide (Lopermid), codeine, or opium tincture, which act through intestinal mucosal opioid receptors to relax smooth muscles in the intestinal wall. This increases the intestinal retention time of nutrients, allowing more water to be absorbed. Nutritional status is largely unaffected if the distal ileum is intact [7]. If the terminal ileum is resected more than 1–2 meters, fat, fat-soluble vitamins and bile acids cannot be absorbed. As a result, macrocytic pernicious anemia due to vitamin B12 deficiency may develop. These patients should be given intramuscular vitamin B12 supplementation. Inability to absorb bile salts can also cause susceptibility to gallstones. Cholestyramine may be useful in such cases. Urinary stones may also occur due to chronic dehydration and acidic urine. This can be solved by sufficient fluid intake and adding 4 g of sodium bicarbonate to the diet to make the urine alkaline [8].

End Ileostomy

When creating an end ileostomy, the vascularity of the ileum should be good and can be brought out of the abdominal wall without tension. The Brooke technique still remains the procedure of choice for many patients. The opening in the peritoneum and fascia should be wide enough to allow the intestine to pass freely; otherwise it may lead to necrosis by reducing blood flow to the intestine and obstructing the intestinal lumen [9]. The stoma opening should be created in the previously marked skin area before the abdominal incision is closed. The abdominal wall fascia and skin are held with a clamp at the same level to prevent the bowel from bending when passing through the abdominal wall. The surgeon gently pulls the clamps medially. A compress is placed in the abdomen under the area where the ileostomy will be opened and the abdominal wall is tented. A piece of skin is excised from the marked ileostomy area. Subcutaneous adipose tissue should not be removed too much because it provides support for ileostomy. The first assistant retracts the skin

and subcutaneous fat tissue with right-angle retractors, while the surgeon reaches the fascia with the help of electrocautery. He then makes a longitudinal incision in the fascia. When he reaches to the lower rectus muscle, the muscle fibers are separated by the help of scissors or Kelly clamp, paying attention to the inferior epigastric vessels. The first assistant places the right-angle retractors between the muscle fibers, and the peritoneum is exposed. Peritoneum is opened with the help of electrocautery. A Kelly or Babcock clamp is passed through the opening in the skin into the abdomen. If the opening is considered to be small, it can be cut further through the abdomen with the help of electrocautery. The intestinal mesentery should be rechecked to ensure adequate blood supply. A Babcock clamp is then passed through the skin opening; the ileum is grasped and pulled toward the skin surface. Gently pushing the ileum from inside the abdomen facilitates the procedure. At this stage it is important to control the direction of the ileum mesentery. The ileum mesentery adjacent to the abdominal wall is then sutured to the parietal peritoneum to prevent volvulus around the ileostomy. In order to create an appropriate ileostomy, the ileum should protrude 4–5 cm above the skin level on the abdominal wall. The orientation of ileostomy and blood supply should be checked again before the abdomen is closed. The compress placed in the abdomen is removed. During maturation of ileostomy, a full-thickness suture is passed through the end of the intestine at 3, 6, 9, and 12 o'clock position, followed by a seromuscular suture through the 3 cm proximal and finally through the subcuticular layer. The sutures are gently pulled and the intestine is everted and the sutures are ligated. Additional sutures can be placed between the initially placed ones through the full-thickness intestine and subcuticular region. It is important that the sutures do not pass through the skin. This can lead to the formation of mucosal islands adjacent to ostomy, which leads to wetness and peristomal skin irritation [10]. Seromuscular sutures, which pass close to the skin level to facilitate ostomy eversion, may not be performed because of the concern that patients with Crohn's disease may be susceptible for fistula formation between ileostomy and skin. Sometimes it may be difficult to perform end ileostomy in obese patients due to abdominal wall thickness. In such cases, it may be convenient to create a loop end ileostomy. This technique, which was first described by Unti et al., allows an ostomy to be performed by reducing overstretch and preventing incision of the small intestinal mesentery [11].

Loop Ileostomy

Loop ileostomy is most commonly performed to maintain a distal anastomosis. Loop colostomy was used to protect left-sided anastomoses for a long time. Data obtained over time revealed the superiority of loop ileostomy in terms of parastomal hernia, device problems, skin problems, and complications during ostomy reversal. Loop ileostomy is performed 12–15 cm proximal to ileocecal valve. When ileostomy is performed for the defunctioning of an ileal pouch anal anastomosis, it is often performed more proximally to avoid tension in the anastomosis [9]. After selecting the appropriate loop of small intestine, a small window is formed on the

mesenteric edge through which the penrose drain passes. The proximal and distal ends of the loop are marked. It is taken out through the ostomy area opened on the abdominal wall. After closure of the abdominal incision, ileostomy is created and matured [10]. Between the afferent and efferent loops, 80% of the efferent bowel loop is opened slightly above the skin level by electrocautery, leaving an intact area in the posterior wall. The distal part of the ostomy is fixed to the subcuticular region of the skin, usually with three absorbable sutures. Three full-thickness absorbable sutures are passed through the end of the proximal leg, followed by seromuscular suture through the 3 cm proximal and finally through the subcuticular layer of the skin. The proximal leg is everted and the sutures are tied. In the areas between these sutures, a few more sutures can be inserted through the full-thickness intestine and through the subcuticular area of the skin. Transparent bags are useful to monitor ostomy in the early postoperative period. If the support rod is used, it can be removed 3–5 days later [11, 12].

Minimally Invasive Ileostomy

A minimally invasive method can be used to create a diverting stoma. It might be more convenient in some patients. Access to the peritoneal cavity can be gained with a Veress needle or using the Hasson technique. After producing pneumoperitoneum, the right lower quadrant is located. The ileum is usually mobile. However, in case of adhesion, it can be released by sharp dissection from the right lower abdomen and pelvic side walls. The determined small bowel loop is held with the help of Babcock grasper. In the area designated for ileostomy, the abdominal wall skin, fascia, and peritoneum are cut open as described previously. The small intestine is taken out. The pneumoperitoneum is then restored to confirm the orientation of the small intestine. Then, pneumoperitoneum is terminated and ostomy is matured [13]. Laparoscopic stoma creation seems to be a viable and safe procedure. The rate of conversion from laparoscopy to open technique ranges from 0% to 15.8%, and adhesions are the most common cause. The rate of intraoperative complications (excluding adhesions) during laparoscopic approach ranges from 0% to 3.1%. The rate of postoperative complications within 30 days after laparoscopic stoma formation ranges from 4.2% to 17.5%. However, all of the comparative series discussed in this study report a significantly lower postoperative morbidity rate in the laparoscopic group than in the open-surgery group. The 30-day mortality rate in the laparoscopic group ranged from 0% to 4.8%. For this result, the laparoscopic group was at a lower risk than the open-surgery group. Another advantage of the laparoscopic approach is that there is a significantly shorter postoperative hospital stay compared to the open approach [14]. Laparoscopic diverting ileostomy can result in various problems, such as the correct orientation of the intestines. Measures can be taken to minimize these technical errors. When creating a laparoscopic stoma, attention must be paid to the bowel (for loop ileostomy) or entanglement of the mesentery (for end ostomy). Some procedures, such as marking the proximal or distal ends and laparoscopic visualization of the intestinal cycle after passing through the fascia,

help the surgeon to verify the correct orientation of the intestines and should always be done. However, obstructive complications occur in approximately 5% of laparoscopically created stomas. It is important to recognize this ileostomy complication early because emergency surgery can reduce postoperative morbidity [14, 15].

Single incision laparoscopic surgery (SILS) has many applications in colorectal surgery. It can also be used to create loop ileostomy. After the skin is elliptically removed in the previously marked ileostomy area, the fascia is cut lengthwise, the fibers of the rectus muscle are separated, and the peritoneum is cut lengthwise to insert the SILS port. After pneumoperitoneum is gained, abdominal cavity is penetrated. Additional trocars are placed and the bowel segment that is suitable for ostomy is determined. After orientation of the bowel is done, Babcock grasper catches the bowel loop and is taken out with the SILS port. Then ileostomy is matured [16].

Ghost Ileostomy

Ghost ileostomy is a pre-stage ileostomy that can be performed to prevent stoma formation in patients at risk of colorectal anastomosis leakage. In both open and laparoscopic surgeries, a window is created in the ileum mesentery with a vascular loop through it. The vascular loop passed through this opening is taken out through a small incision in the right flank. The strap is secured to the skin or gauze on the skin. If anastomotic leakage develops in the postoperative period, ghost ileostomy can easily be converted to loop ileostomy under local anesthesia at the bedside or in the operating theater. The need for relaparotomy or relaparoscopy under general anesthesia is avoided. If no complications occur, the bowel can be repositioned in the abdominal cavity. Ghost ileostomy seems to be a useful technique which does not increase surgical complication risks, and reduces potential risks associated with relaparotomy in patients with anastomosis leakage. However, only six reports have described ghost ileostomy technique and clinical practice in the literature [17]. There is no clear indication of clinical conditions in which ghost ileostomy should be converted to loop ileostomy. Furthermore, it is not clear whether the diagnosis of anastomotic leak should be clinical or radiological. There is no evidence about timing of conversion of ghost ileostomy in the event of an anastomosis leakage. Furthermore, there is no evidence that it is sufficient for surgical resolution. In conclusion, further research is needed to assess the clinical utility of ghost ileostomy. Therefore, ghost ileostomy should not be recommended as a routine technique to avoid loop ileostomy [18, 19].

Continent Ileostomy

Continent ileostomy was described by Nils Kock in 1967. It is a low pressure ileal pouch constructed by using the terminal ileal loop for the storage of intestinal contents. An “Intussusception valve” is at the pouch outlet. Thus, involuntary leakage

from ileostomy is prevented. Patients intubate their pouch 3–4 times a day to empty it. A sponge is enough to cover the ostomy. There is no need for bags [20]. Indications for continent ileostomy are shown in Table 19.2.

Although the majority of patients with conventional ileostomy live unaffected, some do have problems such as hernia, fistula, prolapse, retraction, and leakage. In cases where stoma revision or re-construction fail and intestinal continuity is not possible, patients may be candidates for continent ileostomy. An ileal pouch anal anastomosis (IPAA) may not be possible if the small intestine is not long enough to reach the pelvic floor or if anal sphincter function is insufficient. Patients with rectal cancer and ulcerative colitis may need sphincter resection or pelvic radiation. In these cases, patients who want to avoid conventional ileostomy may be candidates for continent ileostomy. When a pelvic pouch surgery fails, there are three options: end ileostomy, redo-IPAA, and continent ileostomy. There are two attractive aspects to converting an IPAA into a continent ileostomy. The first is the "continuity," and the second is that the intestine used to make the original pelvic pouch can be saved in many cases [21].

Table 19.3 shows contraindications of continent ileostomy

Since the reservoir needs to be emptied by intubation, there should be no physical or mental disability in these patients. There is always the possibility of reoperation in patients with continent ileostomy. Therefore, in patients with familial polyposis and sporadic or family history of desmoid disease, continent ileostomy may not be an appropriate option, since surgery can stimulate desmoid growth. Obesity is a relative contraindication. Excessive fatty mesentery increases the risk of slipping of the valve. Approximately 50–70 cm of intestine is used to perform continent ileostomy. If the pelvic pouch fails, the reservoir must be removed. This leads to bowel loss. Continent ileostomy is not recommended in patients with limited small bowel length due to the risk of short bowel syndrome. Patients who are recommended continent ileostomy should be informed about all complications, including possible risk of reoperation due to pouch dysfunction. Whether this surgery can be recommended in patients with Crohn's disease is controversial. There are high complication rates in the results from large series. To date, there is insufficient evidence to recommend a continent reservoir ileostomy in Crohn's patients. There are two components of continent ileostomy: a reservoir and an outlet

Table 19.2 Indications for continent ileostomy

Dysfunction of conventional ileostomy
Failed pelvic pouch
Patients unsuitable for pelvic pouch
Patient preference

Table 19.3 Contraindications of continent ileostomy

Patients with mental or physical problems
Desmoid disease
Obesity
Limited length of small intestine
Patients who do not consent for the complications
Crohn's disease

valve. With the variation of these components, three types of continent ileostomies can be performed: three-armed S-pouch, Barnett's continent ileal reservoir, and T-pouch [20].

Early complications of continent ileostomy include leakage from suture lines, necrosis in the intussuscepted valve, and bleeding from suture lines. Minor bleeding can be managed by irrigation with saline or epinephrine in saline solution or endoscopic fulguration. Major bleeding, valve necrosis, or perforation require surgical repair. Late complications include valve slippage, prolapse, fistulas, volvulus, perforation, hernia, valve stenosis, or pouchitis [22].

Valve slippage usually occurs in the first 3 months postoperatively. It is rare after 12 months. Valve slippage symptoms are gas or stool incontinence or difficulty in intubation of the sac. Major valve slippage usually requires surgical repair. When a valve cannot be intubated, but the bag remains continent, the patient has a functional full bowel obstruction and needs urgent medical attention. With a pediatric rigid or flexible endoscope, the pouch can be entered under direct vision through the stoma. Functional obstruction can be temporarily relieved by aspirating gas and intestinal contents. Longer drainage can be achieved by placing a catheter over a guide wire inserted through the endoscope channel. The patient should be evaluated for further treatment after this temporary drainage. If this is patient's first dysfunction attack, after 7–14 days of drainage, the intestinal edema is expected to decrease, and the problem can be resolved. At the end of this period, intubation can be tried again. If intubation difficulties continue, the drainage tube should be reinstalled. It should remain in place until the valve is repaired surgically. Valve prolapse occurs when too large of a defect is created to reveal the efferent loop. This problem can be solved by narrowing the opening in fascia [23].

Fistulas can form at the bottom of the valve and allow fecal flow to bypass the valve, causing incontinence. In these cases, the patient notices incontinence but does not have difficulty in intubation, as in the case of valve slippage. Fistulas can occur at any time after surgery. Valve fistulas are caused by technical problems of the valve structure (such as suturing through the walls of the valve and very tight ligation, improper use of staples, excessive electrocautery causing scarring of the intestine, or erosion of prosthetic material) or Crohn's disease. Fistulas can also form between the pouch and the abdominal wall. They usually cause parastomal abscesses, then they drain and mature as an enterocutaneous fistula. Fistulas that develop from the bottom of the valve cause intestinal contents to bypass the valve and incontinence. Abscesses require drainage, and antibiotics can prove to be helpful. Fistulas may respond to drainage, medical treatment, fibrin glue, occlusion, or surgical correction [20].

Pouch dislocation and volvulus are caused by insufficient fixation of the reservoir to the abdominal wall. Volvulus can lead to necrosis of the entire pouch. Catheter perforation might occur, but it is a very rare complication that usually requires surgical repair. Stenosis at skin level may prevent the insertion of the tube. Performing the first construction with very small skin incision, intestinal ischemia, infection, wound healing abnormalities, stoma retraction, or repeated trauma can cause stenosis. It can be repaired by skin level revision or z-plasty repair [22].

The incidence of mucosal inflammation in the pouch (pouchitis) ranges from 10% to 30% in various studies. It becomes manifested by an increase in ileostomy output. The content might be watery, stinking, and sometimes bloody. Patients may also develop abdominal pain, distension, fever, and nausea. The complication is considered secondary to the overgrowth of bacteria and is usually successfully treated with antibiotics (metronidazole or ciprofloxacin) or probiotics and continuous catheter drainage to avoid stasis [24]. The summary of the complications is shown in Table 19.4.

Lepisto et al. reviewed 96 patients who underwent continent ileostomy between 1972 and 2000. They found the cumulative success rate as 71%. The most common cause of pouch excision was nipple valve dysfunction. The success rate of continent ileostomies was significantly lower than ileoanal pouch anastomoses [25].

Colostomy

Indications of Colostomy

Indications for colostomy are shown in Table 19.5. As with ileostomy, colostomy can be constructed as end, loop, and end-loop. End colostomy is typically performed in cases where a restorative procedure is not possible, as in patients with distal rectum tumors that require abdominoperineal resection. It is often preferred in elderly patients who are unable to tolerate coloanal anastomosis or potential complications. Sometimes, because of poor sphincter functions, coloanal anastomosis is not

Table 19.4 Complications of continent ileostomy

Komplikasyon	İnsidans (%)
Pouchitis	10–30
Nipple valve slippage	3–25
Fistula	0–10
Stomal stricture	10
Nipple prolapse	4–6
Stomal necrosis	1–2
Complications that require surgical correction	15–25

Table 19.5 Indications of colostomy

Diverting loop colostomy	End or end-loop colostomy
Low rectal/coloanal anastomosis	Abdominoperineal resection
To relieve distal obstruction	Low anterior rectum resection in patients not suitable for coloanal anastomosis
Rectal trauma/sphincter injury	Hartmann procedure
Fecal incontinence	Fecal incontinence
Radiation proctocolitis	Radiation proctocolitis
Complex rectovaginal, rectourethral, rectovesical fistula	
Perineal necrotizing fasciitis	
Fournier gangrene	

performed after lower anterior resection in very old female patients who have given many births and an end colostomy may be preferred. In emergency cases, end colostomy can be used. Patients with Hinchey 4 diverticulitis (fecal peritonitis) require the Hartmann procedure, which includes resection of the diseased segment of the sigmoid colon and left colon colostomy. In this case, primary colorectal anastomosis is considered unsafe due to fecal contamination. In patients with fecal incontinence, end colostomy may be considered if sphincter reconstruction or neosphincter/sacral nerve stimulation surgery has failed. In rare cases, patients with radiation proctitis, whose non-surgical management is unsuccessful, may require end colostomy [26].

Loop colostomy is used to protect the rectal anastomosis or to divert the fecal flow from distal obstruction, pelvic sepsis, or rectum/sphincter injury. Most of the surgeons prefer loop ileostomy to protect the lower rectal anastomosis because loop colostomy is associated with increased rates of stoma complications and incisional hernia compared to ileostomy. In addition, there is a risk of injury to the marginal arteries that provide the blood supply to the colonic conduit used for colorectal anastomosis during loop colostomy. When staged resection is preferred, loop colostomy can be used to bypass a distal obstructive tumor in patients with an intact ileocecal valve [27].

Rarely, in hemodynamically unstable patients under vasopressor support who have fecal peritonitis, proximal loop colostomy can be performed without resection of the diseased colon following peritoneal lavage. Such an option should always be kept in mind. In cases of pelvic or perineal sepsis, such as Fournier gangrene or perineal necrotizing fasciitis, loop colostomy can be used to divert the stool flow. In patients with complex rectal fistula (rectovaginal, rectovesical, rectourethral) requiring complex surgical repair, stool diversion may be necessary to provide optimal chance of recovery [28].

Colostomy Physiology

Water from the small intestine is absorbed by the colon. Thus, in left-sided colostomies, the content is semi-solid, and once daily discharge is sufficient. The content is slightly more fluid in transverse loop colostomies. However, it is still of the right consistency, and it may be sufficient to empty it once a day. In more proximal colostomies, the amount of remaining colon to absorb water will decrease, so the content will be more fluid. Right-sided colostomies are rare. The biggest problem experienced by patients with right colostomy is that very foul-smelling content is present due to the effect of colonic bacteria [28].

End Colostomy

End colostomies are usually performed in the left lower quadrant. Before the operation, the placement should be marked by the enterostomal therapy nurse. Colon loop to be ostomized should be sufficiently mobilized to prevent tension. Splenic

flexor may need to be removed. In addition, the colon loops that will be ostomized must have sufficient blood flow. Then the stoma region is prepared. Fascia and subcutaneous are pulled medially with clamps. To prevent injury to the intestines, a compress is placed in the abdomen under the area to be opened. The skin is excised in the previously marked area. The area is opened with retractors. Fascia is divided longitudinally by electrocautery. The rectus muscles are separated by scissors or the Kelly clamp, paying attention to the inferior epigastric vessels. The peritoneum is reached by retracting the muscle with retractors. Then the peritoneum is cut longitudinally. When you enter the abdomen, the previously placed compresses become visible. The stoma opening should be wide enough to allow 2 finger access. Sometimes a larger opening may be required in obese patients or in patients with proximally enlarged colon segment due to large bowel obstruction. Then, a Babcock clamp is inserted through the opening, and the cut end of the colon is grasped and taken out from the opening. Meanwhile, the colon can be pushed gently through the abdomen by hand. One must be very gentle at these stages; otherwise the colon may be damaged. Again, care should be taken against the possibility of that the colon might be twisted. For a functioning colostomy, there should be a well-perfused colon segment 2–3 cm above the skin level. The compress placed in the abdomen is removed. After the midline abdominal wound is closed, the stoma is matured with 3/0 absorbable sutures [29]. Although most colostomies are at the same level as the skin, 1–2 cm protrusion above the skin may have its advantages;

- It facilitates the placement of the ostomy device.
- Sometimes, a skin level colostomy may retract in patients who gain weight.

Loop Colostomy

Loop colostomy is usually performed as sigmoid loop colostomy (in the left quadrant of the abdomen) or transverse loop colostomy (in the upper abdomen). Loop colostomies can be performed by open technique or laparoscopically. Sometimes, in weak patients, a trephine loop colostomy (opening an ostomy from the left fossa without laparotomy) can be performed [30]. When performing a trephine loop colostomy in the lower left quadrant, an elliptical skin portion is removed from the pre-determined stoma region. Access to the peritoneal cavity is performed as mentioned previously. Sigmoid colon is located and taken out. Support bar can be used. Then, an incision close to the skin level is made with the help of electrocautery on the distal side of the colon segment. The distal part is sutured with 3/0 absorbable sutures. The proximal part is matured by slightly everting the edges. If placed, the stick can be removed after 4–5 days. When planning a Trephine transverse loop colostomy, it will be useful to determine the position of the transverse colon before surgery. While the patient is lying on his back, a coin is placed on the anterior abdominal wall in the upper quadrant area of the abdomen and the surrounding area is marked. Then a direct graph can be taken. With this strategy, appropriate incision

site planning can be made. In weak patients, it is easier to pull the colon up. The omentum is carefully cut and relocated into the abdomen before the stoma is matured [30].

In open surgery, it is necessary to pay attention to the stoma direction and ensure that it is transmitted to the anterior abdominal wall without tension. For correct orientation, the proximal or distal end of the stoma can be marked with a suture. To create a tension-free stoma, the colon must be mobilized. Told fascia is cut and colon mesentery is released from retroperitoneum. It is necessary to recognize and protect the left ureter and gonadal vessels. For sigmoid loop colostomy, mobilization of splenic flexor is generally not required. However, it should be done when necessary. If sufficient length cannot be acquired despite these strategies, it may be necessary to ligate and cut the inferior mesenteric artery and vein. If this is not enough, the release of peritoneal attachments at the base of the colon mesentery provides extra length. As explained earlier, a 2-finger-width opening is created in the anterior abdominal wall. Then the abdomen is closed and the ostomy is matured. Transparent devices should be used in order to easily observe the complications that may develop in the ostomy in the early postoperative period. When the colostomy starts to function, the patient can receive an appropriate diet. Loop-end colostomy can be created by following the steps described in loop-end ileostomy [31, 32].

Minimally Invasive Colostomy

A loop colostomy can be created laparoscopically. Careful patient selection is of utter importance. Most patients have history of more than one complex abdominal surgery. Care should be taken when deciding minimally invasive surgery in such patients. Access to the peritoneal cavity can be done with the Hasson technique or the Veress needle technique that allows pneumoperitoneum creation [33]. Following the camera trocar entrance, two 5 mm trocars are inserted to move the intestines. If transverse loop colostomy is to be performed, the omentum is separated from the colon and a stoma is created from the proximal part of the transverse colon. Minimal mobilization is usually sufficient for this type of stoma. Electrothermal coagulation devices can be used when necessary to separate the omentum from the colon and mobilize the colon. To create the stoma opening, intra-abdominal gases are discharged before a skin disc is removed from the anterior abdominal wall. Thus, the stoma can be positioned more easily. Toldt fascia is cut with electrothermal coagulation devices or cautery while creating a sigmoid loop colostomy. The colon is released from retroperitoneal attachments. After sufficient mobilization is achieved, the colon segment is held with an atraumatic holder. Intra-abdominal gas is evacuated and stoma opening is created. To facilitate the identification of the colon from the stoma opening, the tool holding the colon is gently manipulated. The colon is then held with a Babcock grasper, the laparoscopic device is released, and the colon is pulled through the stoma opening. The pneumoperitoneum is then re-established to check the accuracy of the colon orientation. If a sigmoid end colostomy is desired, the colon can be intracorporeally split or the colon can be split in the anterior

abdominal wall using the Endo GIA stapler. The distal segment of the colon is relocated back to the abdominal cavity. The proximal end is ripened in the form of a stoma [34].

Turnbull Blowhole Colostomy

It was first described by Dr. Rupert Turnbull in 1953 for the management of patients with toxic colitis who are at high risk of contamination and mortality, where resection is considered contraindicated. The abdominal cavity is entered through the lower midline incision. Bowel segment is prepared. A loop ileostomy is created from the area marked in the right lower abdomen. Subsequently, an incision is made on the anterior abdominal wall in the area corresponding to the dilated colon segment in the left upper quadrant. Overly inflamed colon should be manipulated with extreme care. After the fascia and peritoneum are opened and the colon is identified, the serosal surface of the colon is sutured to the fascia circumferentially with absorbable sutures. Then the colon is cut lengthwise and sewn to the skin with absorbable sutures. Even though rarely performed, this technique may be valuable in patients who cannot tolerate resection [35].

Ostomy Closure

Timing of Ostomy Closure

The early closure of loop ostomy, which is defined as the closure within 2 weeks after index surgery, is considered to be feasible and reliable in patients who have an uneventful recovery and no evidence of anastomosis leakage [5].

The timing of stoma closure remains controversial. There are at least four randomized controlled trials and two meta-analyses in the last 10 years comparing conventional timing (within 8–12 weeks after index surgery) with early timing (within 4 weeks after index surgery) [36–41]. Most of the data is from patients with loop ileostomy who had rectum surgery due to cancer. All studies agree that there is no significant difference between different closure time groups with regard to anastomosis leaks. Anastomosis leakage was not observed in any of the patients who participated in the study after the research with a water soluble contrast enema. In a randomized controlled study, early ileostomy closure (on the eighth postoperative day) resulted in less bowel obstruction, a lower rate of medical complications, and a shorter hospital stay, while a lower rate of wound complications (12 weeks after Index surgery) was observed compared to a late-closure ileostomy [36]. In the Easy study, the lower complication rate was observed at the 12-month follow-up in the group that was closed prematurely after the index surgery (8–13 days after the index surgery) [37]. A small number of patients were analyzed in another randomized controlled trial [38]. He found that early ileostomy closure (sixth day after index surgery) gave better results in terms of ease of closure of the abdominal wall and

closure of ileostomy in terms of operation time and stoma care costs. No major complications (Grade III/IV) were observed in either group. (Grade III: Requiring surgical, endoscopic, or radiological intervention. Grade IV: Life-threatening complication (including central nervous system complications) requiring intermediate care/intensive care unit management.) Duration of hospital stay was similar between groups. In the fourth randomized controlled trial, data of a heterogeneous group of patients undergoing ostomy surgery were recorded (ileostomy or colostomy in elective or emergency situations). Early ostomy closure (14–28 days after index surgery) resulted in a better quality of life and lower cost [39]. The results of two meta-analyses were not different from previous randomized controlled trials. Farag et al. compared four randomized controlled trials in 2017. They did not find any difference in terms of anastomosis leakage, postoperative complications, length of hospital stay, and operation time [40]. Menahem et al. compared six studies in 2018, four of which were randomized controlled trials. While the traditional ostomy closure arm showed less infection in the stoma region, fewer stoma-related complications and small bowel obstruction were reported in the early closure arm (within 14 days after index surgery) [41].

As with the Hartmann procedure, the timing of closure of a temporary end colostomy remains a controversial issue. Few data are available on the subject in the literature. As with the Hartmann procedure, the underlying cause must be completely resolved to close a temporary end colostomy. It may take 3–6 months or even more for the patient's state of health to return to baseline, inflammation, and amelioration of the adhesions. Therefore, closure of Hartmann should be done at least 3 months after the index surgery [5].

In a study by Keck et al., patients who were closed early (before 15 weeks) and late (after 15 weeks) were compared in terms of morbidity and mortality, length of hospital stay, and operative difficulty [42]. There was no difference between the two groups in terms of morbidity, mortality, and anastomosis leakage. However, the length of hospital stay was longer in the early closure group, and the operative difficulty was higher. Other authors propose to wait at least 6 months to allow the adhesion intensity to decrease and pelvic inflammation to resolve [43, 44].

Technical Aspects

In loop ileostomy closure operation, anastomosis can be done with staples or by hand sewing. Stapler technique seems better in terms of decreasing the rate of small bowel obstruction in the early postoperative period and shortening the operation period, without any difference in the anastomosis leak rates compared to hand sewing [5].

Many studies have been conducted to examine the data of patients who underwent loop ileostomy after rectal surgery for rectal cancer [45–48]. In all randomized controlled trials, shorter operative time has been reported on the stapler group. In one of the randomized controlled trials, despite the heterogeneity in index surgery requiring temporary ileostomy, lower small bowel obstruction was found in the

stapler arm. The anastomosis leak rate was higher in the hand-sewn group (2/70 vs. 0/71), but it was not statistically significant (p = 0.2447) [48]. Shelygin et al. reported that overall morbidity rate was lower in the stapler group in 2010 but did not analyze the anastomosis leak rate [46]. In all meta-analyses, there is a consensus that the small bowel obstruction is reduced in the stapler technique. In three of these studies (except for the study of Madani et al.), it was also reported that the operative time in the stapler arm was significantly lower. There was no difference in terms of anastomosis leak [49–52].

Laparoscopic closure of the Hartmann colostomy appears to be a safe and feasible technique but should be performed by experienced laparoscopic surgeons due to the reported high rate of conversion to open technique [5].

As new minimally invasive techniques develop, they are increasingly applied to colorectal procedures, including Hartman procedure, and successful results are reported in small series [53, 54]. In two meta-analyses, laparoscopic and open Hartmann were compared. Siddiqui et al. compared eight studies in 2010 that reported an advantage in terms of lower complication rates and shortened length of hospital stay in the laparoscopic group [54]. More recently, in 2015, after analyzing 13 studies, Celentano et al. reported that there was no significant difference between laparoscopic and open approaches [53].

Ostomy-Related Complications

The incidence of stomal complications ranges from 21% to 70%. Stomal complications can occur at any time but are most common in the first 5 years. The complications occurring in the very early period are mostly due to technical errors. Complications within the first postoperative month are generally associated with the wrong selection of the ostomy site. The complications occurring in the late period are usually related to permanent stoma cases. In general, end ostomies have lower complication rates than loop ostomies. Generally, the most frequently reported ostomy-related complication is peristomal skin lesions due to leakage. Other common complications are retraction, stomal necrosis, stomal stenosis, prolapse, bleeding, and dehydration due to high ostomy output and parastomal hernia. Rarely seen complications are small and large bowel obstruction, peristomal abscess, and fistula formation. Following closure of the stoma, wound infection, delayed healing, and hernia formation may also develop in the stoma area [55].

Whenever possible, patient education and preparation for life with stoma should be started in the preoperative period. Both participating in stoma support groups and counseling by the enterostomal therapy nurse can reduce complication rates and improve long-term outcomes and psychosocial adaptation. Regardless of the indication and type of stoma, preoperative marking of the stoma site by the enterostomal therapy nurse or an experienced surgeon has been shown to reduce the incidence of postoperative complications. There is a general consensus that most common stoma-related complications are associated with inappropriate stoma site selection. Improper stoma site selection leads to problems such as poor patient compliance,

leakage, skin irritation, trauma, difficulty in seeing the stoma, and psychological distress. This might prevent postoperative adaptation and cause further problems in stoma care. In urgent cases, the selection of inappropriate stoma site is more common. Other universal risk factors associated with stoma complications can be listed as lack of experience of the surgeon, stoma height less than 10 mm, obesity, smoking, inflammatory bowel disease, and diabetes [56].

Peristomal Skin Complications

It is common in poorly constructed stomas. To prevent these complications, the ostomy end should protrude 2–3 cm from the skin. Thus, the intestinal contents will empty into the bag without touching the skin. In a retracted stoma, the alkaline small intestine content can irritate the skin. Using convex devices and belts may help to solve the problem [55, 56].

Mucosal implantation may sometimes develop due to the suturing of the ileal mucosa to the skin (Fig. 19.1). This may cause the ostomy edge to be constantly wet, making it difficult for the device to adhere. As a result, the ileal content will irritate the skin. Similarly, in obese patients, ileostomies formed below the umbilicus or at the abdominal folds are more likely to have skin problems. It is important that the stoma adapter is applied by the enterostomal therapy nurse and the patient must be educated by the team. The small intestine contents accumulated in the bag should be

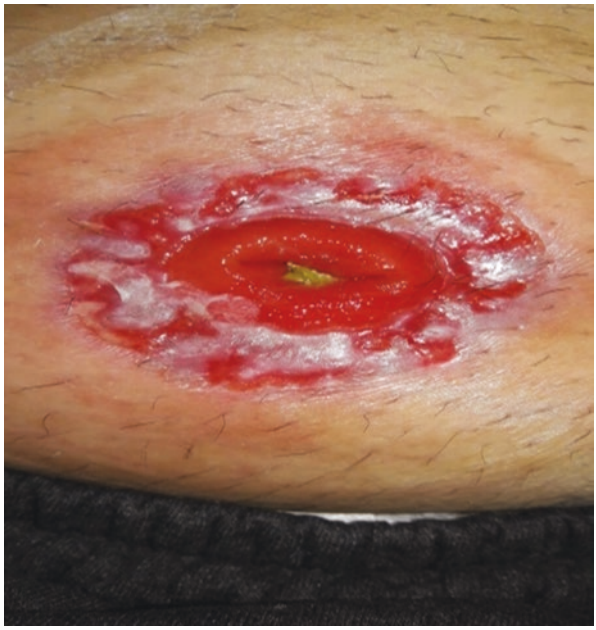

Fig. 19.1 Mucosal implantation

emptied at regular intervals to prevent irritation to the skin. Patients with physical and mental problems and advanced age may have trouble wearing and emptying their bags. In such cases, education of family members is important [55–60].

Peristomal fungal infections are common. It manifests as peristomal erythema with satellite lesions around it (Fig. 19.2). It should be treated with topical antifungal agents. It is covered with a stoma paste and left to dry, and then ostomy device is applied.

Contact dermatitis typically occurs in the area where the stoma device baseplate touches the skin (Fig. 19.3). It is usually caused by an allergic reaction to the baseplate of the ostomy device. Using a different product may fix the problem. Topical steroid use may be beneficial [57].

Peristomal ulceration may be associated with pyoderma gangrenosum in individuals with inflammatory bowel disease (Fig. 19.4). In this type of patients, choosing a disease-free bowel segment while forming a stoma is important to prevent this complication. It can be seen in any time period after the stoma construction. Ulcers are usually full thickness and painful. Other pathologies must be ruled out to make the definitive diagnosis. Punch biopsies should be taken from the edge of the ulcer. Culture should also be taken to exclude infectious agents. These lesions can be treated with topical, oral, or intralesional steroids depending on the degree of ulceration [58]. In order for the stoma device to be placed, the ulcer area must be kept dry. Applying hydrocolloid-coated stoma or antibiotic powder can help resolve the problem. Drying foams can be used in moist ulcers. Topical tacrolimus solutions

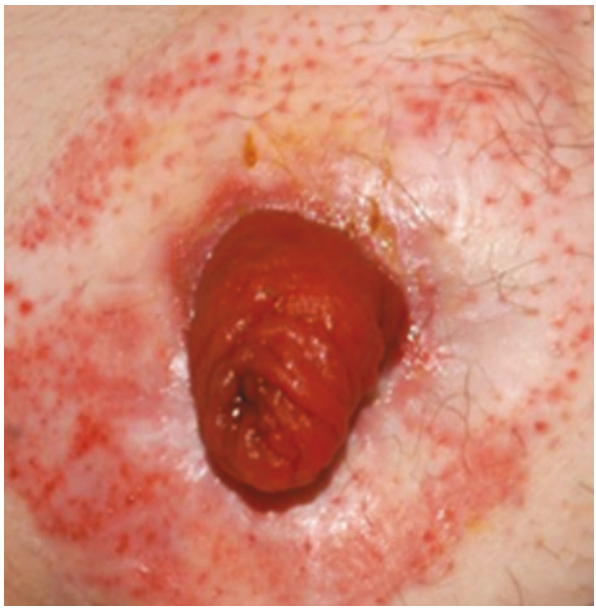

Fig. 19.2 Peristomal fungal infection

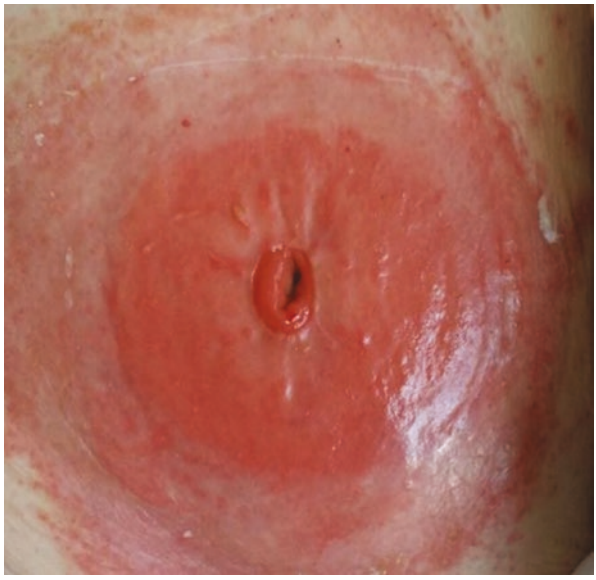

Fig. 19.3 Contact dermatitis

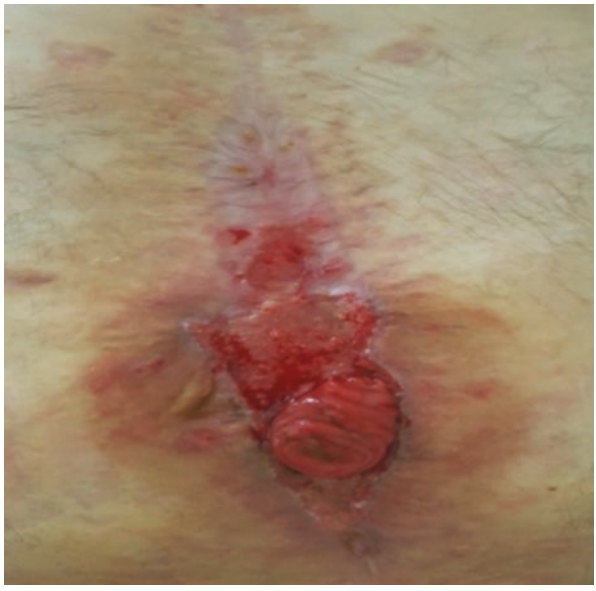

Fig. 19.4 Peristomal ulceration

can be used in resistant cases. In more severe cases, cyclosporine, infliximab, or other immunobiological agents can be used in the treatment of the underlying disease. In severe cases, the ostomy area may need to be changed. However, in some cases, pyoderma gangrenosum may also relapse in that new ostomy site. The best treatment of pyoderma gangrenosum is to close the stoma if possible [59].

Mucocutaneous Separation

Mucocutaneous separation is the separation of the ostomy from the peristomal skin around it (Fig. 19.5). Its incidence ranges widely from 3.96% to 25.3% in the early postoperative period. It is usually a technical complication due to over-tension. Conditions that disrupt wound healing, such as excessive cautery use on the skin or intestinal mucosa, immunosuppression or diabetes, and peristomal infection may also be a factor [58]. The management strategy should be determined depending on the size of the separation. Small separations can be covered with absorbent fillers such as skin barrier powder or an ostomy device wafer. Early diagnosis and aggressive wound care are very important. In case of larger or separations involving whole circumference of the stoma, revision may be required to prevent long-term complications such as retraction or stenosis. Due to anatomical bowel factors or some clinical situations such as a morbid obesity, a suboptimal ostomy may be inevitable. As long as the stoma is alive above the fascia level, definitive management of stoma complications should be decided according to clinical stability and delayed as much as possible [60].

Stomal Necrosis

It has been reported that it occurs in up to 13% of stomata in the early postoperative period (Fig. 19.6). Risk factors include urgent operation, inadequate mobilization of the intestine, excessive mesenteric resection resulting in insufficient arterial blood supply or insufficient venous drainage, and a small opening in the fascia or skin, inflammatory bowel diseases (especially Crohn's disease). Obesity is an independent risk factor for stomal necrosis. Obese patients are seven times more likely to develop stomal necrosis than non-obese patients. Since there is blood support to both afferent and efferent legs, loop ostomies are less prone to necrosis than end ostomies [61]. Ischemia evaluation should be done in the operating room before the

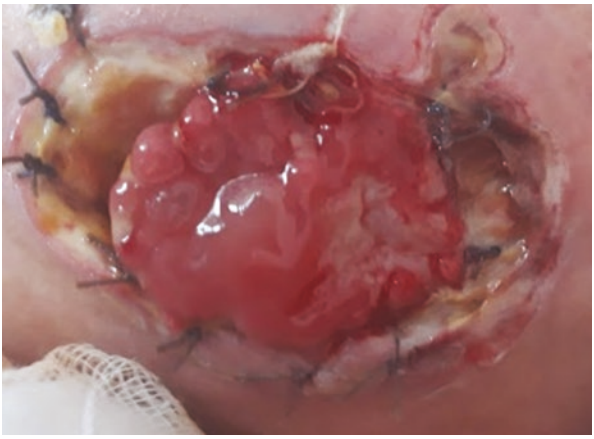

Fig. 19.5 Mucocutaneous separation

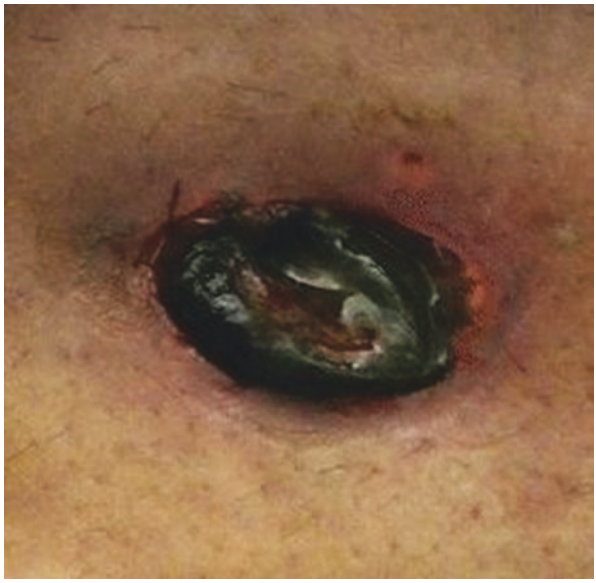

Fig. 19.6 Stomal necrosis

patient leaves the operating room. If in doubt, the stoma should be revised in the first surgery. It may be useful to prepare the intestine segment that is to be used for stoma at the beginning of the operation to save time. Although all rules are followed, stomas may sometimes appear dusky in the early postoperative period. It is necessary to distinguish whether this appearance is due to arterial insufficiency or venous obstruction which develops due to edema in the postoperative period and improves as the edema decreases. A pediatric endoscope or an anoscope can be used to determine the extent of necrosis. Alternatively the mucosa can be examined under light by inserting a test tube into the stoma. If necrosis extends below the fascia level in the abdominal wall, a revision is required immediately. If necrosis is limited in the intestine above the abdominal wall fascia, the patient can be followed. If necrosis progresses, the stoma should be revised. Crusts can be removed with gentle debridement. However, it may result in complications such as stomal retraction and stenosis in the long term [62, 63].

Stomal Stenosis

Frequency of clinically significant stoma stenosis is between 2% and 15%, and it is most commonly seen in end colostomies (Fig. 19.7). Stenosis, which develops immediately after the operation, usually occurs secondary to the size of the small trephine or bowel edema [64]. It can be decompressed with rubber catheters. The balloon of the catheter should not be inflated due to the risk of perforation. Late stenosis can be caused by various causes such as weak surgical technique that leads to ischemia, peristomal abscess, recurrent disease (Crohn's disease), or malignancy.

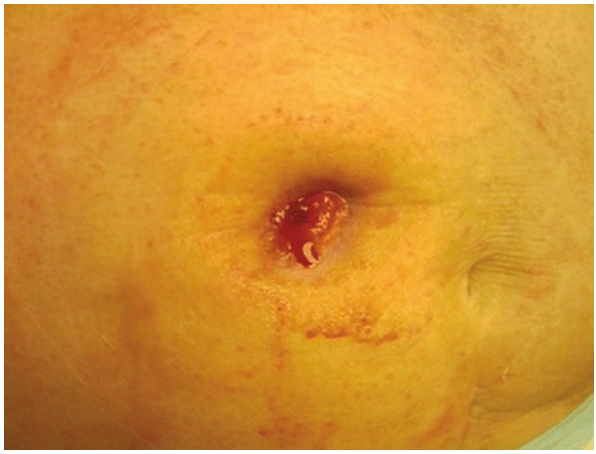

Fig. 19.7 Stomal stenosis

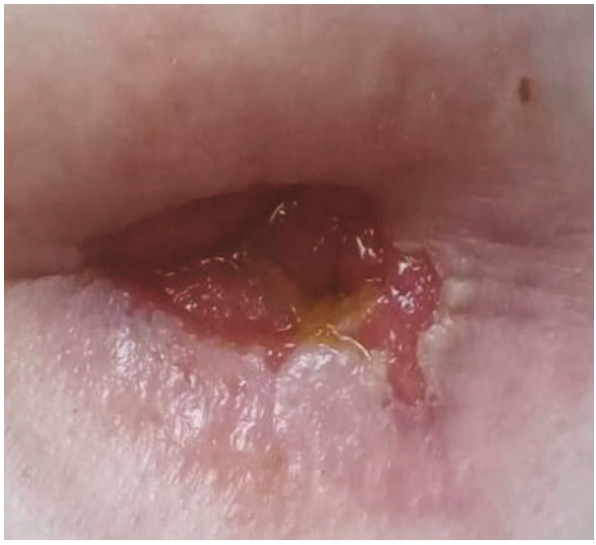

Fig. 19.8 Stomal retraction

Early mucocutaneous detachment and retraction often result in stomal stenosis because of secondary wound healing and contracture. Mild stenoses can often be managed with serial gentle dilatations and dietary changes (such as avoiding insoluble fiber). In more severe stenoses that are associated with inflammatory bowel disease or ischemia, revision is required to create a new tension-free stoma [65].

Stomal Retraction

It is generally defined as a stoma that is 0.5 cm below the skin surface within 6 weeks after stoma creation (Fig. 19.8). It occurs in 14% of new stomas in the early postoperative period. Retraction is generally associated with complications such as

leakage and peristomal skin irritation, mucocutaneous separation, and peristomal abscess [65]. The most common cause is tension in the stoma. It usually develops secondary to inadequate mobilization of splenic flexure in descending colostomies and inadequate mobilization of colon in sigmoid colostomies. Risk factors include obesity-related thick abdominal wall, postoperative weight gain, Crohn's disease, malnutrition, immunosuppression, shortness of intestinal mesentery, and initial stoma height below 10 mm. This complication can be prevented by taking into account the technical details during the creation of ostomy such as adequate mesentery mobilization and the creation of an appropriately sized facial opening, allowing an ostomy height more than 10 mm. During the creation of loop ostomy, most surgeons use a stoma support bar to reduce the risk of retraction [66]. However, the use of support rods during loop ostomy does not decrease the incidence of stoma retraction; on the contrary it increases the complication rates such as necrosis, infection, and dermatitis. In the multicentered randomized controlled study of Zindel et al., which included 78 patients, no difference was observed in the retraction rates, while higher stomal necrosis rates were observed in the group using the rod for loop ileostomy. Retracted stomata with a robust mucocutaneous junction can be managed with convex stoma devices. Additional stomal products such as belts and fasteners can also be used. Despite these measures, surgical revision should be considered if leakage and hygiene problems persist or if there is concomitant stenosis [67].

Stomal Bleeding

The incidence of stomal bleeding is unknown. It can be seen early or late postoperative period or during stoma formation. It usually occurs due to the abrasion of an unsuitable, tightly seated ostomy device. This type of bleeding can be stopped by applying direct pressure, by mucosal cauterization, or by suturing the identified vein. Peristomal varicose veins are seen in patients with portal hypertension of any reason and may cause stomal bleeding. While bleeding can initially be managed by direct pressure and suturing, medical treatments or attempts to reduce portal pressure, such as transjugular intrahepatic portosystemic shunts, are required to reduce the risk of recurrent bleeding. In cases of emergency severe variceal bleeding, disruption of stoma and re-anastomosis may provide a temporary solution [61, 68].

High Output Enterostomy

Dehydration resulting from high ostomy outflow is the most common reason for readmission in the early postoperative period. The incidence of readmission due to dehydration reaches 17%. It is more common in patients with ileal pouch restorative proctectomy, as stoma is made from the ileum that is more proximal [69, 70]. Dehydration related re-hospitalizations are associated with longer and recurrent re-hospitalizations thereafter. Re-hospitalizations have also been associated with acute kidney injury that might develop into severe chronic kidney disease.

In ileostomies, postoperative 3–8 days are the most risky days for dehydration. Attention should be paid to fluid balance and fluid replacement, as patients are frequently discharged from the hospital during this period. They should take electrolyte balanced drinks containing glucose to prevent hyponatremia. Increases in serum aldosterone levels in the long term, defined as ileostomy adaptation, help reduce the effects of water and salt deficit. Before discharge from the hospital, especially patients with ileostomy require diet training that emphasizes water and salt balance and smaller and more frequent meal consumption. In addition, they must demonstrate proficiency in evacuating their devices, changing them, and recording the output [69]. According to ERAS (enhanced recovery after surgery) protocols, most of the patients are discharged without ileostomies fully adapted to water and salt absorption. Enhanced recovery after surgery (ERAS) protocols are multimodal perioperative maintenance pathways designed to achieve early recovery after surgical procedures by maintaining preoperative organ function and reducing the profound stress response following surgery. The key elements of ERAS protocols include preoperative counseling, optimization of nutrition, standardized analgesic and anesthetic regimens, and early mobilization.

They need to be trained to understand and monitor signs and symptoms of dehydration and to take action to minimize the effects of dehydration when necessary. Despite these trainings, high rate of re-admission is observed in patients with recent ileostomy. When treatment is required for high ileostomy output, patients are instructed to avoid foods with high fat and simple sugar content and take 20–30 g of fiber a day. Although fiber will thicken the ileostomy output and reduce symptoms such as leakage and skin irritation, it has little effect on the total amount of water in the stool. If the output remains high, pharmacological treatment is required. Loperamide and diphenoxylate are often used as primary agents. Other options include octreotide, codeine phosphate, and opium tincture [70].

Stomal Prolapse

Prolapse, which can be seen in any type of stoma, is protrusion of a segment of full-thickness bowel from stoma resembling a telescope (Fig. 19.9). It is a late complication. It is more common in colostomies, especially in transverse loop colostomies. Its incidence ranges from 7% to 26%. In loop stomas, efferent (distal) leg prolapse most commonly. Risk factors for prolapse are advanced age, obesity, abdominal wall laxity, large facial defects, bowel obstruction during the creation of stoma, redundant and mobile bowel proximal to stoma, and factors increasing the intra-abdominal pressure such as ascites, chronic cough, and constipation. Studies have shown that mesenteric or fascial fixation does not decrease the incidence of prolapse [64]. Prolapse may cause problems with device attachment in mild forms, causing leakage and psychological distress. Acute prolapse can be manually reduced after mild bedside reduction, cold compress, and osmotic agent application (such as granulated sugar). Belt or girdle-style stoma products can be used to prevent recurrent prolapse. When performing manual reduction, one should start from the end of

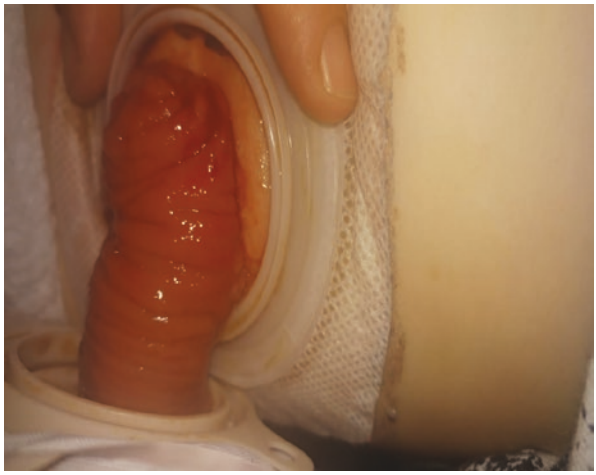

Fig. 19.9 Stomal prolapse

the intestine and gently continue invagination. More severe or chronic complicated prolapse is associated with severe mucosal irritation and bleeding due to carcinoma or strangulation. In such cases, surgical intervention is required. Fortunately, this is rare. The stoma can be constructed in the same place as prolapsed intestine, or in a different area [65].

Parastomal Hernia

It is a kind of incisional hernia which develops due to abdominal wall defect in the stoma region (Fig. 19.10). The frequency of clinically important hernias can be as high as 39%. It is most common in end colostomies. It usually occurs in the late period. The risk factors are similar to stomal prolapse; obesity, abdominal wall laxity or collagen disorders, steroid use, postoperative wound infections, large facial defects, and conditions that increase intra-abdominal pressure such as chronic cough, ascites, or constipation. It is often asymptomatic. Symptoms such as skin irritation, abdominal pain, and bowel obstruction due to difficulties in applying the stoma device may also be seen. Due to its appearance, stoma device can cause psychological problems, and this can decrease the quality of life. Obstruction or strangulation requires urgent operation. There are many studies investigating the techniques that can be used to reduce the occurrence of parastomal hernia. The size of the stoma radius has been widely discussed. The European Hernia Society Guidelines suggest that the size of the facial opening should be as small as possible without sacrificing stoma perfusion [71]. There is a general consensus among surgeons that the stoma opening should be 2 finger-width (2–3 cm). The stoma region should not be used to remove specimens. It has been shown that the use of the stoma opening for specimen removal increases the risk of parastomal hernia. In a study in 2017, Li et al. evaluated 738 patients retrospectively. The stoma region was used for specimen removal in 139 patients, whereas in 599 patients stoma was not used. In

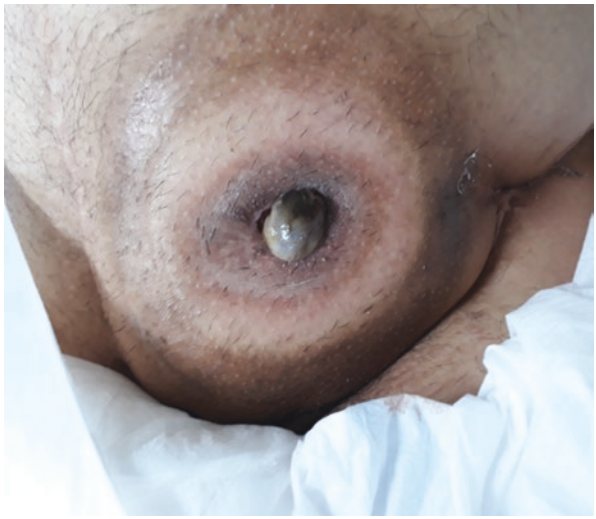

Fig. 19.10
Parastomal hernia

patients in which the specimen was removed through the stoma region, the parastomal hernia was significantly higher (4.2–10.1%, $p < 0.05$) [72]. The stoma can be constructed in the transrectal or pararectal position. Since the rectus muscle fibers are preserved, it has been proposed that the lateral pararectal location may reduce the risk of parastomal hernia. In a Cochrane review, there was no difference between the two techniques. However, this result may be related to the poor quality of the studies (lack of standardization in the surgical procedure, lack of definition, and detection method of the parastomal hernia) [73]. The PARASTOM study, a single-center randomized study, did not demonstrate the superiority of one technique over the other in terms of preventing parastomal hernia; 60 patients who underwent elective transient loop ileostomy were randomized, and no significant difference was found between the groups in terms of parastomal hernia incidence (18.5% in the lateral pararectal group and 13.8% in the transrectal group ($p = 0.725$) [74]. It was found that extraperitoneal tunneling, which is an alternative technique for stoma creation described by Goligher in 1958, is associated with lower incidence of parastomal hernia, especially in patients undergoing laparoscopic abdominoperineal resection and end colostomy. Prospective studies are needed to better define which patient subgroup will benefit most from this technique, given the increase in the duration of operation and the risk of postoperative complications associated with the use of the method [75].

When symptomatic parastomal hernia requires repair, mesh use is associated with lower recurrence rates than primary fascia repair. Based on this information, surgeons tried using a prophylactic patch during the first stoma formation to reduce the incidence of parastomal hernia. The results of numerous small studies support the use of prophylactic patches to reduce the incidence of parastomal hernias. Mesh can be placed as onlay, inlay, or sublay between the anterior abdominal wall layers by open approach or laparoscopy, and results are similar in terms of efficacy and

hernia prevention. There is a general consensus on the use of synthetic non-absorbable patches. In only one study, the STOMAMESH study, no difference was found in the rate of parastomal hernia between prophylactic patch procedures and no patch procedures [76]. A new meta-analysis of 11 RCTs involving 907 patients evaluated the cost-effectiveness of patch use for the prevention of parastomal hernia. The study found that there was no significant increase in operating time and significant cost savings was achieved in synthetic patch group [77].

SMART (Stapled Mesh stomA Reinforcement Technique) and modified SMART techniques are alternatively proposed techniques to reduce parastomal hernia rates. The former was first described in 2011 using a circular staple gun and biological mesh to strengthen the stoma trephine. The latter is a modification of the original technique using the standard polypropylene mesh fixed with a circular punch in its retro-muscular position [78, 79]. The use of a stomaplasty ring called KORING has been proposed for the prevention of parastomal hernia and has promising results in prospective, multicenter, observational experiments [80]. However, more research is needed for these alternative approaches, and no definitive recommendations as of today can be made. Routine use of the biological mesh for the prevention of parastomal hernia is not recommended.

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20 Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the Treatment of Colorectal Peritoneal Carcinomatosis

Mehmet Ustun and Taylan Ozgur Sezer

Introduction

In the past, patients diagnosed with peritoneal carcinomatosis from colorectal cancer were considered to be in the terminal period, and their treatment approach consisted of systemic chemotherapy and palliative surgery, where necessary. The cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) was first introduced by Dr. John S. Spratt from the University of Louisville in these patients in 1980 [1]. However, major advances in the administration of this treatment modality belong to Dr. Paul Sugarbaker who draws attention to microscopic spread as well as macroscopic spread in the peritoneum and directs the treatment target in this direction [2]. The purpose of this treatment modality is to eliminate all macroscopic tumor burden by CRS, which also includes peritonectomy, and microscopic residual disease by HIPEC. However, the main factor in applying this treatment modality is the selection of the right patient due to its high morbidity and cost. Today, CRS + HIPEC is accepted as the treatment modality for selected patients who are diagnosed with colorectal peritoneal carcinomatosis and have a low peritoneal carcinomatosis index (PCI) score [3].

Pathophysiology of Colorectal Peritoneal Carcinomatosis

For peritoneal carcinomatosis (PC), cells from primary tumor must first reach the peritoneal cavity. Cancer cells are shed from the surface of the tumors that show the transmural invasion of the colonic wall and serosal invasion (T4) and reach the peritoneal

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cavity. The dissemination of these cancer cells within the peritoneal cavity is facilitated by intra-abdominal movements, gravity, and the presence of intra-abdominal acid [4]. These shedded tumor cells penetrate the mesothelium, which lines the peritoneal surface and is composed of mesothelial cells, by adhesion molecules and reach the submesothelial connective tissue by attacking these cells. Thanks to angiogenesis and good blood supply of the peritoneum, cancer cells proliferate and tumor implants develop. From these tumor implants, cancer cells are shed into the peritoneal cavity, forming new metastases, and this continues in a cascade [5, 6]. This is the primary mechanism of PC development. However, PC may also develop iatrogenically during primary colorectal cancer surgery by tumor rupture, escape of tumor cells or emboli from blood vessels or lymphatics into the peritoneal cavity during resection [7, 8].

Patient Selection and Prognostic Scoring

CRS + HIPEC administration is a costly procedure with high morbidity, and the success rate is more patient oriented. Therefore, patient selection is of utmost importance in the administration and success of this treatment modality. The patient selection criteria for CRS + HIPEC in the treatment of colorectal PC are given in Table 20.1 [9].

There are scoring systems used both in deciding on patient selection and predicting the response to treatment. The two most important of them are the peritoneal cancer index (PCI) calculated based on the extent of the disease and the completeness of cytoreduction score (CCC score) calculated by measuring the remaining amount of tumor after CRS.

Table 20.1 Patient Eligibility Criteria for Treatment

Patient eligibility criteria for treatment	Exclusion criteria for treatment
Good performance status (ECOG performance status of 0–1)	Poor performance status (ECOG performance status of 2–3)
Good or moderately differentiated tumors	Presence of severe comorbidity
Appropriate tumor biology	Poorly differentiated tumor
Having a possibility for completeness of cytoreduction score to be 0 or 1	Severe malnutrition
No tumor progression on chemotherapy	Peritoneal cancer index of ≥20
Maximum three peripheral resectable liver metastases	Presence of extraperitoneal metastasis
Having good patient motivation	Multiple bilobar liver metastases
Informed consent	Biliary or ureteral obstruction
Acceptable expected quality of life	Large small bowel disease with multiple obstructions
	Massive mesenteric root infiltration not amenable to complete cytoreduction
	Massive pancreatic capsule or pancreatic infiltration requiring major resection or not amenable to complete cytoreduction
	Involvement of the gastrohepatic ligament more than 5 cm

ECOG Eastern Cooperative Oncology Group

Peritoneal Cancer Index (PCI): In this scoring system, peritoneal surfaces are divided into 13 regions (0–12). Accordingly, regions 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 are described as the peritoneal surfaces including the periumbilical region (central region), the right upper quadrant, the epigastrium, the left upper quadrant, the left flank, the left lower quadrant, the pelvis, the right lower quadrant, the right flank, the upper jejunum, the lower jejunum, the upper ileum, and the lower ileum (including the mesos of jejunum and ileum regions), respectively. The diameter of the largest tumor in these specified regions is measured. A score of 0 is assigned when there is no tumor, a score of 1 when the tumor diameter is 0–5 mm, a score of 2 when the tumor diameter is 5 mm to 5 cm, and a score of 3 when the tumor diameter is greater than 5 cm or it is conglomerated (Fig. 20.1). These scores of tumors are calculated for each of these 13 regions, and the sum of each score gives the peritoneal cancer index [10].

Completeness of Cytoreduction Score (CCC score): This scoring system reflects the efficacy of CRS by measuring the remaining amount of macroscopic tumor after CRS. A score of 0 indicates that there is no remaining macroscopic tumor, a score of 1 indicates that the diameter of the largest remaining tumor is <2.5 mm, a score of 2 indicates that the diameter of the largest remaining tumor is between 2.5 mm and 2.5 cm, and a score of 3 indicates that the diameter of the largest remaining tumor is >2.5 cm. Those with a score of 0–1 are considered to be complete, and those with a score of 2–3 are considered incomplete cytoreduction [10].

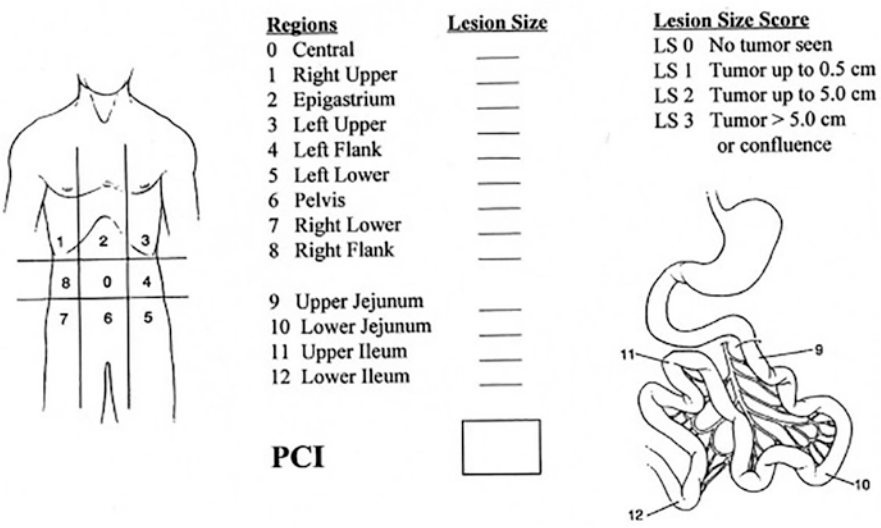

Fig. 20.1 Regions: 0 periumbilical region (central region), 1 the right upper quadrant,2 the epigastrium, 3 the left upper quadrant, 4 the left flank, 5 the left lower quadrant, 6 the pelvis, 7 the right lower quadrant, 8 the right flank, 9 the upper jejunum, 10 the lower jejunum, 11 the upper ileum, and 12 the lower ileum (including the mesos of jejunum and ileum regions)

A PCI value less than 10 is considered to be "mild," and a PCI value greater than 10 to be "severe" disease. Although the prognosis of the mild disease is reported to be better, there are deficiencies in determining the prognosis in this scoring system. In a patient with low PCI, if there is involvement of structures whose resection would be a problem (such as meso root, bladder floor), the prognosis will be poor despite low PCI in this patient. Therefore, the CCC score is essential for determining prognosis. The prognosis will be better if a complete cytoreduction is achieved. Although predictions may be made about the CCC score during the preoperative period, the main CCC score is calculated after the surgery [10].

Other than those mentioned, there are developed scoring systems. The Peritoneal Surface Disease Severity Score (PSDSS), which scores the extent of disease spread, is one of them [11–13]. However, PCI is considered to be superior to this scoring system in predicting overall and disease-free survival [14]. Colorectal Peritoneal Metastases Prognostic Surgical Score (COMPASS) is a more recent scoring system and assesses four parameters (age, PCI score, lymph node status, ring cell histology). Although COMPASS seems superior to PSDSS, future studies are warranted to demonstrate its effectiveness [9, 15, 16].

Cytoreductive Surgery

CRS is the general name of the surgical procedure involving the resection of complete colorectal tumor macroscopically, the resection of organs involved by the tumor, prophylactic resection of organs (large omentum, ovary) at risk of involvement, even if not involved by the tumor, and peritonectomy of the involved peritoneum. In 1995, Dr. Paul Sugarbaker described the CRS stages and their technical characteristics under the heading of peritonectomy procedures [16]. Sugarbaker has described the CRS stages as follows: omentectomy and splenectomy, left upper quadrant peritonectomy, right upper quadrant peritonectomy, cholecystectomy and lesser omentectomy, rectosigmoid colon resection, pelvic peritonectomy, and antrectomy. This method is performed successfully with surgical technical developments and increased experience of the surgeons [17, 18].

The patient is placed in a lithotomy position on the table. However, unlike the normal lithotomy position, gluteal folds are advanced to the end of the operating table, and the legs are extended in leg holders mounted on the operating table to ensure full and comfortable access to the perineum. For venous thromboembolism prophylaxis, the thighs and legs should be wrapped by pressure-exerting mechanisms. This procedure should be performed before anesthesia induction to ensure maximum prophylaxis. Necessary measures should be taken to prevent hypothermia. Genital areas should also be included in the cleaning and preparation of the surgical area, and a urinary catheter and nasogastric tube should be placed in the patient. Also, central catheterization may be requested from the anesthesia team for vascular access [16]. The abdomen should be opened through an incision from xiphoid to the pubis, and xiphoid should be removed. In cases where resection is not feasible, tumor implants are cauterized using a knob tip. CCC score is calculated after the surgery is completed [10].

Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Different techniques for intraperitoneal chemotherapy have been described. These are:

1. Early postoperative intraperitoneal chemotherapy (EPIC)
2. Sequential postoperative intraperitoneal chemotherapy (SPIC)
3. HIPEC

Today, HIPEC is the most commonly used one among these methods in the treatment of colorectal peritoneal carcinomatosis. HIPEC is the intraperitoneal perfusion of chemotherapeutic agents at 42–43 °C to eliminate the remaining microscopic disease after CRS. However, the composition, volume, concentration, duration of administration, and temperature of the chemotherapeutic agent used in the practice may vary [9].

HIPEC is delivered in two ways:

1. *Open technique*: In this technique, after CRS drains are inserted, a synthetic sheet is put on the abdomen, and HIPEC is administered. After HIPEC is completed, anastomoses are performed, and the abdomen is closed [10].
2. *Closed technique*: After CRS, drains and temperature probes are placed, and the skin is temporarily closed. Then, HIPEC is administered. After HIPEC is completed, the skin is opened, anastomoses are performed, and the abdomen is closed [10].

   Some groups make anastomoses before HIPEC and reported that there was no increase in anastomotic recurrence [19].

HIPEC has important advantages compared to systemic chemotherapy. In HIPEC administration, higher concentration for the tumor is achieved compared to systemic treatment by giving chemotherapeutic agents directly into the abdomen, and the peritoneal plasma barrier provides dose-intensive therapy. Thus, a better response for PC is obtained. In addition, the chemotherapeutic agent concentration is lower in the peripheral circulation, and its systemic toxicity is moderate. Better penetration of chemotherapeutic agents into tissues thanks to the hyperthermic administration of the procedure provides a cytotoxic effect against tumor cells by direct effect or augmenting the effect of chemotherapeutics [9].

Many chemotherapeutic agents used in systematic therapy can also be used in intraperitoneal chemotherapy. Mitomycin C, irinotecan, cisplatin, doxorubicin, and oxaliplatin in combination with intravenous 5-FU and leucovorin are used for the treatment of colorectal PC [20]. Today, there are two common methods in HIPEC administration:

1. Mitomycin C with an administration time of 60–90 min at 41 ° C using the closed technique [21]
2. Oxaliplatin (±irinotecan) (460 mg/m^2 of oxaliplatin in 2 L/m^2 of isosmotic 5% dextrose) and then intravenous infusion of 5-FU (400 mg/m^2) with leucovorin

(20 mg/m^2) with an administration time of more than 30 min at 43 ° C (range: 42–44 °C) using the open technique [22]

Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

Pressurized intraperitoneal aerosol chemotherapy (PIPAC) is a current treatment modality used in selected patients, who have no indication for CRS and hyperthermic HIPEC, to alleviate symptoms, to reduce intra-abdominal acid, to induce regression of PC, and to improve the quality of life of the patient. In this method, chemotherapeutic agents are administered laparoscopically into the abdomen using pressurized aerosols. It should be determined that there is no indication for HIPEC and CRS before PIPAC administration. Distant metastases do not prevent PIPAC administration in these patients [23]. There are several studies on the efficacy of PIPAC, a new technique, and these are ongoing. The data obtained indicate that PIPAC may be an option in the palliative treatment of colorectal PC. It is not just palliative treatment; it can also be interesting as a neoadjuvant local treatment with or without systemic chemotherapy [24].

The Role of CRS with HIPEC in the Treatment and Results

There are a large number of studies in the literature about the efficacy and role of CRS with HIPEC in the treatment of colorectal PC. These studies provide important data. In the Swedish peritoneal study (Clinical trial information: NCT01524094) published by Cashin et al. in 2016, it was stated that cytoreductive surgery with intraperitoneal chemotherapy may be superior to systemic oxaliplatin-based treatment in the treatment of colorectal cancer with resectable isolated peritoneal metastases (median overall survival: 25 months vs. 18 months, $p = 0.04$) [25]. Besides, there are important studies providing data that support the increased overall survival due to CRC with HIPEC and their efficacy in the treatment of PC [26–28]. The first results of the PRODIGE 7 study (Clinical trial information: NCT00769405) investigating the efficacy of HIPEC after CRS in the treatment of colorectal PC were published in the American Society of Clinical Oncology (ASCO) Annual Meeting in 2018. After a median follow-up of 63.8 months, the median overall survival was 41.7 months in the HIPEC group and 41.2 months in the non-HIPEC group ($p = 0.995$). The median recurrence-free survival was 13.1 months in the HIPEC arm and 11.1 months in the non-HIPEC arm ($p = 0.486$). The overall postoperative mortality rate was 1.5% in both groups, and there was no statistical difference in the morbidity rate at 30 days. At 60 days, the grade ≥3 morbidity rate was 24.1% in the HIPEC group and 13.6% in the non-HIPEC group ($p = 0.03$). According to the preliminary results of this study, CRS shows satisfactory survival results in the treatment of colorectal PC, and the addition of HIPEC with oxaliplatin does not influence the overall survival [29]. However, the results of this study are valid for HIPEC administration containing oxaliplatin, and the efficacy of HIPEC administration containing different chemotherapeutics is unknown.

New studies can present different results. Today, the role of CRS with HIPEC in the treatment of colorectal PC is updated with the support received from published articles and is now included in the guideline recommendations [30, 31].

The concept of second-look surgery with HIPEC describes a second laparotomy, and, in case of detecting PC, HIPEC administration after a certain time following the initial surgery in patients at risk of developing PC in whom several nodules were detected during initial surgery, complete resection along with primary tumor resection had performed, ovarian metastasis was found, and spontaneous or iatrogenic tumor perforation and intra-abdominal tumor seeding occurred [32]. Adjuvant HIPEC administration is the administration of HIPEC as an adjuvant in the same session during initial surgery in patients in whom a risk of developing PC was observed during primary surgery [9].

Both methods aim to prevent PC before developing. There are studies presenting data on the efficacy of both methods. But for the moment, there is no complete consensus regarding their efficacy and their superiority to each other. In conclusion, all the data in the literature show us that the best way to treat colorectal PC is early treatment or to prevent its development, and the future of treatment will be established on these two bases [33].

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Follow-Up of Patients with Surgical Colorectal Cancer Resection

21

Levent Ugurlu

Abbreviations

ACS	The American Cancer Society
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
CCO	Cancer Care Ontario
CEA	Carcinoembryonic antigen
CRC	Colorectal cancer
CT	Computed tomography
ECOG	The Eastern Cooperative Oncology Group
EUS	Endoscopic ultrasound
ESMO	The European Society for Medical Oncology
FDG	(18F-fluorodeoxyglucose)
JSCCR	Japanese Society for Cancer of the Colon and Rectum
MRI	Magnetic resonance
MSTF	The US Multi-Society Task Force on Colorectal Cancer
NCCN	The National Comprehensive Cancer Network
PET	Positron emission tomography
SUV	Standardized uptake value
TME	Total mesorectal excision

Colorectal cancers (CRCs) are among the most frequently seen cancers worldwide and the fourth leading cause of death from cancer [1, 2]. Every year 145,000 new cases are detected in the USA [1]. The primary treatment of 80% of non-metastatic

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CRCs is surgical resection. The most powerful prognostic tool in these patients is the histopathological analysis of the resected specimen [3].

Five-year survival in patients with CRC is directly related to tumor stage [4]. While 5-year survival rate is 75% in stage 1 CRC, this rate decreases down to 5% in stage 4 disease [5]. Today, TNM classification recommended by the American Joint Committee on Cancer (AJCC) is most frequently and widely used all over the world. In this classification, the level of invasion to the intestinal wall (T), the number of involved lymph nodes (N), and the status of distant metastasis (M) are taken into consideration [6].

Despite potentially curative surgery, modern adjuvant chemotherapy, and/or radiotherapy, recurrent disease will develop in more than 40% of stage 2 or stage 3 patients following primary treatment [7]. Most (90%) of these recurrences will be seen within 5 years, most frequently within 2 years after surgery [8].

The frequency of applying surgical interventions in CRC has increased in line with the increasing rate of diagnosis. However, appropriate postresection follow-up programs have been required. Today, follow-up guidelines of some experienced centers from Europe, the USA, and Japan have been published [9].

Postresection follow-up of CRCs is an important issue and has three main objectives.

1. Determination of residual tumor tissue and local recurrence
2. Detection of synchronous, and metachronous colorectal tumors
3. The detection of metastases in the appropriate period for resection [10]

Therefore, it is important to manage the follow-up programs in compliance with these objectives. Patients diagnosed with CRC carry the risk of synchronous CRC at the time of diagnosis and metachronous CRC after surgical resection [11]. While synchronous CRCs are seen with a frequency of 2–7%, the risk of developing metachronous CRCs within the first 5 years after resection is reported to be 2–12% [12–14].

Colonoscopy is the most commonly used follow-up method for the detection of residual tumors, local recurrence, and metachronous colorectal lesions, whereas computed tomography (CT) is used for the detection of metastases [15–17]. In addition, medical history, physical examination, and measurement of carcinoembryonic antigen (CEA) are recommended in the follow-up guidelines. Inadequate use of follow-up methods may result in encountering advanced stage CRC, while overuse of resources should be avoided in screening programs and for other purposes [9]. Since very few of the previous randomized controlled trials included stage 1 patients or unresectable stage 4 patients, in most guidelines, postresection follow-up recommendations of CRCs have mostly focused on stage 2 and stage 3 cancers [18].

Follow-Up in Stage 1 Patients

There is insufficient data to formulate a guideline for postoperative follow-up in resected stage 1 colon and rectal cancer. In the included guidelines, there are differences between the recommendations. Since cure is achieved in more than 95% of the cases by resection alone, the recommendations are mostly concerned with colonoscopic follow-up [19].

Any follow-up method besides colonoscopy is not recommended for treated colon cancer cases in the guidelines of the American Society of Clinical Oncology (ASCO) [20], Cancer Care Ontario [21], the British Columbia Medical Association [22], and the National Comprehensive Cancer Network (NCCN). NCCN recommends a follow-up strategy for resected rectal cancer as in stage 2 and stage 3 patients. In addition, for patients who underwent transanal excision, endoscopic USG (EUS) or magnetic resonance (MRI)-guided proctoscopy is recommended at every 3–6 months for the first 2 years, then at every 6 months [23].

In a cohort study of the Japanese Colon and Rectum Cancer Association (JSCCR) which had an average follow-up of 7.8 years, the recurrence rate (local recurrence and metastasis) has been reported as 1.3% in lymph node-negative PT1 colon cancer and 1.1% in rectal cancer [17, 24]. Despite this low risk of recurrence, the Japanese guidelines recommend an intensive follow-up program for stage 1 cancers with the view that early detection of recurrences will increase the chance of cure [17]. Similarly, the European Society for Medical Oncology (ESMO) guidelines recommend a follow-up similar to stage 2 and stage 3 in stage 1 CRCs [25].

Follow-Up in Stage 4 Patients

Surgery has a curative potential in CRCs with metastatic disease, survival rates up to 40% have been reported in patients undergoing partial hepatectomy for isolated hepatic metastasis. Although isolated lung metastases are seen more rarely, metastasectomy can provide a 5-year survival rate of 35–45% in these patients [26–28]. There is insufficient data for surveillance in patients with stage 4 CRC. However, following the same logic as stage 2 and stage 3 patients, it is thought that early detection of asymptomatic relapses may potentially increase the rates of patients who will benefit from treatment [10]. Most of the major guidelines do not contain a follow-up strategy for stage 4 CRC patients [21, 25, 29, 30]. However NCCN recommends follow up of these cases just like stage 2 and 3 patients including more frequent screening with CT [23].

Though ASCO recommends follow-up in patients with good performance due to the possibility of re-resection after the detection of recurrence, ASCO has also

indicated that patients who are not suitable for any surgical procedure and cannot tolerate chemoradiotherapy are not suitable for follow-up [8]. In a large-scale cohort study from Japan, the recurrence rate of resected stage 4 patients was detected to be significantly higher (74.7%), and the majority of them were identified in the early postoperative period. In this stage of recurrence, resectability was similar to stage 3, and the impact of surgical resection on survival was found to be the same as in other stages [18]. It has been reported that early detection of asymptomatic recurrences may even exert positive effects on the prognosis of patients not suitable for surgery treated with current aggressive chemoteropathics [31].

Follow-Up in Stage 2–3 Patients

Follow-up recommendations for resected CRCs have been focused on stage 2 and stage 3 diseases. In the 1990s, many randomized controlled trials compared more and less intensive postoperative follow-up results for the detection of recurrence in CRC patients. In the 2000s, several meta-analyses showed positive effects of intensive follow-up programs on the detection of recurrence rate, surgery for recurrence, and postoperative survival [32–36]. Since then, major Western study groups such as ASCO, NCCN, and ESMO have begun to offer intensive follow-up strategies in their treatment guidelines including clinical examination and physical examination; measurement of serum CEA levels; thoracic, abdominal, and pelvic CT; colonoscopy; and proctosigmoidoscopy [15, 37, 38].

The following information should be taken into consideration in the intensive follow-up program to be applied after CRC surgery.

1. More than 90% of recurrences occur in the first 5 years, and most of them are seen in the first 3 years.
2. Metachronous colon cancer will develop in 7% of the patients.
3. The risk of recurrence depends on several factors. TNM classification is the most important factor in determining the risk of recurrence.
4. The aim of the follow-up is to detect metastases at the appropriate time for resection.
5. Follow-up should be performed with patients who can tolerate major surgical procedures and subsequent chemotherapy treatments [10].

The main purpose of follow-up after CRC surgery is to improve survival. In some systematic reviews, intensive follow-up after CRC surgery has shown positive effects on overall survival [24, 32, 35, 39, 40]. Intensive follow-up protocols to improve survival in experienced guidelines differ somewhat [9]. In a meta-analysis including 11 studies with 4055 CRC patients in whom intensive follow-up protocols were or were not applied, it was reported that the probability of detection recurrent disease at an asymptomatic stage and application of curative surgery in these recurrences were more likely in the intensive follow-up group [41].

Studies performed have shown that patients with asymptomatic recurrence are more eligible to curative resection than symptomatic patients which provides better progression-free and overall survival. However, it should be kept in mind that curative surgery may be also possible in symptomatic recurrences. In the Eastern Cooperative Oncology Group (ECOG) study, in which colon cancer recurrences were reported, 25% of the patients with resectable recurrences were symptomatic at presentation [39, 42–44].

History and Physical Examination

In the follow-up of colorectal cancer patients, the patient's history is important to reveal symptoms of the disease recurrence such as newly developed changes in bowel habits, rectal bleeding, abdominal pain, and especially perineal pain in rectal cancer. In addition, physical examination should be performed to detect any signs of recurrence such as ascites, hepatomegaly, and supraclavicular lymphadenopathy. Recurrence rate can be detected in 15–40% of the patients with history and physical examination [8]. However, due to the emergence of symptoms between visits, and asymptomatic lung and liver metastases in the early period, resectable recurrences cannot generally be detected by history and physical examination alone [45, 46]. However, history and physical examination are the first steps in a follow-up strategy [8]. Periodic history taking and physical examinations are recommended in many post-treatment follow-up guidelines by many expert groups as ASCO, ESMO, and NCCN [20, 23, 25, 30]. Since most of the recurrences develop in the first 3 years and were not common after 3 years, clinical visits consisting of history and physical examination have been generally recommended at every 3 months in the first 3 years, then at every 6 months, in the fourth and fifth years.

Carcinoembryonic Antigen (CEA)

Follow-up based on CEA measurements is recommended for the detection of potentially resectable metastases after CRC surgery [40, 47]. CEA was discovered in 1965, and it is the only tumor marker that has been shown to be effective in the follow-up of colorectal cancer patients [48]. Elevated CEA levels, first considered for CRCs, have been subsequently demonstrated in cancers such as stomach and pancreas malignancies and other inflammatory conditions [33, 49, 50]. Measurement of CEA levels in the detection of recurrence after CRC surgery is considered to be the most cost-effective assessment [50]. It is not used in the screening test of CRC because of both low sensitivity and specificity of CEA. However, it correlates with the prevalence of the disease in individuals with known CRC disease, and it has a prognostic value [26]. Studies have shown that there is a time interval of 1.5–6 months between the elevation of serum CEA levels and the detection of disease recurrence [51–54]. The half-life of CEA is known to be about 7 days. After R0 resection, the CEA level can return to normal within 4–6 weeks. Persistent CEA elevation may be

indicative of infiltration or metastasis. The slow increase in CEA levels after surgery is a typical sign of local recurrence. In addition, the rapid increase in CEA levels may be indicative of liver metastases [50, 55]. However, normal postoperative CEA level is not sufficient to exclude the recurrence of the disease even if the preoperative CEA level is high. CEA level does not increase in 30–40% of CRC recurrences. Therefore, while the increase in postoperative CEA probably shows recurrence, normal CEA value does not exclude disease recurrence [56]. CEA follow-up test may show CEA values above 10 ng/ml in smokers [57]. Another reason for false positivity is the deterioration of liver function due to the use of 5-fluorouracil in adjuvant therapy [58]. False positivity is common at 5–10 ng/ml of CEA. Once these values are detected, they should be confirmed a second time and, if still elevated, abdominothoracic CT and colonoscopy should be performed to determine the localization of metastatic/recurrent disease. Positron emission tomography (PET)/CT can be performed in selected patients. Major follow-up guidelines recommend concurrent assessment of CEA levels during clinical visits consisting of history taking and physical examination.

Colonoscopy

Colonoscopy is a standard method with a sensitivity of 95% for local or metachronous recurrence of CRC [59]. The optimal frequency and benefits of postoperative colonoscopy are still controversial. In some of the meta-analyses or randomized studies, although any superiorities have not been detected between colonoscopic follow-ups performed at 3- to 5-year, annual, or shorter intervals [60–62], periodic follow-ups are supported by major groups such as ASCO, ESMO, and NCCN [20, 23, 25, 30, 63]. Follow-up colonoscopy has two purposes. The first is the detection of metachronous lesions that can be seen after 10 years in some patients, mostly within the first 36 months [64]. The second is the detection of anastomotic recurrences within the first 3 years of primary resection in patients who have not undergone total mesorectal excision and/or received pelvic radiotherapy, especially in cases with rectal cancer [65–67]. The benefits of colonoscopic follow-up of CRCs after resection have been demonstrated in several studies. Most of the metachronous tumors detected during these follow-ups were stage 1–2 CRCs, while 56% of them were asymptomatic, and curative surgery could be performed in 87% of these tumors [65, 66, 68–74]. In a study comparing intensive, and routine colonoscopic follow-ups, curative surgery was performed in 2/3 of the patients with intraluminal recurrence in the intensive colonoscopic follow-up group and in only 1/3 of the routine follow-up group. Overall survival rates after CRC recurrence increased in patients in the intensive follow-up group. However, this increase was not statistically significant as demonstrated in the study comparing intensive and routine colonoscopy groups [75]. These findings have demonstrated the positive effects of intensive colonoscopic follow-up in patients with local recurrence and endoluminal

metachronous CRC. However, as endoluminal recurrence affects fewer patients, their impact on overall survival is limited. Complete colonoscopy with high-quality endoscope should be performed before first surgical intervention in CRCs [76, 77]. If surgery is performed due to malignant obstruction and therefore insufficient colonoscopy is performed, repeat colonoscopy is recommended within 3–6 months after surgery to detect synchronous lesions [15, 17, 20, 76]. In addition, colonoscopy is recommended in the postoperative first year for the detection of metachronous tumors [15, 20, 78, 89]. The US Multi-Society Task Force on Colorectal Cancer (MSTF) recommends realization of the first colonoscopy 1 year after curative surgical resection performed for colon or rectal cancers. MSTF recommends realization of the first colonoscopy in the postoperative period for obstructed cancers. MSTF also advices realization of the second colonoscopy after the first colonoscopy 3 years later, and thereafter in the fifth year, provided that no significant pathological findings were observed [76]. ESMO has published separate recommendations for early-stage colon cancer [15], primary colon cancer [30], and rectal cancers [25]. In these three entities, MSTF recommends colonoscopy 1 year after surgery and repeat colonoscopies every 3–5 years if there were no significant abnormal findings. In the absence of a significant finding, ASCO finds third-year colonoscopy unnecessary and recommends colonoscopic follow-up in the first and fifth years [20]. ACS recommends sequential colonoscopies in the first, third, and fifth years [80]. Finally, NCCN recommends first colonoscopy in the first year, second colonoscopy in the third year, and then every 5 years for both colon [81] and rectal cancers [82].

Proctosigmoidoscopy

Advances in rectal cancer surgery (total mesorectal excision (TME)) and the use of neoadjuvant chemoradiation have reduced the local recurrence rates to less than 10% [83–85]. Proctosigmoidoscopic follow-up is recommended for patients with rectal cancer who underwent TME without additional surgery, in patients who underwent submucosal dissection or transanal excision, those with locally advanced rectal cancer who did not receive neoadjuvant radiotherapy, and in patients who did not undergo radiotherapy after rectal cancer surgery because of the risk of local recurrence [20]. There are some differences in follow-up guidelines created by experienced groups. ASCO no longer recommends proctosigmoidoscopy in patients receiving radiation therapy but continues to recommend proctosigmoidoscopy every 6 months for 2–5 years in rectal cancers that have not received radiation therapy [86]. On the other hand, NCCN recommends proctosigmoidoscopy with endoscopic ultrasonography (EUS) and MRI every 3–6 months for 2 years and then every 6 months for 5 years in rectal cancer patients who underwent only transanal excision [23]. According to ESMO, the role of postoperative colonoscopy is not clear-cut. Colonoscopy is recommended in the first year. If no pathology is found, colonoscopy is recommended every 5 years until the age of 75 [25].

Computed Tomography (CT)

CT is the most widely used imaging technique in follow-up to show CRC recurrences [87]. CT is the "gold standard" diagnostic test that was pathologically confirmed in a study of 1226 patients and predicts the recurrence of CRC with 85% sensitivity and 92% specificity [88]. The liver and lung are the most common sites of metastases of CRC [89, 90]. Therefore, imaging of the liver is important in colon and of the lungs in rectal cancer [8]. While, USG was recommended in previous ASCRS protocols and many follow-up guidelines, current recommendations emphasize abdominopelvic CT. When compared with USG, contrast-enhanced CT is more specific in the detection of early-onset hepatic metastases, non-hepatic intra-abdominal metastases such as retroperitoneal or ovarian metastases [78]. Seven randomized studies examined the effect of liver imaging on recurrence and overall survival [60, 91–96]. These studies have shown positive effects of CT on prediction of overall survival and recurrence. According to previous ASCRS data [97] and three randomized trials, more than 12% of patients with chest X-ray can show resectable metastases in the lungs [60, 91, 92]. However, nowadays, cross-sectional images such as obtained in CT are recommended especially in the radiological follow-up of the lungs which are known to be the most common metastatic site of distal rectal cancers [78]. In the European intergroup study in which follow-up with CT was performed, potentially curative resection could be achieved more probably in recurrent cases than in the American intergroup study where follow-up with CT was not performed. At the same time, a longer life expectancy was obtained in the group where routine follow-up was performed compared to the group with pulmonary metastases detected after symptoms emerged [98, 99]. As demonstrated in various studies especially CT screening differs from the methods used in intensive follow-ups with survival advantages [61, 62, 72]. ASCO [20] and CCO [21] recommend computed tomographic follow-up of the abdomen and thorax once a year for 3 years and added tomographic imaging of the pelvis in rectal cancers. ACS [80] recommends follow-up of the abdomen/pelvis and thorax once a year for 5 years with CT. In colon cancers, NCCN [23] recommends CT monitoring of the abdomen/pelvis and thorax every 6–12 months for 5 years. In addition, NCCN recommends CT/abdominal monitoring of the abdomen/pelvis and thorax every 3–6 months for 2 years and then every 6–12 months for 5 years in rectal cancers with high risk of recurrence and rectal cancer resected patients with metastatic disease.

Pet-Ct

FDG (18F-fluorodeoxyglucose) accumulates in malignant tumors and metastatic lesions where glucose consumption increases due to glycolysis and increased glucose transport in the cell membrane [100]. Positron emission tomography (PET) with FDG is widely used in the analysis of cellular metabolism. The 18F-FDG PET/CT is an imaging modality which can provide anatomical and functional

information and is used in the staging and re-evaluation of some cancers [101]. With these features, PET/CT scans all body parts in the same session for the detection of recurrence or metastasis using a single device [102]. SUV (standardized uptake value) is a simplified measure of FDG uptake. It is a relative indicator of metabolism in the lesions being evaluated. Tumor type is influenced by many factors, such as plasma glucose level, body size, and phosphorylation rate. Although SUV value of 2.5 or higher is considered as an indicator of malignant tissue, an SUV value of around 2.5 may be seen in non-malignant regions, whereas 2.5 < SUVmax values may be seen in small tumors [103]. The liver is the most common site of CRC metastases. Different sensitivity rates of FDG-PET/CT for the detection of liver metastases have been indicated in various publications In some publications, it has been reported that FDG-PET/CT is comparable to conventional CT in detecting hepatic or even more advantageous in the identification of extrahepatic metastases [104]. However, there are not enough publications and series to evaluate the efficacy of FDG-PET/CT for pulmonary metastases of CRC and compare it with conventional CT findings [105].

In reliable studies, it has been shown that FDG-PET/CT has a higher diagnostic performance in CRC recurrences, especially in locoregional and lymph node metastases compared with other conventional imaging methods [106]. FDG-PET/CT has been used in some of the studies on staging and postoperative follow-up in patients with CRC. In these studies, it has been reported that it was a highly sensitive and specific method for the detection of small colorectal recurrences in patients with elevated CEA and normal conventional imaging findings [107]. The results of recent studies have shown the positive effects of FDG-PET/CT on the management of diseases. On the other hand, it has been reported that sensitivity of FDG-PET/CT may decrease in detection of subscentimetric lesions, and yield false-positive results meaning that small metastatic deposits may not be seen [108], Besides, FDG-PET/CT may be mistakenly evaluated as false-positive in benign inflammatory conditions or false-negative in patients with high blood glucose levels and those that recently received chemotherapy [104, 109]. In conclusion, although some studies have shown efficacy of FDG-PET/CT in detecting early recurrences and secondary tumors [110–113], this benefit is balanced by false-negative and false-positive results obtained. FDG-PET/CT has no place in routine follow-up yet. It is not included in postoperative follow-up guidelines in CRC patients prepared by experienced groups such as ASCO [20] and NCCN [23]. Until more data are available on FDG-PET/CT, which is increasingly used to detect disease recurrence in recent years, the prevailing tendency is that it should not to be routinely used in the monitoring.

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Infectious Disease Approach to Colorectal Surgery

22

Sukran Kose and Muge Ozguler

Introduction

Colorectal surgery is mostly applied for disorders and diseases of the colon, rectum, and anus [1]. The most common pathologies that related to colorectal surgery are colorectal cancers, diverticular intestinal disorders, adhesions and strictures, pilonidal sinus, hemorrhoidal diseases, anal cancers, anal abscess, anal fissure and fistula, rectal prolapse, and rectocele [2].

There are some postoperative complications about colorectal surgery, and these complications can cause to increase hospitalization and ventilation days, mortality rates, and costs. One of the important complications after colorectal surgery is infectious problems [3]. Infectious complication rates are observed in <10% of patients with appropriate antimicrobial prophylaxis, whereas 30–60% of patients do not receive appropriate prophylaxis. Fecal fistula, intra-abdominal abscesses, peritonitis, and septicemia are other infectious complications, but these are much less common [4].

In this study, it is aimed to present the approach to fever and infectious complications that are seen after colorectal surgery.

Fever in Patients After Colorectal Surgery

Many reasons can cause fever in patients who have undergone any surgery. Careful management of fever is required in patients in perioperative course [5]. The cause of fever may be as simple as a drug reaction or as dangerous as a life-threatening

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infection. But sometimes the cause of fever may not be found [6]. Lower fevers (<38.9 °C) have been considered to be associated with noninfectious reasons, whereas higher temperature may be an alert for an infectious reason [7]. In a study, fever ≥38 °C has been noted in 61 patients, and the source of infection has been found in seven (11.5%) of the patients. Infection has been detected in 12 (5.4%) out of 223 patients without fever. Sensitivity and specificity rates of fever of 38 °C as a predictor of infection have been reported as follows: 37% and 80%, respectively [8]. Therefore, noninfectious and infectious reasons of the fever should be determined in these patients.

Timing of fever after surgery can contribute to differentiating several reasons that may cause fever [9]. Fever that occurs 48 h after surgery is generally considered to be infectious, while fever within 48 h is generally considered to be associated with noninfectious causes [10]. Fevers that are observed in between days 1 and 4 have been reported as rarely related to an infection [11]. Fever that is observed on or after postoperative day 5 has a significance for an infectious focus [12]. In a study about idiopathic postoperative fever, no infectious reason has been found in 80% of patients on the first day of surgery [10]. Any focus of infection such as wound infection (42%), urinary tract infection (UTI) (29%), or pneumonia (12%) has been determined in 90% of patients with fever >5 days after surgery [5]. In a review, fevers in the first 4 days after surgery have been determined as much less associated with infectious etiology as are fevers in >4 days [12].

Noninfectious Causes

Mostly observed noninfectious causes of fever are presented below [7].

Atelectasis

While postoperative atelectasis is thought to be the cause of fever in previous experiences, numerous studies have shown that it is not related to fever in currently. Atelectasis is not related to fever or degree of fever. In a study, the presence of fever has been reported in 40% of patients who had elective abdominal surgery. Chest film has been done and atelectasis has been found in 57% of febrile patients. When the fever threshold was 38.0° C, only 47% of the patients had atelectasis [7].

Pulmonary Embolism

In the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, fever >38 °C has been found to be related only to acute pulmonary emboli in 57% of their series of 35 patients, whereas fever with no reason has been observed in 14% of the 311 patients [13]. The properties of fever that are observed with pulmonary embolism are generally as follows: rarely more than 38.3 °C, emergence of a short time and peak on the day of pulmonary embolism, and disappear slowly in a week. Septic thrombophlebitis may be a cause of septic pulmonary emboli, and higher postsurgical fevers are seen in these patients [14].

Adrenal Insufficiency

Acute adrenocortical insufficiency is a reason for postprocedural fever. It is required for prompt differential diagnosis because it is a life-threatening condition and has high rates of morbidity and mortality [15].

Malignant Hyperthermia

Malignant hyperthermia is another life-threatening clinical syndrome of hypermetabolism. Inhalational anesthetic agents, muscle relaxants such as succinylcholine, and other drugs may cause malignant hyperthermia. It happens in sensitive individuals with abnormal calcium regulation in the skeletal muscle. Substantial amount of calcium that is released from sarcoplasmic reticulum of the skeletal muscle causes hypermetabolism. Metabolic and respiratory acidosis, heat production, elevation at the level of carbon dioxide, increased oxygen spending, hyperkalemia, active sympathetic nervous system, disseminated intravascular coagulation, and multi-organ dysfunction and failure are results of hypermetabolism in malignant hyperthermia [16].

Alcohol Withdrawal

In alcoholics, fever may be seen as an indicator of withdrawal syndrome. In a study, no infectious cause of fever has been found in 1/3 of patients with alcohol withdrawal syndrome [17].

Others

The other non infectous causes are hematoma, dehydration, drug fever, factitious fever, myocardial infarction, neoplasms, pancreatitis, pheochromocytoma, pericarditis/Dressler's syndrome, thrombophlebitis, thyrotoxicosis, and tissue trauma [18].

Infectious Causes

Surgical Side Infections (SSI)

Approximately 4–10% of patients who applied interventions related to the colon and 3–27% of patients who applied interventions related to the rectum suffer from SSIs [19]. SSI is not only a factor for increasing the cost of healthcare; it also affects the patient's recovery and survival [20]. In a study about antimicrobial prophylaxis in colon procedures, significantly lower mortality rates (11.2% for control vs. 4.5% for treatment) and SSI rates have been observed [21]. For this reason, it is important to define an effective method to reduce the incidence of SSI [22].

Surgical side infections are defined as infections occurring in the superficial and deep components of the surgical field up to 30 days after surgery or within 1 year if a surgical implant is present [20]. In the guideline of the Center for Disease Control and Prevention, superficial and deep incisional and organ/space SSIs are described [23].

Superficial Incision (Involving Only the Skin or Subcutaneous Tissue of the Incision)

Superficial SSI is defined as an infection that occurs within 30 days after surgery. It involves only the skin and subcutaneous tissue where the incision occurred. Superficial SSI is accompanied by at least one of the following factors: purulent drainage with or without laboratory endorsement from the surgical area, detected microorganism from specimen culture that aseptically obtained from the surgical site, at least one of the following signs or symptoms of infection such as pain or tenderness, localized swelling, redness, or heat, and intentional opening of the superficial incision by the surgeon and diagnosis of SSI by the surgeon or attending physician [23].

Deep Incisional (Fascia and/or Muscular Layers)

Infections seen in the subcutaneous fascia and muscles within 30 days postoperatively in non-implanted patients and within 1 year after surgery in patients with implants are considered deep surgical site infections. It is accompanied by following signs are present: purulent drainage from the deep incision, spontaneous dehiscence of the deep incision or is purposely opened by the surgeon and culture-positivity or not cultured when the patient has symptoms such as fever or localized pain or tenderness [23].

Organ/Space Infections

Organ/space infections are defined as an abscess or other infection findings in the site of deep incision (excluding skin incision, fascia, or muscle layers) at physical examination, during reoperation, or by histopathologic/radiologic examination [23].

Organized abscesses are another infectious cause of fever in patients who have colorectal surgery. If the abdominal cavity is contaminated, an abscess formation may be seen. Patients with fever, nausea, and vomiting and abdominal pain after an intra-abdominal procedure should be evaluated for anastomotic leak and abscess formation. Generally, abscess formation can occur in as early as 1 week or as late as a few months after surgery. Any of interventional, open procedure, laparoscopic, endoscopic, or robotic surgical techniques, has a risk for microbial inoculation to peritoneum. After diagnosis, prompt incision and drainage, and source control by a surgeon, obtaining abscess material for gram stain and culture and initiating broad-spectrum antibiotics should be applied for effective management of patients [11].

Necrotizing soft tissue infections (NSTIs) contain clinical presentation of invasive necrotizing fasciitis, Fournier gangrene, clostridial gas gangrene, and invasive streptococcal cellulitis. Prompt evaluation, diagnosis debridement, and antimicrobial treatment are required in NSTIs [24].

Microbial Etiology of SSI

Superficial SSI is mostly caused by the patient's own skin flora or microorganisms in the environment. Adherence to surgical instruments causes contamination of the incision [25].

In healthy human intestinal microbiome, bacteria, viruses, and eukaryotes coexist [26]. Colonic bacteral flora is blamed as the main cause of SSIs if seen after elective colorectal procedures [27]. Large amount of bacterial load in the colon has been associated with increased SSI which is observed after elective colorectal resections [28].

Numerous studies have shown that bacterial translocation plays an important role in increasing the incidence of postoperative infections. Bacterial translocation is defined as the delivery of bacteria from the intestinal lumen to normally sterile region [29, 30].

In colorectal procedures, infective organisms arise from the intestinal lumen. *Bacteroides fragilis* and other mandatory anaerobes are the most frequently isolated organisms from the intestine, and their concentration is higher than aerobes. *Escherichia coli* is the most observed aerobe. *B. fragilis* and *E. coli* make up about 20–30% of the feces content. These microorganisms are the most frequently isolated pathogens in surgical side infections which are seen after colorectal surgeries [22].

In a study, the intercourse between the compound of the intestinal microbiome and anastomose leakage (AL) has been studied, and low microbial variety and high amounts of *Lachnospiraceae* and *Bacteroidaceae* have been found to be significantly associated with AL [31–33].

Risk Factors for SSI After Colorectal Surgery

When compared with other surgical procedures, the risk of SSI after colorectal surgery has been observed higher. Generally, lower rates of infection (about 3–5%) are observed in surgical procedures involving "clean" procedures. However, more surgical side infections (10–30%) are seen in procedures involving infected, necrotic, or dirty tissue such as colorectal surgery [34].

There are many factors that affect wound healing and determine the potential for infection. These factors include patient-related (endogenous) and surgery-related (exogenous) variables. While some variables such as age and gender cannot be changed, other potential factors such as nutritional status, tobacco use, proper use of antibiotics, and intraoperative technique can be changed [25].

The procedure (type and duration) may influence the rate of infections. Compared to intraperitoneal colon resection, higher rates of infection are detected by rectal resection. Other risk factors are prolonged operation (>3.5 h), impaired immune response, corticosteroid treatment, old ages (>60 years), hypoalbuminemia, bacterial or fecal contagion of the surgical field, accidental perforation or spillage, obesity, perioperative red blood cell transfusion, hyperglycemia, and hypothermia [22].

In a cohort that is related to colorectal surgery, it has been reported that risk of surgical site infection was increased in porter of *Enterobacteriaceae* that can produce beta lactamase if cephalosporin-based prophylaxis was given preoperatively. Alteration in intestinal microbiome due to surgery or unsuitable prophylactic antibiotherapy may worsen patient's status [35].

Other Sources of Infection After Colorectal Surgery

Urinary Tract Infection (UTI)

UTIs are known as the most common hospital-acquired infections. Eighty to ninety percentage of UTIs are found to be related to catheters. One of the risk factors for UTIs is anorectal surgery. Often, fever attributed to UTI appears 3–5 days after surgery. For effective management, urine analysis and culture should be done. Pathogens that are in *Enterobacteriaceae* such as *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Pseudomonas*, and *Serratia* are the most common pathogens in UTIs. If there are severe systemic signs and symptoms, antibiotics should be initiated promptly. Empiric antibiotic should be effective on most common pathogens that cause postoperative UTI, and antibiotic resistance profiles should be considered when initiating antibiotics [7].

Pneumonia

An increased risk for postoperative pneumonia is observed in almost all surgical patients. Risk factors for postoperative pneumonia are decreased mobility and inspiratory effort due to pain and difficulty coughing. The risk of pneumonia increases if mechanical ventilation is applied even for a short duration. Also, aspiration is another risk factor for postoperative pneumonia [36]. Leukocytosis count, serological test (such as CRP), and chest radiogram or if required CT should be done, and sputum culture should be obtained for effective management of postprocedural pneumonia. Broad-spectrum antibiotics that act on hospital-acquired pneumonia agents should be given. The antibiotics should be deescalated according to culture and antibiogram results [7].

Catheter-Related Bloodstream Infections

Indwelling peripheral and central catheters cause to increase risk for insertion-site infections, thrombophlebitis, and bloodstream infections. Contamination of catheter or catheter hub occurs by the spread of pathogens from the skin flora and touching with unwashed hands and with contaminated fluids or devices and through the bloodstream from another infected field. In the management of a febrile patient with a catheter with colorectal surgery, other causes of infection should be investigated and excluded immediately [37]. Simultaneous blood cultures should be taken from catheter lumens and peripheral venous vessels. After removal of the catheter, broad-spectrum antimicrobials should be started if the fever is still high, the patient's systemic signs and symptoms still persist, and laboratory findings related to infectious diseases are still present. The antibiotics should be deescalated according to culture and antibiogram results [38].

Infected Prosthetics

Prosthetic material such as abdominal mesh or vascular grafting may result as complicated surgical infections, if material is contaminated. If prosthetic materials are the potential source of infection, they should be removed promptly [39].

Clostridium difficile Infections

Infections caused by *Clostridium difficile* are commonly caused by received antibiotics within the past 2 months. It is stated that 20–50% of hospitalized patients are colonized with *C. difficile*. When protective bacterial flora of the colon changes, antibiotic-related *C. difficile* infections are started to be observed. Fecal-oral contamination, touching contaminated environmental surfaces, and the hands of healthcare providers may cause *C. difficile* transmission. When *C. difficile* infection is suspected, fluid resuscitation should be initiated immediately. Vancomycin (oral or per rectum as an enema) or intravenous or oral metronidazole should be applied empirically after the stool is obtained for cytotoxic analysis. Toxic megacolon is a surgical emergency requiring emergent subtotal colectomy. Fecal transplantation can be considered as an option in suitable patients [40].

Anastomotic Leak

Anastomotic leak (AL) is defined as a linkage between hollow viscera lumen and the peritoneal cavity at the anastomotic level [41]. AL rates has been reported in patients who had right hemicolectomy and after colonic cancer surgery with rates as follows: 8.1% and 6.4%, respectively [42]. In a systematic review and meta-analysis, AL has been reported as 11% after rectal cancer surgery [43]. AL causes septic complications and increased hospitalization days, delayed adjuvant chemotherapy, or no chemotherapy [41].

Others

Cholecystitis, parotitis, prostatitis, sinusitis [18]

Diagnose and Management

For effective management of these patients, a history and full physical examination should be done. Measuring postoperative fever has been found to have limited value in predicting infectious-noninfectious causes [8]. If the patient is hemodynamically stable in the immediate postoperative period, routine temperature measurement and subsequent detailed laboratory or diagnostic studies are not required. Diagnostic cultures for detecting any infectious sources should not be done rapidly during this period [7].

Systemic inflammatory response, sepsis, severe sepsis, and septic shock may be seen with fever [7]. In appropriate patients, complete blood counts and if required direct radiographies and computed tomography (CT) should be done. Blood culture, catheter cultures, urine cultures, and sputum and specimen cultures should be obtained in this period. The microorganisms that are detected in the culture of a sample which are taken according to the rules of asepsis/antisepsis can be thought to be the cause of infection [9].

Treatment

Appropriate antibiotic that is effective to causative organisms should be initiated, if surgical site infection is suspected. Removing of sutures, incision, and drainage is strongly recommended for surgical site infections. In addition to incision and drainage, using an antibiotic that is effective to *Staphylococcus aureus* are recommended in patients who show signs of systemic inflammatory response syndrome (SIRS) (fever >38 °C or <36 °C, >24 breaths/min, tachycardia >90 beats/min, or white blood cell count >12,000 or <400 cells/μL). An antibiotic active against MRSA is recommended in patients with SIRS and immunodeficiency and abscesses. In patients who have surgical site infections with significant systemic response such as erythema and induration extending >5 cm from the wound edge, temperature >38.5 °C, heart rate >110 beats/min, or white blood cell (WBC) count >12,000 μL^{-1}, systemic antimicrobial treatment with incision and drainage is suggested as beneficial [44].

Effective antimicrobials to methicillin-susceptible *S. aureus* (MSSA) such as first-generation cephalosporins or an antistaphylococcal penicillin and effective antimicrobials to methicillin-resistant *S. aureus* such as vancomycin, linezolid, daptomycin, telavancin, or ceftaroline, if risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), are recommended strongly for treatment of surgical side infections in IDSA guideline [44].

For infections after gastrointestinal surgery, a cephalosporin or fluoroquinolone in combination with metronidazole is recommended for coverage of gram-negative bacteria and anaerobes [44].

Due to polymicrobial etiology, vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem plus ceftriaxone and metronidazole is recommended strongly for empiric antibiotic treatment of necrotizing fasciitis and Fournier gangrene [44].

In treatment of group A streptococcal necrotizing fasciitis, penicillin plus clindamycin is recommended [44].

Prevention

Enhanced recovery after surgery (ERAS) protocol is a new approach developed for better management of surgical patient care. It includes a series of perioperative interventions to speed up recovery after major operations. The outcomes are influenced by the type and width of surgical field, susceptibility to perioperative stress, and quality of perioperative care. These preparations include education and advising, stopping of smoking, alcohol and addictive drugs before operation, preoperative exercise programs, effective preoperative fasting, abstinence of routine preoperative mechanical bowel preparation, optimization of preoperative metabolism, giving prophylaxis to prevent infection and thromboembolism, and providing euvolemia and normothermia [45].

Preoperative Preparation

The World Health Organization (WHO) has published guidelines and recommendations for prevention of SSIs. These recommendations can be classified as preoperative, intraoperative, perioperative, and postoperative [25].

Preoperative General Recommendations

Preoperative bathing: Bath or shower with either a plain soap or an antimicrobial soap is recommended before surgery. *Decolonization with mupirocin with or without chlorhexidine gluconate body wash* for the prevention of *S. aureus* infection in nasal carriers is recommended strongly for patients undergoing cardiothoracic and orthopedic surgery with known nasal carriage of *S. aureus*, and it is recommended moderately in other types of surgery with known nasal carriage of *S. aureus*.

Hair removal: The WHO recommends that in patients planning surgical procedure, either hair should either not be removed, or, if absolutely necessary, it should be removed only with a clipper. Shaving is strongly discouraged at all times, whether preoperatively or in the operating room.

Surgical site preparation: Alcohol-based antiseptic solutions are recommended for surgical site skin preparation. Antimicrobial skin sealants are not recommended after surgical site skin preparation for reducing postsurgical SSI.

Surgical hand preparation: The WHO recommends surgical hand preparation before donning sterile gloves with either a suitable antimicrobial soap and water or a suitable alcohol-based handrub by scrubbing [25].

Other related recommendations of WHO are perioperative discontinuation of immunosuppressive agents, screening of extended spectrum beta-lactamase (ESBL) colonization, and the impact on antibiotic prophylaxis. It is not recommended due to the lack of evidence. The WHO recommends conditionally not to discontinue immunosuppressive medication prior to surgery for the purpose of preventing SSI. The WHO also suggests conditionally administration of *oral or enteral multiple nutrient-enhanced nutritional formulas* in underweight patients who undergo major surgical operations for the purpose of preventing SSI [25].

Immune-modulating nutrition: Effects of immune-modulating formulas have been presented to literature previously. Various features of these nutrients are the following: better cell membrane stability, increased cell-mediated immune responses, advanced gastrointestinal mucosal entirety, weakening of the inflammatory response to stress, and increased blood flux to ischemic tissues [46]. In patients particularly diagnosed with malnutrition or cancer and planned to undergo gastrointestinal surgery, short-term benefits of immune nutrition have been demonstrated previously [47].

Patients with *alcohol consumption* are more likely to get infections after surgery. Alcohol avoidance before procedure can provide significant decline in alcohol withdrawal, delirium, surgical site infection, and wound dehiscence and also increase the immune function and wound healing. In patients who use alcohol during the preoperative period, wound separation, bleeding, cardiovascular and pulmonary complications, anastomosis leakage, neurological complications, and especially

infections are observed more likely. Approximately 50% decreasing postoperative morbidity can be observed if abandonment of alcohol and cigarette is provided 6–8 weeks before elective surgery [45].

Preoperative medications are effective factor for postoperative infections. The routine administration of preoperative multiple agents is not recommended if patients have no apparent increased risk for pulmonary aspiration. Nonparticulate antacids may be preoperatively used in patients who have increased risk for pulmonary aspiration, but routinely administration of preoperative antacids is not recommended to reduce the risk of pulmonary aspiration if patients have no risk for pulmonary aspiration. Preoperatively administration of antiemetics are recommended only in patients who have risk for postoperative nausea and vomiting. Also, it is not recommended using preoperative anticholinergics to reduce the risk of pulmonary aspiration [45].

Preoperative hemoglobin level: There are various complications associated with blood transfusion. These are the risk of disease transmission, overload, hemolysis, coagulopathy, acute lung injury, allergic reaction, and febrile nonhemolytic reactions. In the past few decades, the level of hemoglobin that triggers blood transfusion has been incessantly decreasing [45].

Preoperative Antibiotic Prophylaxis

Routine preoperative prophylaxis with intravenous antibiotics is recommended in many guidelines in colorectal surgery. In studies and a meta-analysis, routine use of prophylactic antimicrobials has been shown to be necessary in all patients who are undergoing colorectal procedures [22].

Preoperative antibiotic administration is recommended 60 min before the surgical incision in the IDSA guideline [22]. Antimicrobials such as fluoroquinolones and vancomycin should be started 120 min before the surgical incision in order to maintain the required tissue concentration [48].

The prophylactic antimicrobials that are used for preventing infections related to colorectal surgery should be effective for intestinal flora. The choice of appropriate antimicrobial prophylaxis (oral/intravenous) and optimal antimicrobial agent for colorectal surgery is not yet clear [22].

Cephalosporins are known as the most common prophylactic antibiotic and are often administered as a single agent in most surgeries. Most intravenous antimicrobials have been evaluated for prophylaxis in colorectal procedures. Single-agent first-generation cephalosporins (cefazolin and cephalothin) have been observed ineffective in most studies [22]. This ineffectivity is due to the lack of activity to *B. fragilis*. The cefazolin and metronidazole combination provides effective activity against to pathogens [49].

In IDSA guideline, cefazolin + metronidazole, cefoxitin, cefotetan, ampicillin-sulbactam, ceftriaxone + metronidazole, and ertapenem are recommended for prophylaxis before colorectal surgery. For colorectal procedures, ceftriaxone 2 g is recommended when used as a single dose in combination with metronidazole. Ampicillin-sulbactam is an alternative regimen for prophylaxis [22].

In general, antimicrobial prophylaxis should not be continued for more than 24 h and should be stopped when the procedure is completed and the surgical site is closed [49]. In studies, no significant difference has been found between single-dose and multidose administration of the same antibiotic in terms of infection rates. In a study, a single dose of cefotaxime plus metronidazole has been detected significantly more effective than three doses of cefotaxime alone [50]. In a recent review, it has been emphasized that there is no benefit in extending the prophylaxis period [49]. There is no evidence that the doses given after completion of the operation are more effective [22].

If the duration of the operation prolongs two half-lives of the antimicrobial or there is extreme blood loss (i.e., >1500 mL), intraoperative redosing may be required to ensure adequate serum and tissue concentrations of the antimicrobials [48]. Redosing interval should be determined according to the time of applied antibiotics preoperatively, but not at the beginning of the procedure. Significantly higher SSI rates with a single dose of cefazolin have been observed in procedures exceeding 3 h. Prophylaxis with an antimicrobial that has longer half-life can reduce the need for redosing of antimicrobials during long procedures [22].

Surgical side infection rates of >10% have been detected in more than half of the studies evaluating second-generation cephalosporins with anaerobic activity (cefoxitin and cefotetan). Third-generation agents, cefotaxime and ceftriaxone, have been examined in some studies; postoperative SSI rates have been found as 8–19% with single-agent use. Studies evaluating the combination of second- or third-generation cephalosporins with other intravenous agents, most commonly metronidazole, have been previously presented [50]. Except one of these studies, the combination of second- or third-generation cephalosporin with metronidazole has been found to have no more efficacy than cephalosporin alone. The routine antimicrobial prophylaxis with third- or fourth-generation cephalosporins is not recommended as it may cause the development of resistant organisms [22, 49].

Intravenous ampicillin-sulbactam or amoxicillin-clavulanate has been determined as effective as i.v. combinations of gentamicin and metronidazole, gentamicin and clindamycin, and cefotaxime and metronidazole for preventing SSIs in elective colorectal surgery [22]. In a study, adult patients undergoing elective colon or rectal procedures have been evaluated for a single high dose of gentamicin (4.5 mg/kg i.v.) plus metronidazole 500 mg i.v. versus multiple standard doses of gentamicin (1.5 mg/kg) plus metronidazole given preoperatively and every 8 h in 24 h postoperatively, and mechanical bowel preparation had done before surgery. Similar results have been found, and no differences have been observed for deep and superficial incisional SSI rates between groups. Markedly less superficial SSIs have been seen in the single-dose group (22.2%) when compared with the multidose group (55%) in procedures lasting longer than 3.5 h [51].

Ertapenem is a carbapenem that approved for the prophylaxis of SSIs after elective colorectal procedures. Cefotetan is also approved for surgical prophylaxis in elective clean-contaminated colorectal operations [22]. In a study, ertapenem has

been found to be superior to cefotetan for SSI prevention. As a result of this study, ertapenem can be evaluated as an alternative to cefotetan and cefoxitin. Due to concerns about increase in resistant organism, routine ertapenem administration should not be applied for surgical prophylaxis [52]. Clindamycin plus an aminoglycoside, an aztreonam, or a fluoroquinolone and metronidazole plus an aminoglycoside or a fluoroquinolone are recommended as alternative agents for prophylaxis of SSIs after colorectal surgery [49].

Information on oral prophylactic antimicrobial agents which were given for prophylaxis of colorectal surgery have been obtained only from studies with the mechanical intestinal preparation (MBP). The most administered combination for this purpose is an aminoglycoside (neomycin and kanamycin) plus an agent that has an anaerobic activity (erythromycin or metronidazole) [53].

Postprocedural surgical side infection rates have been found in neomycin plus erythromycin and neomycin plus metronidazole groups as follows: 0–11% and 2–13%, respectively [54]. SSIs rates of <10% have been detected in each of the combination of neomycin and tetracycline, neomycin and clindamycin, and neomycin and tinidazole [22]. In cases where metronidazole is used as the sole agent, SSI rates of 12–15% have been previously reported [55].

In some studies, comparison has been done between oral antimicrobials versus i.v. agents. In a study, similar efficiency has been found between oral neomycin plus oral erythromycin versus intravenous cefoxitin and intravenous ceftriaxone plus intravenous metronidazole [56]. But in another study, inferior efficiency has been found between oral neomycin plus oral erythromycin and intravenous cefoxitin in patients undergoing elective colorectal surgery. For procedures lasting longer than 4 h, oral neomycin and erythromycin has been found more effective than i.v. cefoxitin [57].

Significantly higher infection rates have been determined in the oral neomycin and erythromycin group (41%) when compared with the single-dose intravenous metronidazole and ceftriaxone group (9.6%) [58]. In another study, a comparison has been done between oral and intravenous administrations of metronidazole and kanamycin, and an increased rate of postoperative sepsis (36% vs. 6.5%, respectively), kanamycin-resistant *E. coli*, more excessive bacterial burden, and antimicrobial-related pseudomembranous colitis has been seen in the oral group [59].

In studies about postoperative SSI, rates have been reported in between 0% and 7% in the groups of oral neomycin and erythromycin plus intravenous administration of a cephalosporin [22].

In a review, significantly lower infection rate has been found with the combination of oral plus intravenous prophylaxis when compared with intravenous alone or with oral prophylaxis alone [49]. In a retrospective study, patients who had been applied with mechanical bowel preparation (MBP) and oral antimicrobial prophylaxis before colectomy have been evaluated, and significant lower rate of postoperative infections have been detected when compared with patients who administered intravenous prophylaxis alone [60].

Mechanical Bowel Preparation (MBP) and the Use of Oral Antibiotics

Since the intestinal microbiome is a potential risk factor for postoperative complications, studies are underway on some perioperative approaches, such as mechanical bowel preparation (MBP), to reduce SSI. But there are differences about dosage, time, and regimen between studies [61]. The drugs in the combination should have activity against to both facultative gram-negative and anaerobic bacteria. Decreasing the intraluminal fecal mass and the bacterial load could provide an additive contribution for lower SSI risk. The WHO recommends preoperative oral antibiotics combined with mechanical bowel preparation to reduce the risk of SSI at elective colorectal surgery. Avoidance of mechanical bowel preparation alone (without oral antibiotics) is recommended for reducing SSI in patients at elective colorectal surgery. The risk of possible mechanical disruption of a constructed anastomosis may be decreased by preventing hard feces [25]. Lower rates of anastomotic leak, ileus, reoperation, length of stay, readmission, and mortality have been also found with this approach [62]. Polyethylene glycol and sodium phosphate are the most commonly applied cathartics for MPB [25].

An eubiotic environment has been emphasized as important for normal wound healing, including anastomosis repair after colorectal surgery in animal models [63]. In the eubiotic state, bacteria remain harmless and do not cause infections, whereas in the case of changes in the local environment, bacterial invasion, tissue inflammation, and also complications associated with colorectal surgery, such as anastomotic leakage (AL), SSI, and prolonged postoperative ileus (PPI), may be seen in the management of the patients [64].

In addition to intravenous prophylaxis, a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole with MBP combined is recommended. Oral antimicrobial therapy is recommended as three doses over approximately 10 h in the afternoon and evening before the operation and after the MBP [22].

There are some disadvantages of MBP. These can be summarized as distressed, time-consuming and expensive, requires hospitalization before surgery, abdominal pain, bloating, fatigue, fluid and electrolyte imbalance risk for intraoperative spillage in poor preparation, histological changes in the colorectal mucosa, potential bacterial translocation and anastomotic disruption, explosive gases, overgrowth of *Escherichia coli* and *Clostridium difficile* in extended bowel-cleansing protocols [65], acute phosphate nephropathy [66] associated with oral sodium phosphate bowel cleansing [67], potential adverse effects of oral antibiotics, and emergence of resistance [25].

Probiotics Therapy

The probiotics therapy can provide positive outcomes for patients undergoing gastrointestinal surgery [68]. Probiotics can contribute to maintaining the gut microbiome. Horvat et al. [69] showed that preoperative administration of prebiotics in elective colorectal surgery had positive additive effect in preventing a postoperative

inflammatory response as mechanical bowel cleaning. The use of probiotics in patients with surgery has been presented as an optimistic approach to prevent postoperative infectious complications. Probiotics have been shown to have a protective effect on the epithelial barrier [68, 69].

Intraoperative Measures

Alcohol-based antiseptic agent is recommended for intraoperative skin preparation unless contraindicated [70].

Iodine-impregnated adhesive drapes (compared with no adhesive drapes) have little difference in SSI risk.

Perioperative oxygenation: The WHO recommends strongly that adult patients undergoing general anesthesia with endotracheal intubation for surgical procedures should receive an 80% fraction of inspired oxygen intraoperatively and, if feasible, in the immediate postoperative period for 2–6 h to reduce the risk of SSI.

Maintaining normal body temperature (normothermia): Using warming devices in the operating room and during the surgical procedure for patient body warming with the purpose of reducing SSI is suggested. Mild perioperative hypothermia and subsequential physiological changes such as thermoregulatory vasoconstriction, lower subcutaneous oxygen tension, deterioration in oxidative killing of neutrophils, reduced collagen deposition, and decreased wound healing may cause SSI [71].

Use of protocols for intensive perioperative blood glucose control: The use of protocols for intensive perioperative blood glucose control for both diabetic and nondiabetic adult patients is suggested in patients with surgical procedures to reduce the risk of SSI.

Maintenance of *adequate circulating volume control (normovolemia)*: Goal-directed fluid therapy (GDFT) is suggested intraoperatively to reduce the risk of SSI. Intraoperative and postoperative GDFT has been found beneficial for reducing the SSI rate when compared to standard fluid management [25].

Use of surgical gloves: The panel decided not to formulate a recommendation due to the lack of evidence to assess whether double gloving or a change of gloves during the operation or the use of specific types of gloves is more effective in reducing the risk of SSI.

Drapes and gowns: Either sterile, disposable nonwoven or sterile, reusable woven drapes and gowns are suggested for the purpose of preventing SSI.

Changing of surgical instruments: Due to the lack of evidence, there is no recommendation about using a new set of sterile instruments at the time of wound closure [25].

Incisional wound irrigation: There is inadequate evidence about saline irrigation of incisional wounds before closure for the purpose of preventing SSI. Evaluating the use of irrigation of the incisional wound with an aqueous povidone-iodine (PVP-I) solution before closure is suggested for the purpose of preventing SSI, particularly in clean and clean-contaminated wounds. It is recommended that *incisional*

wound irrigation with an antibiotic should not be used for preventing SSI due to uncertain evidences between the benefits and harms.

Antimicrobial-coated sutures: Triclosan-coated sutures are suggested for the purpose of reducing the risk of SSI independent of the type of surgery as moderate suggestion and conditional category [25, 70].

Wound protector devices: Considering the use of wound protector devices is suggested in clean-contaminated, contaminated, and dirty abdominal surgical procedures for the purpose of reducing the rate of SSI.

Prophylactic negative pressure wound therapy is suggested in patients with primarily closed surgical incisions and high-risk wounds as low suggestion and conditional category [25].

Warming of the intravenous fluids before infusion: Appropriate technical equipment is recommended [72].

Postoperative Measures

For the purpose of preventing SSI, *prolongation of surgical antibiotic prophylaxis (SAP)* after completion of the operation is not recommended, strongly. It is suggested that preoperative antibiotic prophylaxis is not to be continued in the presence of a wound drain for the purpose of preventing SSI. *Using any type of advanced dressing* instead of a standard dressing is not suggested primarily on closed surgical wounds. Asepsis and antisepsis rules should be applied during wound care [25, 70].

In conclusion, postoperative fever is seen mostly after colorectal surgery. Differential diagnose is required between normal physiologic response to surgery and any of pathologic conditions. Infectious and noninfectious causes should be determined in each person who undergo colorectal surgery. It should be managed jointly with the surgeon and clinician of infectious disease according to guidelines. For less SSIs, preoperative recommendations should be applied.

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Pathologic Features of Colorectal Carcinomas

23

Sevil Sayhan and Dudu Solakoglu Kahraman

Classification of Tumours of the Colon and Rectum

Colorectal carcinoma is observed as the second most common cancer in women and the third most common cancer in men. Colorectal tumours are classified by the WHO (World Health Organisation) [1]. The classification is summarised in Table 23.1.

Pathogenesis

Heterogeneous molecular phenomena including genetic and epigenetic anomalies lead to development of colon adenocarcinoma. Most colorectal carcinomas develop via conventional pathways and follow the classic adenoma-carcinoma sequence of pathogenesis, and the remaining cases evolve through either the hypermutant or the ultramutant pathway. Three pathogenetic mechanisms have been described in cancers as follows: (1) chromosomal instability resulting in marked alterations in DNA somatic copy numbers with DNA gains/amplifications and loses/deletions, (2) the microsatellite instability pathway associated with defects in DNA mismatch repair and accumulation of mutations in microsatellite repeat regions of the genome and (3) defective proofreading polymerase with a very high mutation rate (ultramutant) [2, 3].

The most frequently seen genetic changes in the conventional colorectal adenoma-carcinoma pathway are mostly inactivating mutations which include alterations in APC, KRAS, TP53, SMAD4 or PIK3CA genes; the mismatch repair genes MLH1, MSH2, and POLE. APC; and account for the development of up to %80 of sporadic colon tumours and typically involve in the mutation of APC seen in the

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Table 23.1 Classification of colorectal tumours

Malignant epithelial neoplasms
Adenocancer, NOS
Serrated adenocancer
Adenoma-like adenocancer
Micropapillary adenocancer
Mucinous adenocancer
Poorly cohesive cancer
Signet-ring cell cancer
Medullary adenocancer
Adenosquamous cancer
Carcinoma, undifferentiated, NOS
Carcinoma with sarcomatoid component
Neuroendocrine tumour NOS
Neuroendocrine neoplasm, grade 1
Neuroendocrine neoplasm, grade 2
Neuroendocrine neoplasm, grade 3
L-cell neoplasm
Glucagon-like peptide-producing neoplasm
PP/PYY- producing neoplasm
Enterochromaffin cell carcinoid
Serotonin- producing neoplasm
Neuroendocrine cancer, NOS
Large cell neuroendocrine cancer
Small cell neuroendocrine cancer
Mixed neuroendocrine non-neuroendocrine neoplasm (MINEN)

early stage of the neoplastic process [4, 5]. Mutations in the APC reduce its ability to direct degradation, and hence accumulation of β-catenin with resultant abnormal signalling through the WNT pathway occurs. Activating KRAS mutations that promote growth and prevent apoptosis are seen at a later stage of carcinogenesis. The SMAD4 gene is usually inactivated by deletions of a large part of chromosome18q or less often by mutations which reduce signalling via TGF-β inhibitory pathway. In sporadic colon cancers, mutations of the TP53 gene often determine the late stage of adenoma to carcinoma transition. Serrated and other types of adenocarcinomas associated with defective mismatch repair follow an alternative pathway. Pathway precursor lesions are serrated polyps including hyperplastic polyps, sessile serrated lesions, traditional serrated adenomas and mixed polyps. Serrated polyps usually have BRAF and less often KRAS-activating mutations and CpG island methylator phenotype [6, 7].

Macroscopic Features

Colon adenocarcinomas manifest as exophytic, endophytic, ulcerative, annular lesions with variable degrees of fibrosis (Fig. 23.1). Tumours of the proximal colon tend to form polypoid lesions and rarely cause obstruction. Distal colon tumours tend to invade the colon circumferentially and produce ‘napkin-ring’ constrictions and luminal narrowing [8, 9].

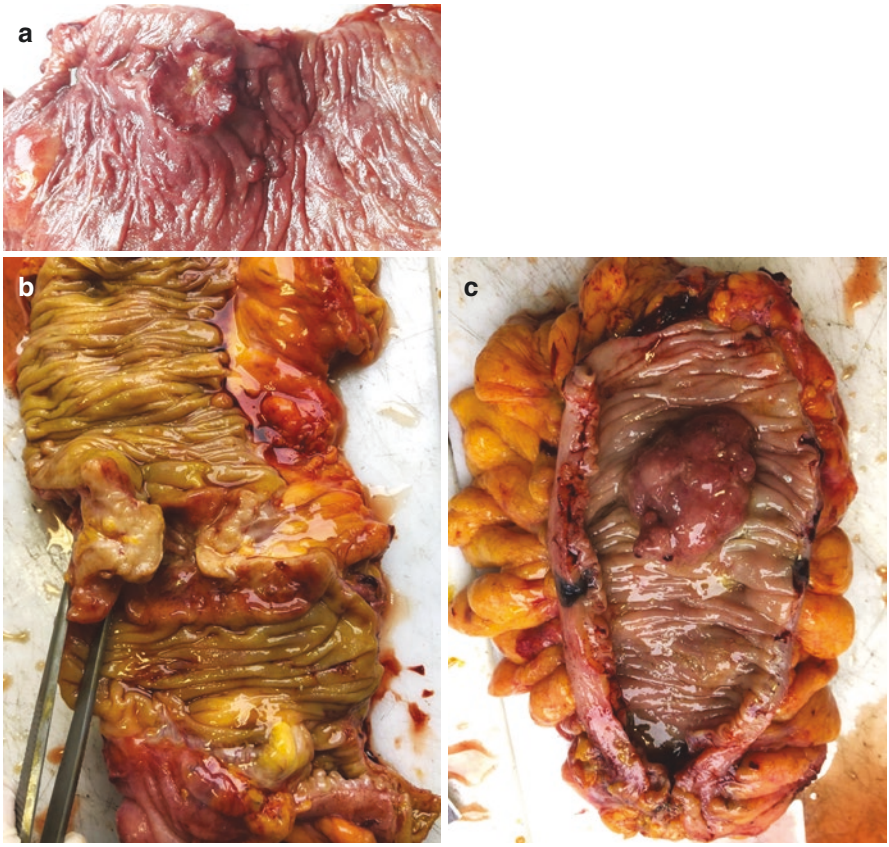

Fig. 23.1 Macroscopic appearance of ulcerated (**a**), scirrhous (**b**) and polypoid (**c**) colorectal adenocarcinomas

Histopathology

Colorectal carcinomas develop from mucosal epithelium, and most of carcinomas are adenocarcinomas. Several subtypes of colorectal carcinomas exist.

Adenocarcinoma, Not Otherwise Specified (NOS)

This histologic type include well-differentiated, moderate- and low-grade ACs (adenocarcinomas). Variable sized glands with diverse configurations containing moderate or little amount of stroma exist. Glandular epithelial cells have tall, columnar to cuboidal and polygonal configurations with higher mitotic indices (Fig. 23.2). Glandular lumina are usually filled with 'dirty necrotic debris, and variable desmoplastic components'. In addition to typical glandular epithelium neuroendocrine cells, Paneth cells, squamous cells, melanocytes and trophoblasts can be observed [8, 9].

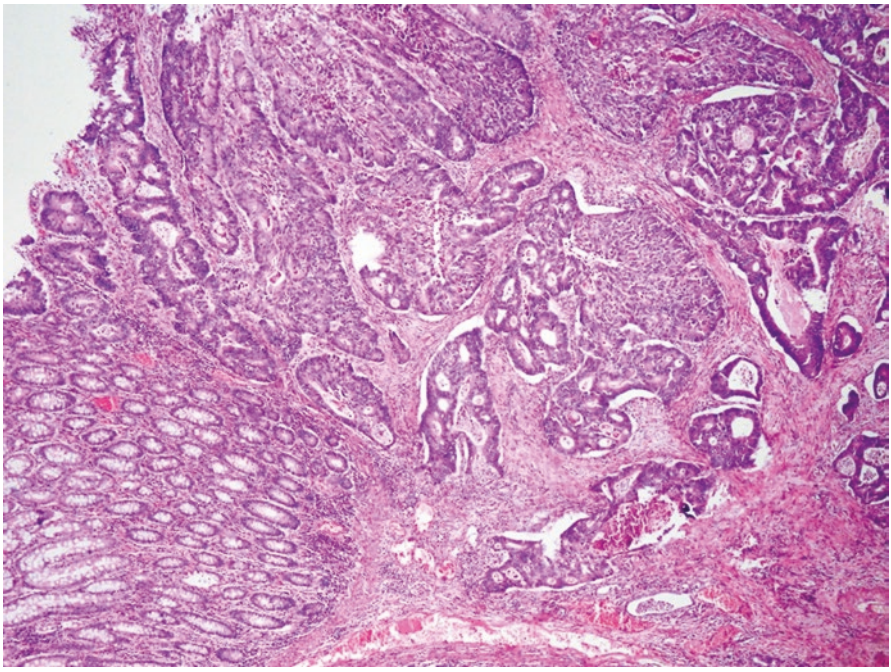

Fig. 23.2 Intermediate-grade adenocarcinoma, NOS of the colon (HxE, ×40)

Mucinous Adenocarcinoma

This is the most frequently seen histologic subtype. Mucinous adenocarcinomas comprise >50% extracellular mucin contain apparent malignant epithelial clumps, layers or individual tumour cells (Fig. 23.3). Tumour cells occasionally compose of a variable number of signet ring cells with a gelatinous cut surface. Prognosis is the same with adenocarcinoma NOS [8]. Mucinous tumours invade greater proportion of right colon. They are more common in females, young individuals and patients with Lynch syndrome. They are more likely to present at advanced stage of the tumour [9]. Microsatellite instability (MSI) is more frequently detected in adenocarcinoma NOS. But the presence of MSI alone does not have any independent prognostic value [10, 11]. Grading should be made based on the degree of glandular formation and epithelial maturation. Carcinomas have mucinous areas, and <50% of them should be categorised as having a mucinous component [1].

Signet Ring Cell Carcinoma

In this histologic subtype, more than 50% of the tumour cells contain apparent intracytoplasmic mucin, typically with displacement and moulding of the nucleus (Fig. 23.4). Signet ring cell carcinomas account approximately 1% of all colorectal

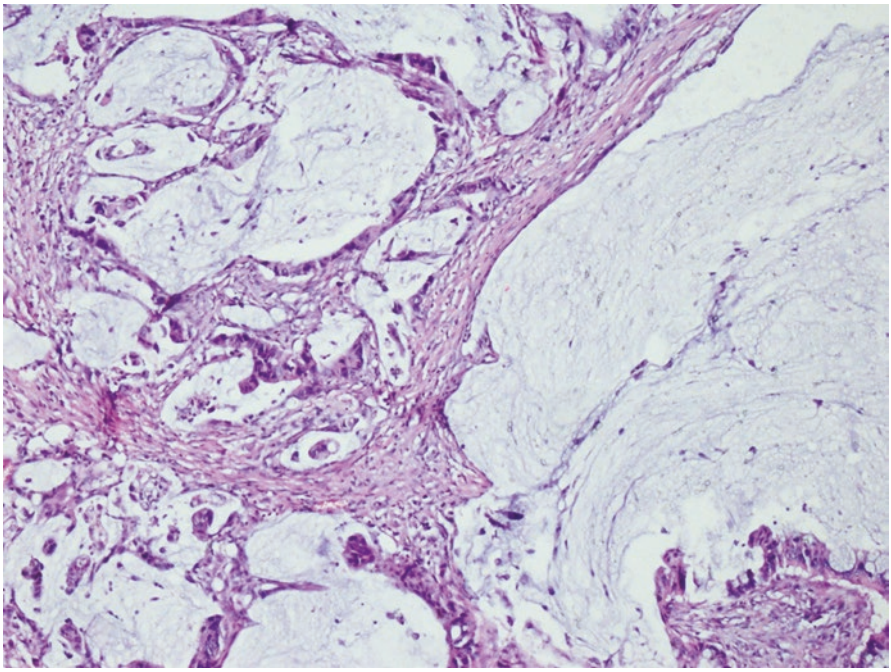

Fig. 23.3 Mucinous carcinoma of the colon (HxE, ×100)

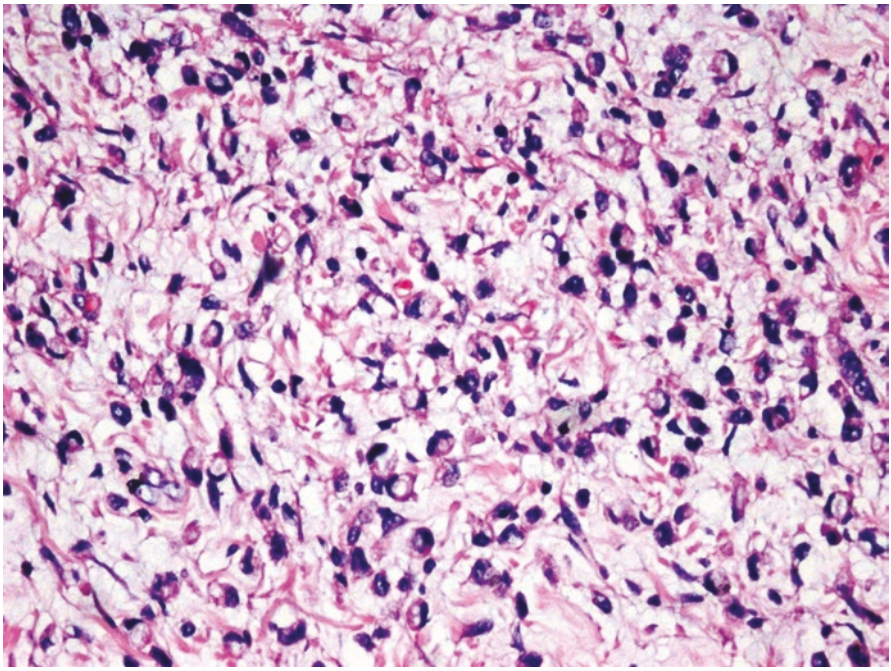

Fig. 23.4 Signet ring carcinoma of the rectum (HxE, ×400)

carcinomas and tend to be localised in the right colon. They are usually ulcerating tumours diagnosed at an advanced stages of the disease. Multiple metastases rapidly develop at variable locations. This type is associated often with MSI and Lynch syndrome [12]. Signet ring cell carcinomas occupying less than 50% of the tumour are categorised as tumours having a signet ring cell component.

Medullary Carcinoma

In this type, the tumour cells have layers of malignant cells with abundant eosinophilic cytoplasm and vesicular nuclei containing prominent nucleoli. Marked infiltration of the lymphocytes and neutrophils is observed (Fig. 23.5). Tumour cells may have an organoid or a trabecular architecture [13]. Its prevalence is estimated as 4% in the single-centre studies [14, 15]. These tumours are more common in women, and they are localised on ceacum or proximal colon [16]. Frequently MSI associated with BRAF mutations are detected [14]; however, usually, this tumour has a good prognosis [15]. This type is immunohistochemically characterised with loss of CDX2 and CK20.

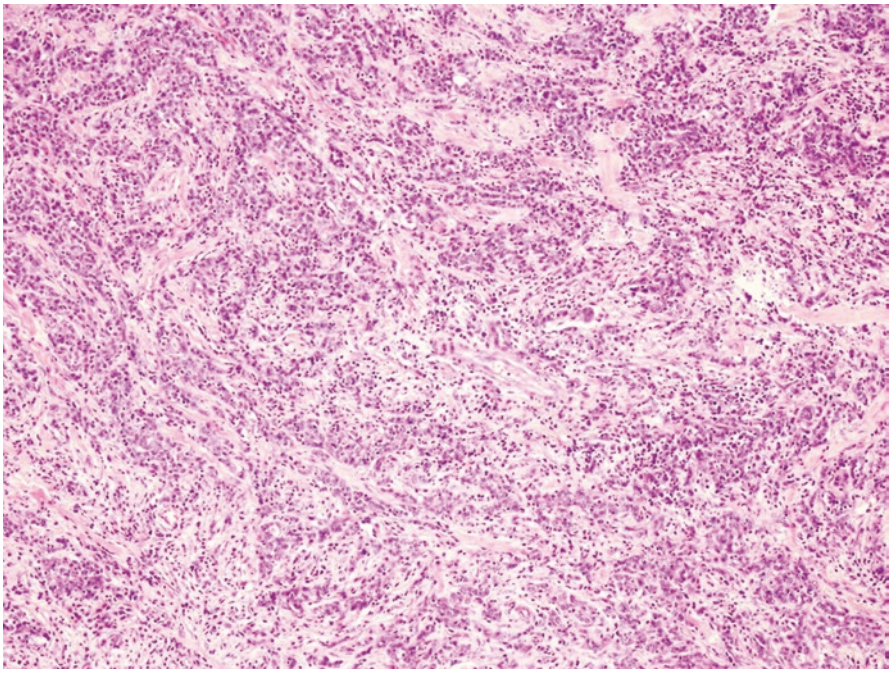

Fig. 23.5 Medullary carcinoma of the colon (HxE, ×100)

Serrated Adenocarcinoma

This type is morphologically similar to polyps with glandular serration. They arise from hyperplastic or serrated precursor lesions or occur spontaneously. Epithelial serrations, cells with low nucleus/cytoplasm ratio and abundant clear or eosinophilic cytoplasm are characteristic features. Vesicular nuclei with peripheral condensation of chromatin, usually without any or only focal necrosis, is seen. Serrated adenocarcinomas constitute 10–15% of all the colorectal carcinomas [17]. These tumours are associated with a high degree of methylation (CIMP) [9].

Micropapillary Adenocarcinoma

In this subtype, there are small clumps of tumour cells within stromal spaces resembling vascular channels (Fig. 23.6). Micropapillary component should be seen in ≥5% of the tumour to establish the diagnosis. In the single-centre series, its estimated incidence rates vary approximately from 5% to 20% [18–20]. High risk of lymph node metastasis, poor prognosis due to lymphatic, extramural vascular and perineural invasion are characteristic features of this type.

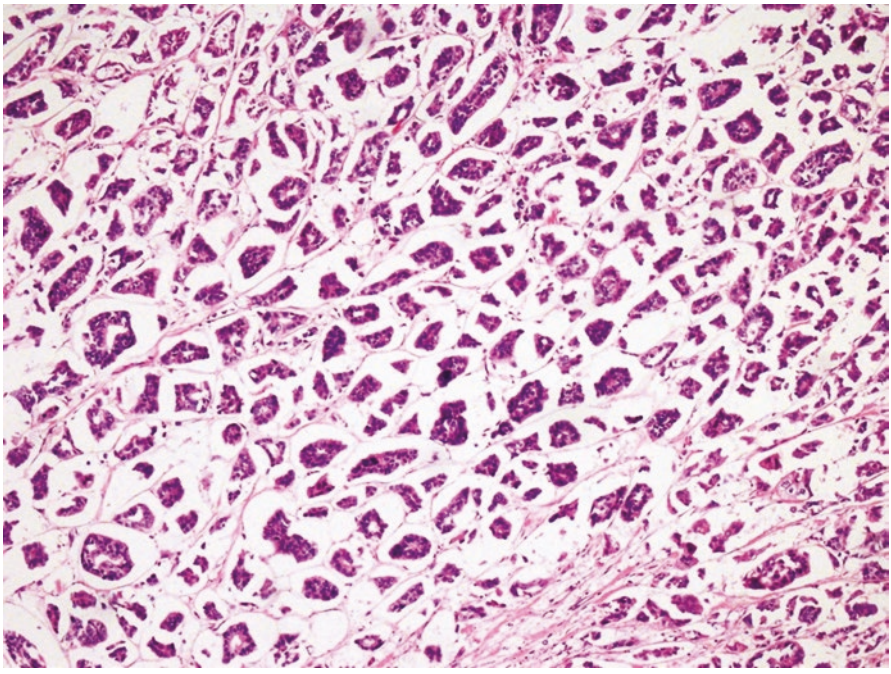

Fig. 23.6 Micropapillary adenocarcinoma of the rectum (HxE, ×100)

Adenoma-Like Adenocarcinoma

This subtype has been previously described as 'villous adenocarcinoma.' It resembles low-grade villous adenoma, and its invasive component occupies ≥50% of the tumour. There is minimal desmoplastic reaction and pushing growth pattern (Fig. 23.7). Its incidence varies from 3% to 9% [21, 22]. It may be difficult to detect invasive component by examining endoscopic biopsy specimens. Frequently KRAS mutation is revealed. Prognosis is good [21].

Adenosquamous Carcinoma

This subtype has features of both adenocarcinoma and squamous cell carcinoma, either as separate components or in combination (Fig. 23.8). Its incidence is <0.1% [23, 24]. These tumours may be associated with chronic ulcerative colitis. They are evenly distribution between the right and left colon and often present at a higher stage when compared with commonly seen adenocarcinomas [25].

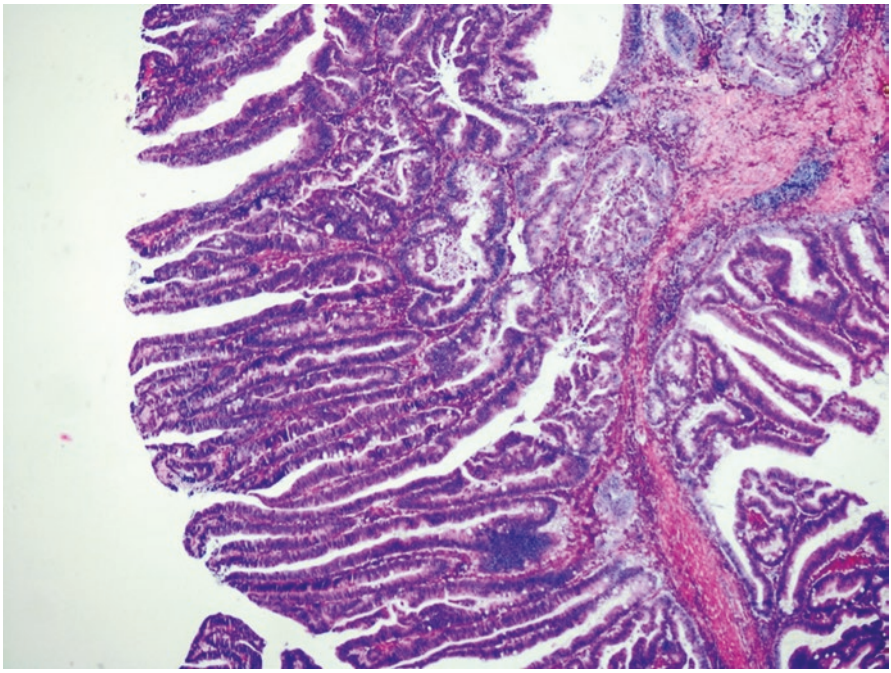

Fig. 23.7 Villous adenoma like carcinoma of the sigmoid colon (HxE, ×100)

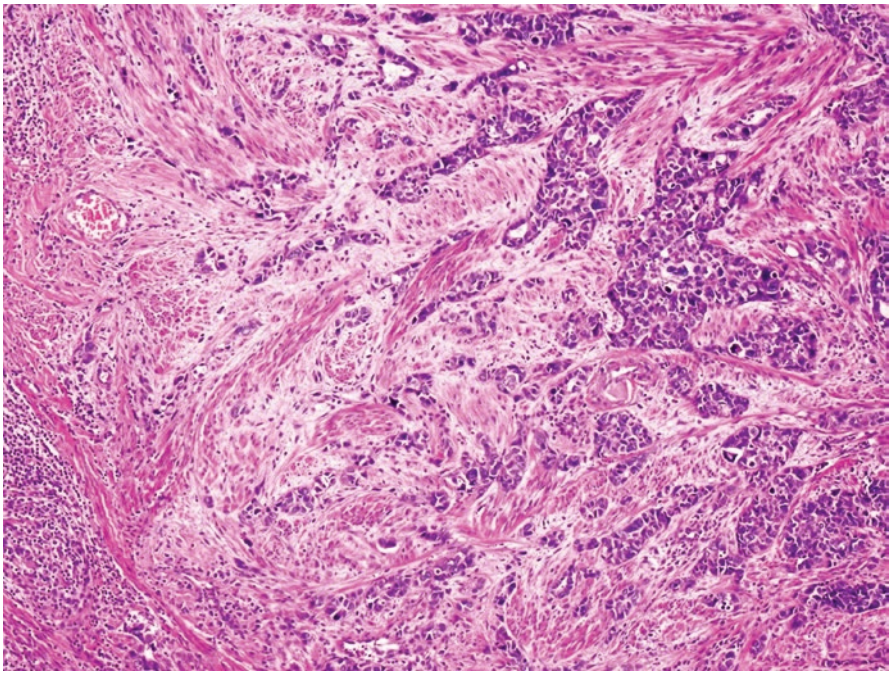

Fig. 23.8 Adenosquamous carcinoma of the colon (HxE, ×100)

Carcinomas with Sarcomatoid Components

This subtype has partly undifferentiated histology and sarcomatoid appearance such as spindle cell components or rhabdoid features [26–28]. Large bulky tumour is its characteristic macroscopic feature. Microscopic examination demonstrates rhabdoid cells with abundant intracytoplasmic eosinophilic rhabdoid bodies. Pleomorphic giant and spindle cells, variable degrees of glandular differentiation may be seen. Loss of nuclear immunostaining for SMARCB1(INI1) is seen [28]. Usually disease has a poor prognosis [27].

Undifferentiated Carcinoma

These carcinomas demonstrate evidence of epithelial differentiation but without obvious glandular formation. They are bulky with soft consistency. Extensive necrosis with layers of cells, cords and trabecular structures is noted. These types of carcinomas may be composed of monomorphic or pleomorphic cells (Fig. 23.9). Pure undifferentiated carcinoma is rarely seen. Most often they are associated with adenocarcinomas. The presence of an undifferentiated component increases the likelihood of the development of the tumour with DNA MMR deficiency [9].

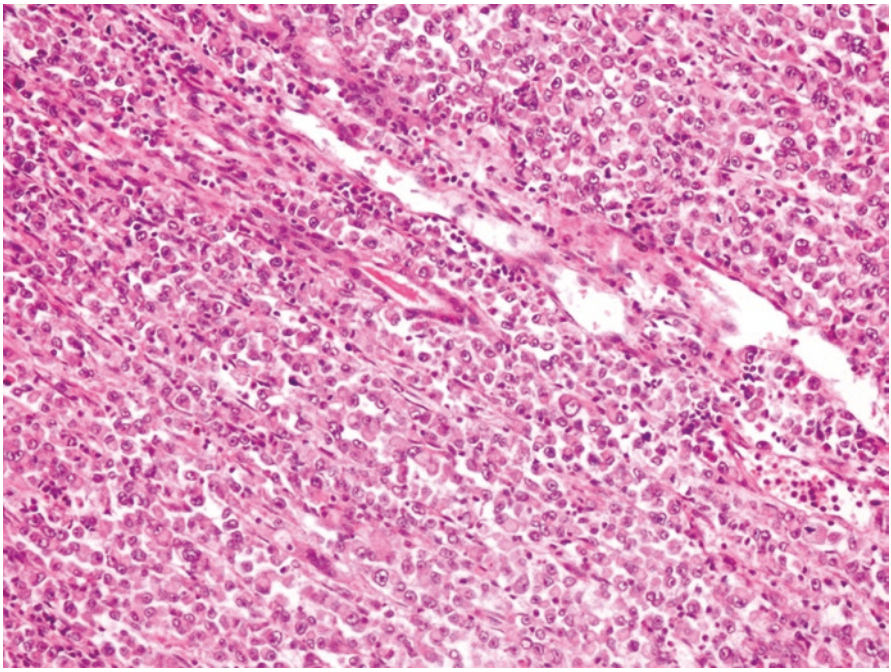

Fig. 23.9 Undifferentiated carcinoma of the colon (HxE, ×200)

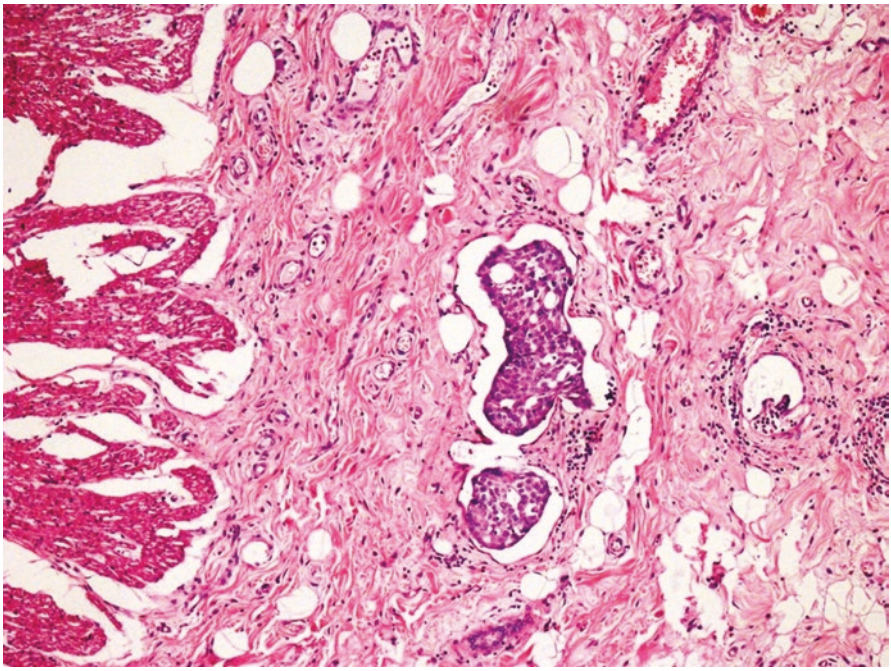

Fig. 23.10 Lymphatic invasion in the colonic submucosa (HxE, ×40)

Important Prognostic Factors

Lymphatic Invasion

Single or groups of tumour cells invade lymphatic (Fig. 23.10). In some studies, lymphatic invasion has independent prognostic factor, particularly in patients with lymph node-negative disease [29–32].

Intramural and Extramural Vascular Invasion

Vascular invasion is seen within bowel wall (intramural vascular invasion IMVI) or tumour cells invade outside muscularis propria (extramural vascular invasion EMVI) vascular. IMVI is associated with poor prognosis. Incidence of EMVI is relatively higher with worse prognosis when compared with IMVI.

Perineural Invasion

In perineural invasion, tumour cells invade periphery of the nerve (Fig. 23.11). At least they should invade one third of the nerve circumference [33]. It is associated with advanced tumour stage, other risk factors, likelihood of local and distant recurrence and poor prognosis [34].

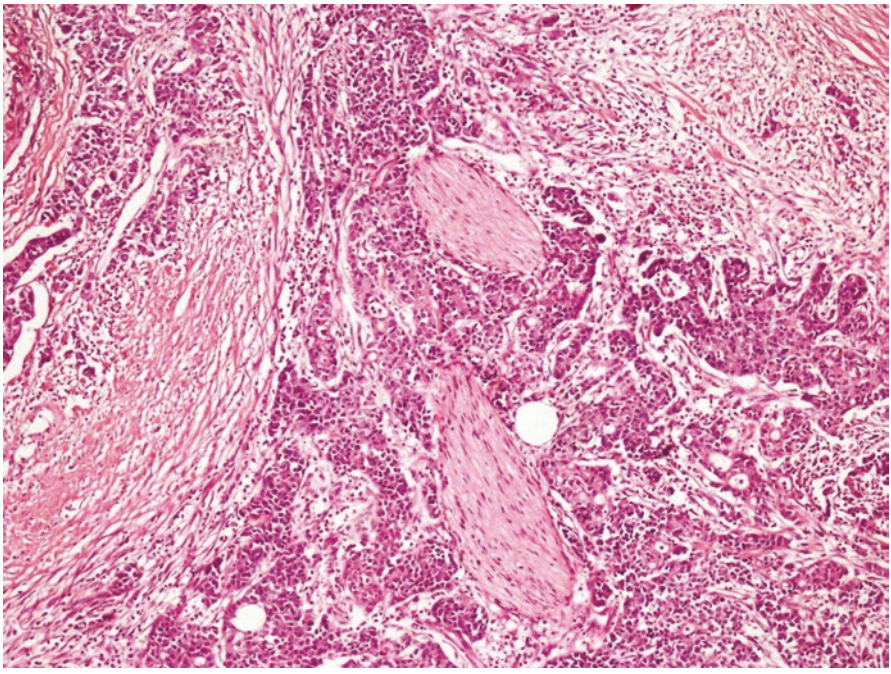

Fig. 23.11 Perineural invasion in the colonic submucosa (HxE, ×40)

Tumour Budding

Tumour budding, meaning a detachment of tumour cells at the invasive front of colorectal carcinoma (CRC) in a hotspot into single cells or clusters ≤5 tumour cells. Many studies have shown that high- grade tumour budding in a polypoid tumour is an important risk factor for nodal involvement [35, 36]. Additionally tumour budding has been shown to be a worst prognostic factor in stage II disease [37, 38]. Tumour budding is known as the morphological hallmark of epithelial-mesenchymal transition [39]. There are two types growth pattern: infiltrative and pushing border [40]. Pushing border pattern has a better prognosis and lower stage than infiltrative growth pattern.

Immune Response

Multiple types of immune responses to colorectal carcinomas have been detected. Usually, the presence of an intense inflammatory response of any type is associated with favourable impact [41–43]. Intratumoural lymphocytes and Crohn-like reaction improve prognosis [44]. Both immune responses are associated with MSI [45, 46]. The presence of tumour-infiltrating lymphocytes at the invasive front of the tumour has important prognostic factor [47].

Resection Margins

Although margins of the surgical resection or excision specimen are rarely positive, but if the tumour is located closer to the longitudinal margins, local recurrence frequently occurs [48]. Circumferential resection margin closer (≤1 mm) to the tumour with surgical positivity has a strong impact on local recurrence and overall survive [49]. Basal margin of the excisional biopsy specimen is more important than its lateral margins [50]. Achievement of the optimal planes of surgery for resection of rectal and colonic tumours is strongly correlated with good outcome [51–53] (Fig. 23.12).

Response to Therapy

Neoadjuvant therapy is applied for T3, T4 and node-positive colorectal carcinomas. Radiotherapy, radiochemotherapy or systemic treatment may be performed according to tumour involvement. A variable tumour response may be seen (Fig. 23.13). For the evaluation of tumour response, various classification systems have been proposed, but none is perfect [54].

Diagnostic Molecular Pathology

There are two different histopathological classifications of colorectal carcinomas at a molecular level including genomic (DNA-based) classification created by The Cancer Genome Atlas (TCGA) and transcriptomic classification (RNA-based) [2, 3].

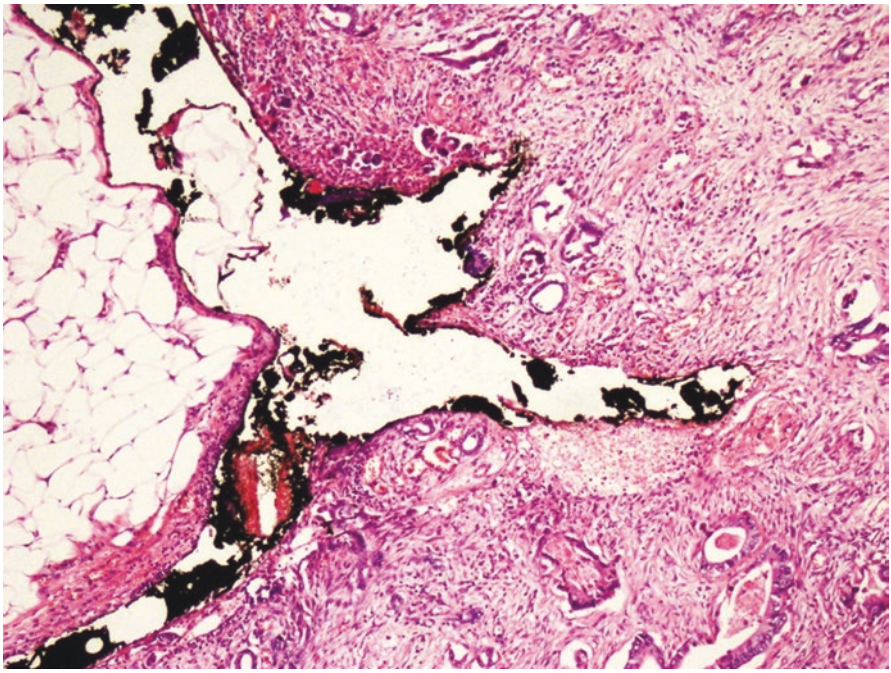

Fig. 23.12 Adenocarcinoma at the resection margin of the rectum (HxE, ×40)

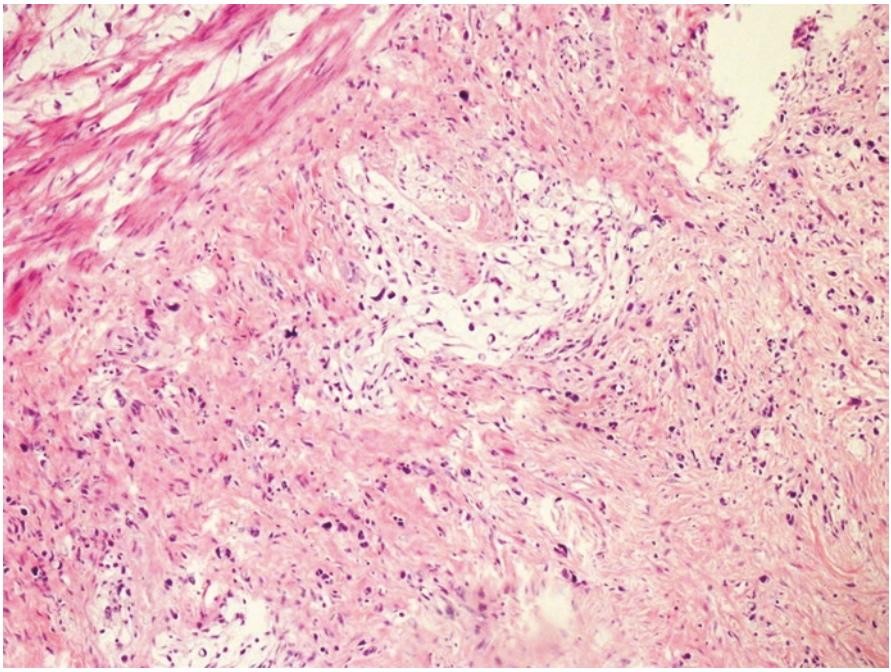

Fig. 23.13 Partial response to radiochemotherapy (HxE, ×100)

Genomic Classification

According to this classification, two groups are identified based on mutation rates as hypermutated and non-hypermutated cancers which are associated with the MSI and chromosomal instability.

Hypermutated patients (~15% of CRCs) have high frequency of MSI because of defective DNA mismatch repair. This condition may be sporadic associated with MLH1 promoter, hypermethylation or inactivation of DNA mismatch repair. These tumours have the CpG island methylator phenotype. As in the case with Lynch syndrome, a small group of cancers have either inherited or somatic mismatch repair gene mutations. There are also ultramutated cancers with a characteristic nucleotide base change spectrum [1].

In non-hypermutated patients (~85% of CRCs), low frequency of mutations and microsatellite stability (MSS) are detected. Higher-frequency DNA somatic copy number alterations, such as chromosomal segment losses and gains have been identified in these patients. In this group, recurrent mutated genes consist of APC (%80), TP53 (%60) and KRAS (%45) genes. Mostly signalling pathways are affected. Accordingly, activation of the WNT, MAPK and PI3K growth signalling pathways and inactivation of the TGF-β and p53 inhibitory pathways have been identified [3].

Transcriptomic Profiling

According to the consensus reached by The Colorectal Cancer Subtyping Consortium (CRCSC), there are four main molecular subtype groups [55]. First category is hypermutated MSI cancers, CMS1 (MSI-immune, %14). Other molecular subtypes include CMS2 (canonical, %37), CMS3 (metabolic, 13%) and CMS4 (mesenchymal, 23%). CMS1 colorectal cancers are hypermutated MSI associated with MLH1 silencing and with CpG island methylator phenotype with frequent BRAF mutations. CMS1 is associated with strong immune activation with prominent tumour-infiltrating CD8+ cytotoxic T lymphocytes and thereby indicating potential responsiveness to immune checkpoint inhibitors [3].

Staging (TNM)

The invasive potential of the colorectal carcinoma is the most important indicator of the tumour behaviour. The TNM staging system, which has replaced the Dukes system, is the system most widely used in North America [55, 56]. The protocol applies to all colorectal carcinomas. It excludes carcinomas of the vermiform appendix and neuroendocrine neoplasms. Subdivision of T1 and T3 colorectal carcinomas has important prognostic significance.

Nodal status is associated with a number of positive lymph nodes in the region of the primary tumour. Tumour deposits are important if there aren't any positive lymph nodes and categorised as N1c [57]. Micrometastases (no metastasis >2 mm) are expressed by the addition of an abbreviation (mi). Isolated tumour cells present as single cells or small cluster of cells of ≤0.2 mm in their greatest diameter are not assessed as lymph node metastases [58].

Table 23.2 TNM classification

T-Primary tumour			
TX	Primary tumour cannot be assessed		
Tis	Carcinoma in situ: Invasion of lamina propria		
T1	Tumour invades submucosa		
T2	Tumour invades muscularis propria		
T3	Tumour invades subserosa or into non-peritonealised pericolic or perirectal tissues		
T4	Tumour directly invades other organs or structure and/or perforates visceral peritoneum		
T4a	Tumour perforates visceral peritoneum		
T4b	Tumour directly invades other organs or structures		
N-Regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in 2–3 regional lymph nodes		
N1a	Metastasis in one regional lymph node		
N1b	Metastasis in 2–3 regional lymph nodes		
N1c	Tumour deposit(s), i.e. satellites, in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue without regional lymph node 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		
M-distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Metastasis confined to one organ (liver, lung, non-regional lymph node(s) without peritoneal metastases		
M1b	Metastasis in more than one organ		
M1c	Metastasis to the peritoneum with or without other organ involvement		
Stage			
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage II	T3, T4	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1, N2	M0
Stage IIIA	T1, T2	N1	M0
T1	N2a	M0	
Stage IIIB	T1, T2	N2b	M0
T2, T3	N2a	M0	
T3, T4a	N1	M0	
Stage IIIC	T3, T4a	N2b	M0

(continued)

Table 23.2 (continued)

T4a	N2a	M0	
T4b	N1, N2	M0	
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

Distant metastases include M1a (involving one organ without peritoneal metastases), M1b (spread to multiply organs) and M1c (metastases to the peritoneum with or without other organs) [58]. TNM classification is summarised in Table 23.2.

Prognosis

The literature includes several studies focusing on the prognostic and predictive markers of colorectal cancers. Prognostic markers are used to indicate risks that predict the course of a disease, while predictive markers are relevant for guiding the cancer treatment. Predictive markers fall into three categories as follows: category I, markers validated by many proven studies; category II, markers partially proven and/or under development by many studies; and category III, other predictive biomarkers.

Category I Biomarkers

Ras Genes

Ras oncogenes play the most important role in the colorectal cancers. Especially KRAS and NRAS have therapeutic significance [59, 60]. Mutation of codons 12, 13, 59, 61, 117 and 146 in the KRAS and NRAS genes is associated with ineffective anti-EGFR therapy. Approximately 50% of colorectal carcinomas have RAS mutation and can't be treated with anti-EGFR antibody therapy. Only 40–60% of RAS wild- type patients respond to this treatment [61].

BRAF Gene

BRAF oncogene is most important in the treatment of melanoma [62], hairy cell leukaemia [63], lung adenocarcinoma and thyroid cancer [64]. BRAF mutations in and around amino acid 600 carry an adverse prognosis. Mutations of BRAF are of use for elimination of Lynch syndrome. Patients with colorectal carcinoma and mutation of BRAF pV600E don't benefit from anti-EGFR therapy [65].

Microsatellite Instability

The defective mechanism related to DNA mismatch repair genes induces mutations. From a therapeutic decision-making standpoint, the presence of MSI is important in

two aspects [66]. Firstly, in BRAF-wild-type cases, MSI is associated with a good prognosis. If BRAF status is not taken into consideration, MSI reduces the benefit of fluorouracil-based chemotherapy. Colorectal carcinomas with MSS and BRAF mutation usually indicate poor prognosis. Secondly, in the cancer immunotherapy, the presence of MSI is important. Many studies have reported significant responses achieved in MSI cancers (colorectal and others) to PDL1 inhibitors in patients irresponsive to conventional therapy [67, 68].

TNM Staging of Cancers of the Colon and Rectum

Category 2 Biomarkers

Limited number of recent studies have been performed in MSS colorectal carcinomas and earlier stage disease status [69]. Pathologists have been at the forefront of the analysis of adaptive immunity in colorectal carcinoma and validated the reproducibility of scoring systems in multicentre studies [47]. However, today, this approach is valuable only as a disease classification and a prognostic tool rather than being a predictive one.

Category 3 Biomarkers

Transcriptomic classification is one of the most important classification systems in colorectal carcinoma. There are specific gene expression signatures that able to predict recurrence after surgery. Both the Oncotype DX test [70] and the ColDx test [71] provide a score for recurrence in intermediate-stage colorectal carcinoma and are used for patient stratification. In RAS-wild-type colorectal carcinomas, PIK3CA mutations may be associated with a worse clinical outcome and irresponsiveness to targeted therapy using anti-EGFR monoclonal antibodies [72, 73]. In addition, mutations in PIK3CA may predict successful adjuvant therapy with acetylsalicylic acid in colorectal carcinomas [74].

c-Met mutation, aberrant expression, activation, and amplification have been reported in colorectal carcinomas [75].

Liquid biopsy, i.e. analysis of the patient's peripheral blood, has been used to diagnose metastatic colorectal carcinoma and to detect predictive markers of response. In addition to all the potential biochemical tests used for the detection of circulating tumour cells, exosomes or cell-free DNA, KRAS and BRAF mutations can be currently identified in some centres [76, 77].

Colorectal Neuroendocrine Neoplasms

Neuroendocrine neoplasms (NENs) of the colon and rectum are colorectal epithelial neoplasms with neuroendocrine differentiation.

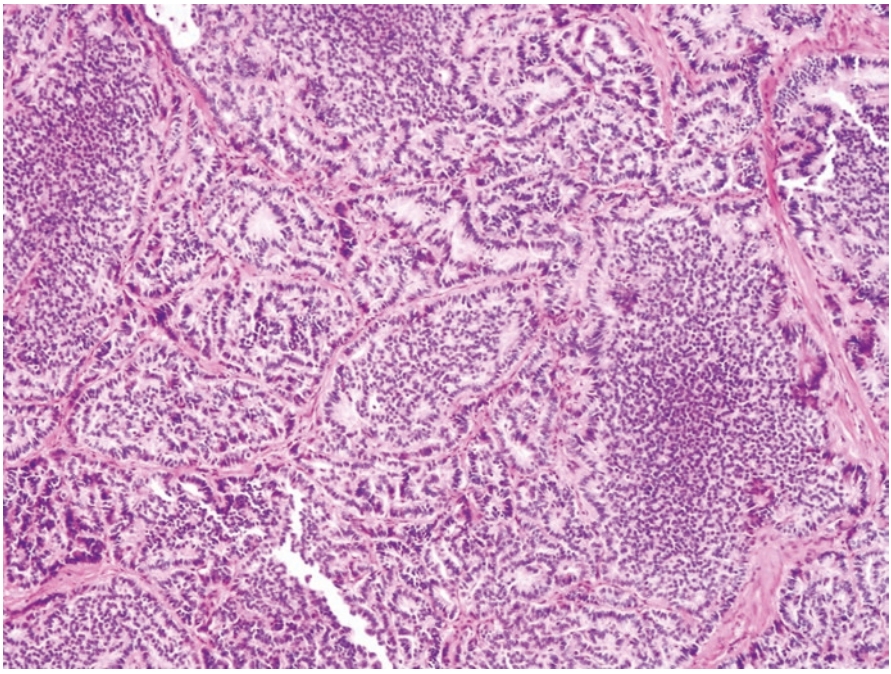

Fig. 23.14 Well-differentiated neuroendocrine tumours of the colon (HxE, ×100)

Table 23.3 Grading for colorectal NENs

Terminology	Differentiation	Grade	Mitotic rate (mitoses/2 mm^2)	Ki67 index
NET, G1		Low	<2	<3%
NET, G2	Well differentiated	Intermediate	2–20	3–20
NET, G3		High	>20	>20%
NEC, small cell type (SCNEC)	Poorly differentiated	High	>20	>20%
NEC, large cell type (LCNEC)	Poorly differentiated	High	>20	>20%
MİNEN	Well or poorly differentiated	Variable	Variable	Variable

NET, neuroendocrine tumour, *NEC* neuroendocrine carcinoma, *SCNEC* small cell neuroendocrine carcinoma, *LCNEC* large cell neuroendocrine carcinoma, *MİNEN* mixed neuroendocrine-non-neuroendocrine neoplasm

This group include well-differentiated neuroendocrine tumours (NETs) (Fig. 23.14), poorly differentiated neuroendocrine carcinomas (NECs) and mixed neuroendocrine non-neuroendocrine neoplasms (MINENs) [1].

NETs are graded as G1, G2 or G3 on the basis of proliferative activity as assessed by mitotic rate and the Ki67 proliferation index [78]. Mitotic rates are expressed as the number of mitoses/2 mm^2 (equalling ten high-power fields at 40× magnification

and an ocular field diameter of 0.5 mm) as determined by counting 50 fields of 0.2 mm^2 (Table 23.3). Ki67 proliferation index is determined by counting at least 500 cells in the regions of highest labelling (hotspots). Previously the G3 category neuroendocrine neoplasms were considered to be poorly differentiated like NECs. But NETs have different features that show organoid pattern (e.g. nests, ribbons and cords), uniform nuclear features, coarsely stippled chromatin and minimal necrosis. NECs have either small (SCNEC) or large cells (LCNEC). They have also a less nested architectural pattern that manifests as layers or tightly packed fusiform nuclei with finely granular chromatin or more rounded markedly atypical nuclei with prominent nucleoli. Necrosis is frequently present and is abundant. NECs occasionally include non-neuroendocrine carcinoma components such as adenocarcinoma or squamous carcinoma. In mixed neoplasms, each component should occupy ≥30% of the whole neoplasm. They are termed 'mixed neuroendocrine non-neuroendocrine noplasms' (MİNENs) (Fig. 23.15). The MİNENs usually don't contain well-differentiated neuroendocrine tumours. Besides, recently, genomic data have suggested that NETs and NECs are unrelated [1].

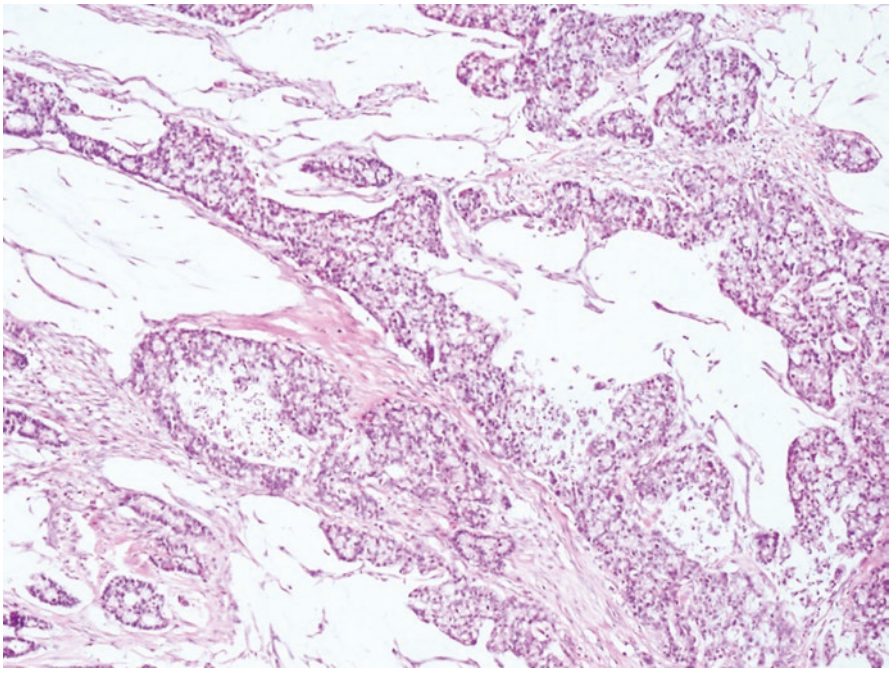

Fig. 23.15 Mixed neuroendocrine non-neuroendocrine neoplasm (MINEN) with small cell neuroendocrine carcinoma and mucinous carcinoma (HxE, ×100)

Macroscopic Features

NENs of the rectum and the colon are two different diseases. Rectal NENs are usually small lesions, of low to moderate histological malignancy, associated with good prognosis. NENs of the colon, however, are larger than other NENs of the GIS. Besides, they are often aggressive, poorly differentiated and associated with a poor prognosis [79].

Histopathology

Neuroendocrine tumours are composed of the solid islet, glandular or trabecular cells with abundant cytoplasm and monomorphic nuclei that show salt and pepper chromatin appearance. Occasionally mild or moderate atypia can be seen. Necrosis usually absent or minimal [80, 81].

Neuroendocrine carcinomas have large trabeculas or palisading structures with widespread necrosis. Their cells show severe atypia with atypical mitoses. Small or large cells can be seen. These tumours are termed as small cell or large cell NEC accordingly to their cellular characteristics.

MİNENs are usually composed of poorly differentiated NEC component and adenocarcinoma component [1]. Unusually NETs and adenomas can be seen in MİNENs [82].

Immunohistochemically enterochromaffin cell (EC-cell) NETs are positive for chromogranin A, synaptophysin and serotonin, while L-cell NETs are positive for synaptophysin and PYY, glicentin and/or GLPs (GLP-1 and GLP-2) and focally chromogranin A. Colorectal NETs are frequently positive for SSTR2A [83–85].

NECs are scantly or faintly positive for chromogranin A but diffusely positive for synaptophysin and CD56 and may be positive for neuron-specific enolase [86–88]. CDX2, TTF1 and SSTR2A [85, 89, 90].

Grading

Colorectal NENs are graded like other gastroenteropancreatic NENs (see Table 23.3).

Molecular Pathology

Colorectal EC-cell NETs may have low genetic abnormal burden. But NECs have genetic abnormalities which consist of mutations in TP53, RB1, APC, KRAS, FHIT, DCC and SMAD4, MEN 1 and BRAF genes. Scarce number of studies investigating MİNENs have suggested that same mutations are also present in NECs [91–95].

Staging

There are two different staging systems for NETs and NECs. Staging system for well-differentiated neuroendocrine tumours has been excerpted from the 2017 TNM classification of malignant tumours (Table 23.4). NECs are classified according to the criteria for classifying carcinoma.

Table 23.4 TNM staging of well-differentiated neuroendocrine tumours of colon and rectum

TNM Clinical Classification			
T-Primary tumour			
TX	Primary tumour cannot be assessed		
T0	No evidence of primary tumour		
T1	Tumour invades lamina propria or submucosa or is no greater than 2 cm in size		
T1a	Tumour less than 1 cm in size		
T1b	Tumour 1 or 2 cm in size		
T2	Tumour invades muscularis propria or is greater than 2 cm in size		
T3	Tumour invades subserosa or non-peritonealised pericolic or perirectal tissues		
T4	Tumour perforates the visceral peritoneum or invades other organs		
N-regional lymph nodes			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis		
M-distant metastasis			
M0	No distant metastasis		
M1	Distant metastasis		
M1a	Hepatic metastasis only		
M1b	Extrahepatic metastasis only		
M1c	Hepatic and extrahepatic metastases		
Stage			
Stage I	T1	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T3	N0	M0
Stage IIIA	T4	N0	M0
Stage IIIB	Any T	N1	M0
Stage IV	Any T	Any N	M1

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Genetic Knowledge of Colorectal Cancer

24

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Cancer Genetics

Cancer is a polygenic, multifactorial disease. It occurs as a result of the interaction of the genetic factors with environmental factors. In vertebrates, tissues and organs are formed by the complex organization of many different cell groups. The cancers that occur in a tissue or organ are classified into different groups such as carcinoma, sarcoma, melanoma, lymphoma, and leukemia depending on the cell type from which they originate. Carcinomas are the largest group originating from epithelial cells and responsible for more than 80% of cancer-related deaths. Epithelial cells cover the exterior of the body, the surfaces of all internal organs, body cavities, and canals. Cancers of epithelial cells with a tissue covering functions form squamous cell carcinomas, and cancers of epithelial cells with specialized functions such as producing certain products and releasing them into body canals and cavities form adenocarcinomas. More than 90% of colorectal cancers are adenocarcinomas. The remaining percentage of colorectal cancers are malignant carcinoid, lymphoma, neuroendocrine carcinoma, squamous cell carcinomas, and other very rare types [1–3].

To the extent that we understand cancer genetics and cancer biology, we can identify individuals at risk and develop tailor-made treatments. In other words, as the genetic information obtained increases, the chances of preventing the person from developing cancer and the chance of early detection and effective treatment will increase. The initial approach to get the needed genetic information bases on the taking of the personal and familial medical history. By taking the family history, the inheritance pattern of hereditary cancer syndromes (autosomal dominant, recessive, and X linked) can be obtained. At this point, effective genetic counseling is very important in process management. Genetic counseling is the process of

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communication between genetic specialists and patients to inform individuals and their families about the relevant health problem, available genetic testing, and management options [4].

Accurately recognizing and identifying individuals and families at high risk of developing cancer is crucial for primary care and other health-care providers. DNA-based tests can be used to identify a particular pathogenic variant as the cause of hereditary risk and to determine whether family members carry the disease-related variant. Even if only one person is tested, it is possible to reach a result that will affect the lives of all family members. Because of this result, other family members who have not thought about the disease before may also have screening tests for early diagnosis. The rate of occurrence of phenotypic feature in an individual carrying pathogenic variant is called penetrance. As with many cancer types, penetrance in adult-onset diseases may vary depending on the age and sex of the person carrying the variant. For some family members, this process may be worrying and may delay or refuse to test. To conclude that an individual has an increased risk of cancer that can possibly lead to specific lifesaving interventions such as colonoscopy, prophylactic mastectomy, and salpingooopherectomy [5].

Characteristics of hereditary cancers:

1. Presence of multiple primary tumors
2. Bilateral involvement
3. To be seen at a young age
4. Rare histological structure
5. Detection of rare sex
6. Congenital defects
7. Associated with an inherited precursor lesion
8. Associated with a rare disease

In the patient's family:

1. Identifying the same or related tumor in the first-degree relative and having one of the above individual characteristics
2. Two or more first-degree relatives with tumors in the same or related region
3. Two or more first-degree relatives with tumor types of a known familial cancer syndrome
4. Two or more first-degree relatives with rare tumors
5. Presence of the same site or related tumors in three or more relatives in two generations

People are becoming more and more aware of hereditary cancers and genetic tests, and they are increasingly applying to genetic clinics for these tests. In some countries, it is possible to access these tests over the Internet. In particular, thanks to technological advances in the field of genetics, many genes can be studied at the same time, and even exome or genome studies can be performed in many centers [4].

Genetics of Colorectal Cancers (CRC)

CRC is a very common disease. Approximately 145,600 new cases are detected each year in the USA, and approximately 51,000 CRC-related deaths occur. Approximately 9% of cancer-related deaths are due to CRC. It is the third cause of cancer incidence and cancer-related death in both men and women [6]. Colorectal cancers are a group of diseases caused by genetic predisposition, nutritional habits, lifestyle, and environmental factors. The greatest proof of this is that the incidence of colorectal cancer is different in each country. More than 90% of colorectal cancers are adenocarcinomas. The remaining percentage of colorectal cancers are malignant carcinoid, lymphoma, neuroendocrine carcinoma, squamous cell carcinomas and other very rare types [7].

Colorectal cancers may occur due to changes in a number of well-defined colorectal cancer-related genes so far, as well as inherited factors that create familial risk for colorectal cancers but have not yet been identified. Interestingly, in recent studies, nutritional and environmental factors have also been shown to play a role in the etiology of colorectal cancer through a number of genetic changes. The best examples of these genetic interactions between nutrition and the environment are the single nucleotide polymorphisms that can alter the metabolism of the risk or protective factors (such as folate, alcohol, vitamin D, calcium, fiber, fruit/vegetables, and red/processed meat) [8].

Of these genetic factors, the ones which are well-defined, highly penetrant, and associated with a specific clinical (syndrome) cause hereditary colorectal cancers; and the ones which are less penetrant but still increase the familial burden cause familial colorectal cancers. Patients whose genetic predisposition cannot be proved clearly and who have no family history are evaluated in the sporadic colorectal cancer group. Approximately 80% of all colorectal cancers are sporadic, 10–15% are familial, and 5–10% are hereditary. Molecular genetic evaluation of families with colorectal cancer includes known and highly penetrant genes. However, the rate of detecting a germline mutation in these genes in colorectal cancers is around 5–6%. In familial colorectal cancers, the clinical criteria that lead to hereditary colorectal cancers are often not met. Therefore, testing of hereditary colorectal cancer-related genes in this patient group will not be informative. This result leaves a large familial colorectal cancer group that cannot be diagnosed. The etiology of this large group of patients may be due to other genetic and epigenetic factors involved in carcinogenesis by low penetrating genes. As discussed in the following sections, low penetrating genes, gene-gene and gene-environment interactions, epigenetic modifications, and other environmental exposures are being investigated in hereditary colorectal cancers [9].

Molecular Pathogenesis of Colorectal Cancer

As with other types of cancer, pathogenic variants in certain specific genes can cause colorectal cancer. These pathogenic variants can occur in oncogenes, tumor

suppressor genes, and genes linked to DNA repair mechanisms. Point mutations that occur through life are not associated with hereditary syndromes and affect only the cells involved. The cancers that develop from these point mutations in somatic tissues are called sporadic cancers and constitute 70% of all colorectal cancers. The molecular pathogenesis of sporadic cancer is heterogeneous because pathogenic variants may target different genes. However, approximately 70% of cases of CRC follow a particular sequence of mutations that causes a specific morphological sequence called the "adenoma-carcinoma" sequence. The first mutation occurs in the APC gene, a tumor suppressor gene, and triggers the formation of nonmalignant adenomas, also called polyps. Approximately 15% of these adenomas are expected to develop into carcinomas within a decade. This APC mutation is followed by mutations in KRAS, TP53, and finally DCC (DCC Netrin 1 Receptor) [10].

Genomic instability is very important in the development of colorectal cancer. The pathogenic mechanisms leading to genomic instability are grouped as chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP).

1. *The chromosomal instability pathway (CIN)* is also considered the classic pathway leading to 80–85% of all CRC cases. This pathway results in the aneuploid tumors because of the imbalances in the number of chromosomes. Mechanisms underlying CIN include the defects in genes that are critical to the maintenance of normal cell function, such as APC, KRAS, PI3K, and TP53. APC mutations cause β-catenin to transduce into the nucleus and induce transcription of genes that lead to tumorigenesis and invasion. Mutations in KRAS and PI3K lead to continuous activation of MAP kinase, which increases cell proliferation. Finally, loss of function mutations in TP53, which encodes p53, the main control point of the cell cycle, leads to loss of control in the cell cycle [11, 12].
2. *The microsatellite instability pathway (MSI)* is caused by a phenotype that is hypersensitive to mutation due to the loss of DNA repair mechanisms. In tumors with microsatellite instability, the ability to repair short DNA strands or tandem repeats (two to five base pairs repeats) is reduced; therefore, mutations tend to accumulate in these regions. MSI and the importance of this mechanism will be discussed in the next sections [13].
3. Another common mechanism for CRC development is epigenetic instability, which is responsible for the *CpG island methylator phenotype (CIMP)*. CIMP tumors are characterized by loss of expression by silencing by hypermethylation of oncogene promoter regions. Genetic and epigenetic mechanisms in colorectal cancer play a role in the development of cancer, but the mechanism of methylation occurs more often than point mutation. BRAF mutations and microsatellite instability in many CIMP tumors are examples of the combined effect of genetics and epigenetics in CRC development [14, 15].

The Effect of Genomic Aberrations on CRC Formation

New genomic techniques allow the identification of multiple genomic aberrations that cause colorectal cancer. In addition to mutations, various chromosomal changes and translocations often play an important role in CRC development. All of these aberrations affect important signaling pathways such as WNT, MAPK/PI3K, and TGF-β and control of normal cell cycle [16].

1. *The WNT pathway* plays an important role in stem cell differentiation and cell growth. Therefore, changes in this pathway may lead to tumor development. Changes in the WNT pathway in CRC can also lead to reduced cell adhesion, affecting cell migration and metastasis. Although the main genomic aberration associated with the WNT pathway in CRC is APC mutations, there may be other changes targeting this pathway. Although APC is the most common mutated gene in CRC, it is not a prognostic marker. Although β-catenin is commonly overexpressed in CRC cancers and is located in the WNT pathway, it is often not a useful marker for prognosis. However, overexpression of c-MYC induced by activation of the WNT pathway is considered both a metastasis marker and a good prognostic factor associated with survival [17–20].
2. Both *MAPK and PI3K pathways* are related to cell proliferation and survival. Therefore, changes that affect these pathways provide proliferative advantages in tumor cells. KRAS, BRAF, and PIK3CA (PI3K) mutations are the most common mutations in CRC. KRAS mutations in exon 2 codon 13 are associated with poor prognosis as well as low survival, whereas mutations in exon 2 codon 12 are associated with more advanced tumors and metastases. BRAF mutations are a predictor of poor prognosis associated with lower survival rates, especially in tumors with microsatellite instability. Although V600E, the most common BRAF mutation in many types of cancer, is a poor prognostic factor for metastatic cancer, advances in personalized medicine and the use of BRAF V600E inhibitors in combination with other MAPK/PI3K pathway inhibitors have provided an advantage in the treatment of metastatic CRC. In contrast, KRAS and other rare BRAF mutations are associated with treatment resistance, thus leading to monotherapy failure and poor prognosis. PIK3CA mutations are also common in colorectal cancer and are associated with a worse prognosis accompanied by KRAS mutations. Similarly, tumors with both exon 9 and exon 20 combined mutations of PIK3CA have a worse outcome than tumors with only one of these mutations. Loss of PTEN which downregulates the PI3K pathway is associated with increased risk of death and poor survival in metastasis [21–29].
3. The *TGF-β pathway* also plays a role in basic cellular processes such as growth, differentiation, or apoptosis. However, sporadic mutations in TGF-β and pathway are not significant in colorectal cancer and therefore are not significant as prognostic markers. Loss of 18q is one of the major genomic abnormalities associated with the TGF-β pathway in colorectal cancer, and chromosomal

changes involving TGF-β are strongly associated with the CIN pathway in CRC. Chromosome 18q encodes two very important tumor suppressor genes, such as SMAD2 and SMAD4, and in case of loss, loss of apoptosis and loss of control in the cell cycle occurs. Current studies show a poor correlation between 18q loss and poor prognosis/shorter survival rates [30].

4. *TP53* is one of the most important tumor suppressor genes and the main control point of the cell cycle. Increased proliferation and tumor progression can be seen in Tp53 loss. Loss of 17p is a common event in CRC because it plays a role in the classic adenoma-carcinoma sequence. Furthermore, although there is an association between TP53 loss and lower survival rates, it is not considered a useful prognostic marker [31, 32].

The genomic structure of the tumor is clinically significant in CRC. The presence of more than two genomic aberrations in CRC shows significantly better survival than a tumor with two or fewer aberrations. No correlation was found between specific chromosomal abnormalities and survival. Other studies have also shown that increased genetic instability or increased chromosomal abnormalities in CRC are associated with a positive outcome. The underlying mechanisms are still unclear, but increased genomic instability has been suggested to activate various cell death mechanisms.

Molecular analysis of somatic DNA aberrations is one of the fundamentals of modern and personalized treatment approaches. With the introduction of molecular mechanisms, both prognostic predictive powers will be increased, and targeted therapeutic agents will be developed with increasing frequency [33].

Hereditary Colorectal Cancers

Diseases in this group constitute about 5–10% of all colorectal cancers. Colorectal cancers of the hereditary group are characterized by well-known, highly penetrant genetic factors and associated clinical presentations. For this reason, many of them are defined as “syndromes.” Apart from these well-known “colorectal cancer-related genes, memiş cancer-related genes that have not previously been associated with colorectal cancer” have also been shown to play a role in the etiology of hereditary colorectal cancers. As with many different cancers, genetic predisposition causes colorectal cancers to occur at an earlier age. It is known that almost one-third of colorectal cancers, especially before the age of 50, is associated with a “germline” mutation that causes genetic predisposition. Germline mutations are the mutations that a person (usually) receives from his or her parents, which he or she carries in all body cells and will be transmitted to the next generation with a 50% chance. During the proliferation of trillions of cells throughout the human lifespan, the genome is also replicated trillions of times. Thus, errors inevitably occur in the newly formed DNA sequences. Mutations that occur in a DNA sequence of the body cells at a given moment in life after the conception are called the “somatic” mutations. Somatic mutations are effective only in the person they

appear to and are not passed on to future generations. New mutations may occur in DNA due to frequent cell division or adverse environmental factors such as radiation, chemical substances, and ultraviolet rays, and normally repair mechanisms are activated against such new mutations. If there is significant damage that cannot be corrected, that cell is directed to the controlled cell death, "apoptosis." However, if there are defects in these repair mechanisms or mechanisms such as cell cycle regulation to direct these cells to apoptosis, these cells may become cancerous [33].

In hereditary colorectal cancers, the patient may have a germline mutation in one of the colorectal cancer-related genes, such as tumor suppressor genes, such as DNA repair genes. If a somatic mutation occurs in the remaining normal copy of the gene at some point in life, it is called the "Knudson's second hit hypothesis"; this can lead to cancer. In a patient without a germline mutation, a sporadic colorectal cancer with a genetic etiology can develop if both copies of the colorectal cancer-related gene are damaged by subsequent somatic mutations. Hereditary colorectal cancers are classified into two main groups as hereditary non-polyposis colorectal cancer (HNPCC) and hereditary colorectal cancers with polyposis according to histopathological evaluation [34]:

Hereditary Non-polyposis Colorectal Cancer (HNPCC)

There is a high amount of DNA replication and genetic recombination in cells that are constantly dividing. During these DNA replications and genetic recombination processes, a non-complementary nucleotide can sometimes be inserted into the newly produced (daughter) sequence. These errors of DNA polymerases should actually be corrected by their own proofreading mechanisms. However, DNA polymerase correction mechanisms are not sensitive enough, and errors can escape from the correction mechanism. An incorrectly produced daughter sequence may lead to an incomplete or defective protein. These errors should be corrected for the correct transmission of genetic information and the maintenance of normal cell function. Cells have different repair mechanisms against different types of defects. The mismatch repair (MMR) mechanism is used to correct these mismatch errors in the daughter sequence during replication and genetic recombination procedures. The MMR mechanism is a complex mechanism consisting of many components. In order to replace the faulty nucleotide, recognition, excision, resynthesis, and ligation of the sequence are required, respectively [35].

The defective region in the DNA sequence is recognized by the mutSα heterodimer formed by proteins which are the products of the MSH2/MSH6 genes and mutSβ heterodimer formed by the products of the MSH2/MSH3 genes. While the mutSα detects and binds to small errors (1–2 bases), mutSβ detects and binds to larger errors (2–16 bases). This binding triggers the formation of a new complex. This complex is formed by the combination of MutSα (MSH2/MSH6) or MutSβ (MSH2/MSH3) and MutLα (MLH1/PMS2) components. Binding of the mutSα/MutLα or MutSβ/MutLα complexes to the defective DNA segment results in a single strand breakage with the endonuclease activity of MutLα, allowing the EXO1

exonuclease, PCNA, and RPA proteins to cut off the binding site. In the final step, the DNA polymerase inserts the correct base to the position, and the single-strand breakage is corrected with DNA Ligase 1. Accurate and efficient operation of the entire delicate and complex mechanism is critical to a healthy cell life cycle. The MMR mechanism increases replication accuracy by 100–1000 times and is essential for the continuity of genomic integrity. Disorders in the MMR mechanism cause the accumulation of mutations in the cell and cause genomic instability, either leading to apoptosis of the cell or initiating an uncontrolled proliferation cycle leading to tumor development (Table 24.1). In MMR-related cancer susceptibility syndromes, the patient often has a germline mutation in one of the MMR genes. When a somatic mutation occurs in the other allele, this is also called the "loss of heterozygosity"; this leads to a homozygous mutation in the MMR gene. Cells carrying this homozygous mutation can cause cancer. The person carrying a germline

Table 24.1 Mismatch repair complexes, involved heterodimers, associated genes, and phenotypes

Mismatch repair complex	Involved heterodimers	Function	Associated genes and proteins	Associated phenotypes
MutSα	MSH2/MSH6	Mismatch recognition (1–2bp), excision	MSH2, MutS Homolog 2	Hereditary nonpolyposis colorectal cancer 1 (#120435); Muir-Torre syndrome (#158320); Mismatch repair cancer syndrome (Turcot syndrome) (#276300)
			MSH6, MutS Homolog 6	Hereditary nonpolyposis colorectal cancer 5 (#614350); Endometrial cancer (#608089); Mismatch repair cancer syndrome (Turcot syndrome) (#276300)
MutSβ	MSH2/MSH3	Mismatch Recognition (2-16bp), excision	MSH2, MutS Homolog 2	Hereditary nonpolyposis colorectal cancer 1 (#120435); Muir-Torre syndrome (#158320); Mismatch repair cancer syndrome (Turcot syndrome) (#276300)
			MSH3, MutS Homolog 3	Endometrial cancer (#608089); Familial adenomatous polyposis 4 (#617100)
MutLα	MLH1/PMS2	Excision (Endonuclease activity)	MLH1, MutL Homolog 1	Hereditary nonpolyposis colorectal cancer 2 (#609310); Muir-Torre syndrome (#158320); Mismatch repair cancer syndrome (Turcot Syndrome) (#276300)
			PMS2, PMS1 Homolog 2	Hereditary nonpolyposis colorectal cancer 4 (#614337); Mismatch repair cancer syndrome (Turcot syndrome) (#276300)

heterozygous mutation in the MMR gene has a predisposition/increased risk for MMR-related cancers. Another consequence of the defects in the MMR mechanism is the increased mutation rate of the whole genome due to the failure of the error correction mechanism. The increased mutation rate manifests itself in especially the microsatellite regions, which are already the low-stable regions. Microsatellite regions are DNA regions that are irregularly distributed throughout the genome, where sequences of 1–6 bases are repeated. The repetitive nature of microsatellites increases the likelihood of errors called strand slippage during replication. Strand slippage may result in insertion- or deletion-type mutations in the newly generated sequence. These errors, which will normally be corrected by the MMR mechanism, will not be corrected in tumor cells in cells with homozygous MMR gene mutations. Owing to this phenomenon, it became possible to use microsatellite instability (MSI) as a biomarker. The size of certain microsatellites varies from community to community and from person to person, but the same pattern must be observed in all cells of an individual [36, 37].

In the tumor cells of an individual with MMR-related cancer, a different pattern of a microsatellite is detected other than the ones from normal cells. This can be demonstrated by molecular genetic methods for selected specific microsatellite markers, and the patient can be identified as MSI-high, MSI-low, or MSI-negative (microsatellite stable).

Hereditary non-polyposis colorectal cancer is an autosomal dominant cancer predisposition disease. The incidence of hereditary non-polyposis colorectal cancer in all colorectal cancers ranges from 1.7% to 4.2%. As mentioned above, hereditary colorectal cancers are manifested by specific clinical presentations; thus, clinical features, family history, and histopathological evaluation are crucial for identifying at-risk individuals and planning tests for disease diagnosis [37, 38].

Hereditary non-polyposis colorectal cancer (HNPCC) refers to patients who meet the Amsterdam criteria. The original Amsterdam criteria include the definition of hereditary non-polyposis colorectal cancer, which was put forward in accordance with the recommendations of the "International Collaborative Group on HNPCC" meeting in 1990. In 1999, the criteria were revised by the same group, and the definition of hereditary non-polyposis colorectal cancer was redesigned with the following criteria currently in use. According to these criteria, for the diagnosis of hereditary non-polyposis colorectal cancer, at least 3 family members must be diagnosed with colorectal cancer, endometrial or related cancers (such as stomach, ovaries, ureter/kidney pelvis, small intestine, hepatobiliary and skin); at least one of these 3 persons must be a 1st degree relative of the others; at least two generations must be affected; at least one patient must be diagnosed before age 50. For the detected colorectal cancer, familial adenomatous polyposis must be excluded and tumors must be confirmed by pathological examination. The sensitivity and specificity of the Amsterdam II criteria for the diagnosis of hereditary non-polyposis colorectal cancer are estimated at 22% and 98%, respectively [39–41].

The Bethesda criteria, first published in 1997 and then revised in 2004, are attempting to determine which patients with hereditary non-polyposis colorectal cancer are eligible candidates for the MSI test. For the first time at the 1997

meeting, a standard definition for MSI was proposed. Accordingly, MSI is defined as the change in length due to the insertion or deletion of repeating units into a microsatellite region in tumor tissue compared to normal tissue. According to the Bethesda criteria, using this definition the patients meeting below criteria are candidates for MSI testing: patients diagnosed with colorectal cancer before the age of 50; patients with synchronous or metachronous tumors or hereditary colorectal tumor-related tumors; patients diagnosed with MSI-high tumor before 60 years of age; patients diagnosed with colorectal cancer and more than one first-degree relatives under 50 years of age diagnosed with colorectal cancer-related cancer; and patients diagnosed with colorectal cancer and at least two or one second-degree relatives diagnosed with colorectal cancer-related cancer. The sensitivity and specificity of the revised Bethesda guideline for the diagnosis of hereditary non-polyposis colorectal cancer are estimated at 82% and 77%, respectively [42, 43].

Hereditary non-polyposis colorectal cancer group consists of two main categories according to their molecular structure: MSI-low or negative, MMR-proficient (MMR-p) and MSI-positive, MMR-deficient (deficient) (MMR-d).

MMR-Proficient (MMR-P) Hereditary Non-polyposis Colorectal Cancers

No germline mutation can be detected in MMR genes in half of the patients who meet the Amsterdam criteria for hereditary non-polyposis colorectal cancer. These patients are evaluated in the MMR-proficient hereditary non-polyposis colorectal cancer or Familial Colorectal Cancer Type X (FCCTX) group. MMR-adequacy of the patients was demonstrated by tumor immunohistochemistry and/or MSI molecular genetic testing. FCCTX shows an autosomal dominant inheritance pattern, the genetic basis of which is not clearly known, but a germline mutation in a gene named RPS20 was identified in a 2014 study using linkage analysis, exome sequencing, and functional analysis of four generations of an FCCX family. This is the only genetic etiology identified so far for FCCTX. Patients in the FCCTX group had a lower risk of developing colorectal cancer than those in the MMR-deficient group (standard incidence rate of 2.3–6.1) and higher mean age at diagnosis (50–60 years to 40 years). Furthermore, FCCTX has not been shown to be associated with extracolonic cancers [44, 45].

MMR-Deficient (MMR-d) Hereditary Non-polyposis Colorectal Cancers

There are germline mutations in different MMR genes in MMR-deficient group diseases. MSH2, MLH1, MSH6, and PMS2 germline mutations in Lynch syndrome; MSH2, MLH1, and MSH6 germline mutations in Muir-Torre syndrome; and MSH2, MLH1, MSH6, and PMS2 germline mutations in Turcot syndrome cause MMR deficiency and microsatellite instability. There are also a group of patients with MMR deficiency in Lynch-like syndrome and sporadic colorectal cancers [45].

Lynch Syndrome

Although Lynch syndrome was previously used as an equivalent definition of hereditary non-polyposis colorectal cancer, nowadays Lynch syndrome defines a unique entity, a subgroup of hereditary non-polyposis colorectal cancers. Lynch syndrome accounts for approximately 2–3% of all colorectal cancers and is an autosomal dominant predisposition to a group of epithelial cancers due to pathogenic variants in certain genes. Genes that play a role in the etiology of Lynch syndrome are classified as MSH2 (41%), MLH1 (37%), MSH6 (13%), and PMS2 (9%) according to their identifiable germline mutation. Apart from germline mutations, deletions in the EPCAM gene may also silence the MSH2 gene epigenetically, which plays a role in the etiology of Lynch syndrome. Although cancer susceptibility is transmitted as autosomal dominant and germline mutation is found in heterozygous form, at the tumor tissue level, these gene defects become homozygous by a second somatic mutation or epigenetic silencing [46].

Although Lynch syndrome is primarily associated with hereditary colorectal cancers, the incidence of other epithelial cancers has increased with the effect of defects in MMR genes. Lifelong cancer risks in Lynch syndrome vary according to the affected MMR gene and gender. Overall, the lifetime risk of colorectal cancer (highest in MLH1 and EPCAM defects) is 10–75%, and the second most common endometrial adenocarcinoma risk (highest in MSH6, MLH1, and MHS2 defects) is estimated at 14–71%. For the rare extracolonic tumors, ovarian cancer is in the range of 1–20%; risk of urinary tract cancer is in the range of 2–15%; risk of gastric cancer is in the range of 1–13%; the risk of small bowel cancer ranges from 1% to 12%; prostate cancer risk is estimated to be in the range of 4–10%; and pancreatic cancer risk is estimated in the range of 1–6% [33].

MMR gene defects and associated MSI positivity are very important for the diagnosis and prognosis of Lynch syndrome because colon cancers due to Lynch syndrome have different clinical and histopathological features compared to sporadic cancers. Colorectal cancers due to Lynch syndrome tend to be localized on the right side of the colon, tend to be multiple synchronous and metachronous, and tend to have poorly differentiated histopathology. In addition, lymphocytic peritumoral inflammation (Crohn's reaction) and microsatellite instability are common in tumor tissue. All these features may change surgical and medical treatment approaches and even chemotherapeutics to be selected [47].

Determining the gene in which the germline mutation is involved will change the genetic counseling and prophylactic follow-up approaches. For example, it has been shown that MSH2 gene defects bring about an almost threefold higher incidence of extracolonic malignancy than MLH1 gene defects. Moreover, PMS2 and MLH3 gene defects are associated with brain tumors. For these reasons, it is important to identify carriers of mutations in Lynch syndrome in order to provide the necessary follow-up examinations to increase the early detection rate of cancers. Different approaches have been developed to identify individuals at risk and to identify patients who are at risk for Lynch syndrome. Using clinical data from family history

and histopathological evaluation, Amsterdam II criteria are used to capture patients at risk of mutation in Lynch syndrome. In addition to the Amsterdam II criteria, it is aimed to determine the probability of carrying germline mutations in MMR genes and/or the risk status of other individuals in the family by using tumor localization, tumor molecular genetic findings, MSI status, and similar data in models such as MMRpredict, MMRpro, and PREMM. All of these models have superiority to each other from different angles. Bethesda guidelines are also used to determine which are candidates for MSI testing among patients with colorectal cancer [35].

MSI Evaluation of the Tumor

The possibility of patients carrying MMR gene defects is determined by the MSI test. In 1997, the National Cancer Institute (NCI) workshop defined MSI and proposed a reference panel for analysis with five microsatellite markers. Based on these results, MSI classification guidelines were developed. Accordingly, the "Bethesda Panel" contains five microsatellites: two mononucleotide repeat regions (BAT25, BAT26) and three dinucleotide repeat regions (D2S123, D17S250, D5S346). According to the original recommendations (1997), if two or more of these five microsatellite sequences are mutated (instable), the tumor is called MSI-high (MSI-H). If only one of the five microsatellite sequences in the tumor DNA has been mutated, the tumor is called MSI-low (MSI-L). If none of the five microsatellite sequences in the tumor DNA have been mutated, the tumor is called microsatellite stable (MSS). Different panels have been developed to increase the sensitivity of the original Bethesda panel which have been modified, but the most commonly used panel is the original Bethesda panel [35, 43].

Germline Molecular Genetic Evaluation (MMR/EPCAM)

Among patients with colorectal tumors, the ones who meet below criteria are suitable for MMR/EPCAM germline mutation assays:

- Patients with microsatellite instability (MSI molecular genetic or immunohistochemical methods)
- Patients whose MSI assessment could not be performed but Lynch syndrome is highly suspected (meeting the Bethesda criteria)
- Patients who meet the Amsterdam criteria

The diagnostic molecular genetic approach to Lynch syndrome mainly involves sequence analysis of five MMR genes (MLH1, MSH2, MSH6, PMS2, EPCAM). However, in recent years, thanks to the improved technology and decreased costs, the phenotype directed "Sanger sequencing analysis" of selected genes in selected patients has been replaced by the use of "next-generation sequence analysis" (NGS) of multigene panels in a larger group of patients. However, the selection of patients to be tested with certain criteria will still be important, as it will prevent situations such as false positives, unnecessary test costs, and increased patient stress. Prior to these molecular genetic tests, genetic counseling should be given to families, and informed consent must be obtained about limitations of the tests and uncertain

results. The importance of pre-test genetic counseling is much more important in the use of expanded multigene panels of cancer-related genes that have not traditionally been associated with Lynch syndrome. In Lynch syndrome, almost 80% of detectable germline mutations are found in MSH2 and MLH1 genes, while the remaining 20% are found in MSH6 and PMS2 genes. EPCAM gene deletions occur in 1–3% of all Lynch syndrome patients. The most common variants in MMR genes are small insertions and deletions or large rearrangements leading to premature termination of protein synthesis. Fewer variants are missense, synonymous, and intronic variants. It is known that 5–20% of the pathogenic variants in MMR genes and almost all of the EPCAM variants occur due to large deletions and rearrangements. Therefore, in addition to sequence analysis in MMR and especially in EPCAM gene analysis, copy number detection methods such as MLPA should be used as a complementary test [35, 48].

A wide range of test approaches, such as sequence analysis completed by deletion duplication analysis, can be used to clarify the majority of cases by molecular genetics. In rare cases, MSI positive colorectal cancers resulting from structural/somatic promoter hypermethylation (MLH1 inactivation) of the MLH1 gene cannot be detected by these methods. This possibility should be kept in mind in patients who have positive MSI in the evaluation of tumor tissue and have no germline or somatic mutation in molecular analysis. Patients in this group are not considered in Lynch syndrome but in the group of "MMR-deficient sporadic hereditary non-polyposis colorectal cancers" which developed MSI due to MLH1 hypermethylation [49].

With the use of NGS analysis, the amount of genetic data obtained increased significantly by the analysis of wider genomic targets. This has emerged the variants that cannot be classified or variants of unknown significance (VUS) as an important challenge in genetic counseling. Sequence variants detected by molecular genetic analysis are classified into three groups as pathogenic/likely pathogenic variants, variants of unknown significance (VUS), and benign/likely benign variants [33].

- "Pathogenic/likely pathogenic" variants are the variants with sufficient evidence/strong evidence to classify them as pathogenic, known or accepted to cause the disease. If a pathogenic MMR/EPCAM mutation is detected in one patient, Lynch syndrome is diagnosed. Other family members at risk are investigated for this mutation. The absence of this mutation in a person at risk indicates that he or she does not (very likely) have Lynch syndrome [33].
- "Variants of unknown significance" (VUS) are the variants that do not have sufficient data to make a clear classification or have conflicting data in the literature. In some cases, pathogenic or benign nature of these variants can be supported by family studies. Evaluation of population frequencies and use of in silico analysis tools may provide additional information about the nature of variants. In addition, the use of databases and guidelines created by organizations such as the International Society for Gastrointestinal Hereditary Tumors (InSiGHT), which are based on hereditary colorectal cancer genes, may increase the success rate of classification. Despite all available data, there is no definitive guide to the use of

variants of unknown significance (VUS) in patient management. However, due to the ever-increasing genomic information, periodic re-analysis and re-classification of these variants may contribute to understanding the nature of these variants [33, 50].
- Benign/likely benign variants are those that are considered to have no clinical effect and that are not reported.

Lynch-Like Syndrome

Patients who meet the Amsterdam II criteria and revised Bethesda criteria with MSI but whose molecular genetic etiology cannot be detected in MMR genes are defined in Lynch-like syndrome (LLS). Studies in this patient group have shown that other genes associated with the DNA MMR pathway may play a role in the etiology of Lynch-like syndrome. In addition, higher sensitivity analyses of classical MMR genes have been shown to contribute to the etiology of this patient group [51].

Muir-Torre Syndrome

Muir-Torre syndrome is a rare, autosomal dominant, MMR-deficient hereditary non-polyposis colorectal cancer syndrome. Other than colorectal tumors, sebaceous tumors (sebaceous adenoma, epithelioma or carcinoma and/or keratoacanthoma) and other visceral malignancies are seen. Muir-Torre syndrome is caused by germline mutations in the MLH1, MSH2, or MSH6 genes. MSI is detected due to the MMR gene defect. Awareness of skin lesions in patients with Lynch syndrome increases the diagnosis of this disease [47].

Turcot Syndrome

Hereditary non-polyposis colorectal cancer and familial adenomatous polyposis represent two major hereditary colorectal cancer groups. Turcot syndrome 1 or Turcot syndrome 2 is considered in both groups with non-polyposis or polyposis colorectal cancer. If a patient with colorectal cancer develops a brain tumor, Turcot syndrome comes in to question. Turcot Syndrome 1 is an MMR-deficient hereditary non-polyposis colorectal cancer syndrome characterized by MMR gene defect. Turcot syndrome 2 is associated with the APC gene, not MMR genes. Diseases are inherited as autosomal dominant. Apart from colorectal cancer, glioblastoma in Turcot syndrome 1 and medulloblastoma in Turcot syndrome 2 can be seen [52].

MMR-Deficient Sporadic Hereditary Non-polyposis Colorectal Cancers

Non-hereditary/sporadic colorectal cancers can also show microsatellite instability. This MSI is often associated with spontaneous hypermethylation of the promoter region of the MLH1 gene. If MSI is positive in colorectal cancer, important information about whether the tumor is sporadic or hereditary can be obtained by looking at MLH1 promoter methylation because it is specific to sporadic colorectal cancer. Another important aspect of this condition is that 40–87% of all sporadic MSI tumors with MLH1 hypermethylation have a missense mutation in the BRAF oncogene (often V600E mutation). This mutation is not seen in the MSI of Lynch syndrome due to MMR defects [35].

Hereditary Colorectal Cancers with Polyposis

Colorectal Polyps

Colorectal tumors have a broad spectrum ranging from benign tumors to invasive cancer and are predominantly of epithelial origin (adenomas or adenocarcinomas). Epidemiological studies have shown that the detection of colon adenoma increases the risk of developing colon cancer in an individual. At the end of 20 years of follow-up, the risk of cancer increased by 25% compared to normal. Polyps are generally not neoplastic. The polyps can be in hyperplastic, juvenile, hamartomatous, inflammatory, and lymphoid types. In some cases, however, hamartomatous and juvenile polyps may turn into cancer. The conversion of polyp to cancer is referred to as the adenoma-carcinoma sequence. More than 95% of CRCs are carcinomas, of which about 95% are adenocarcinomas. It is well-known that adenomatous polyps are benign tumors that may undergo malignant transformation. They may be tubular, tubulovillous, and villous, and the villous type polyps have the highest malignancy potential. In addition, the large size of the adenoma and the degree of dysplasia are factors that increase the potential for conversion to cancer [53, 54].

Familial Adenomatous Polyposis (FAP)

FAP is one of the best described and well understood by hereditary colon cancer syndromes. Classic FAP is an autosomal dominant inherited syndrome characterized by multiple adenomatous polyps in the colon and rectum that develop after the first decade of life, resulting from mutations in the APC gene. It occurs every 7000–22,000 live births and is equal in both sexes. Duodenal tumors, desmoid tumors, nonepithelial benign tumors, congenital hypertrophy of the retinal pigment epithelium (CHRPE), thyroid cancer, brain tumor, pancreatic cancer, hepatoblastoma, and stomach cancer can also be seen in FAP patients. The APC gene is a tumor suppressor gene localized in the 5q21 region, encoding a protein of 16 exons, consisting of 2843 amino acids, resulting in autosomal dominant FAP and its variants as a result of germline mutations. In approximately 25% of cases, a de novo mutation is detected without a family history. More than 1000 mutations have been identified; they mainly consist of frameshift, premature stop codon-forming mutations, and deletions. In addition, large, submicroscopic deletions are common causes of FAP. While it shows complete penetrance in terms of colon polyps, variable penetrance is seen in terms of extracolonic manifestations [55–59].

In addition to the inherited germline pathogenic variant, a somatic mutation in the other allele is required for adenoma in FAP syndrome. Detection of mutations in both alleles results in loss of functional APC protein in a cell and abnormal accumulation of beta-catenin. Ultimately, the transcriptional activation of the Wnt (Wingless-type) signaling pathway and target genes controlling cell growth takes place. The Wnt signaling pathway is an evolutionarily conserved signaling pathway that is also necessary for embryonic development. It also plays a central role in the regeneration of the intestinal epithelium. CRC is thought to occur as a result of the expansion of colonic crypt cells during this epithelial renewal. Normal APC protein appears to inhibit the accumulation of cytosolic and nuclear beta-catenin by

mediating phosphorylation and resulting degradation of beta-catenin. Loss of functional APC protein by germline or somatic variants results in the nuclear deposition of beta-catenin, which binds and activates the transcription factor Tcf-4. By activating beta-catenin/Tcf-4, it causes cell proliferation by inducing resistance to apoptosis by preventing intestinal crypt epithelial cells from entering G1 arrester and terminal differentiation during proliferation. This mechanism is associated with the loss of tumor suppression of the APC gene. However, it has been shown that C-terminal Truncated APC protein increases cell survival by regulation of the BCL2 gene with the effect of gain of function and activates colon epithelial cell proliferation in cell culture by inducing cell migration through the guanine nucleotide exchange factor called Asef. This effect is a typical oncogenic effect. In addition, germline or somatic pathogenic variants in the APC gene contribute to tumorigenesis by causing chromosomal instability [17, 60–64].

There are many studies investigating the clinical relationship with the localization of the pathogenic variant. According to the results of these studies, pathogenic variants between codon 169 and 1249 lead to the classical FAP table, especially 1250–1464. Detection of pathogenic variants among codons leads to a classic FAP table characterized by dense polyps in the colon in general. The AFAP (attenuated FAP) table is generally associated with variants seen in the upstream region of exon 4 and downstream after 2/3 of exon 15. Pathogenic variants codon 463–1444 are associated with congenital hypertrophy of the retinal pigment epithelium (CHRPE). Variants between codons 1445 and 1578 are associated with desmoid tumors. Variants codon 279–1309 cause duodenal polyps. Finally, variants codon 686–1217 cause medulloblastoma. Variants in the region of the APC gene promoter (1B) were generally found in the table of gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). The variant APC I1307K is a low-penetrance variant of uncertain clinical significance and is found almost exclusively in Ashkenazi Jews. Colonic adenoma and adenocarcinoma are seen in those carrying this variant twice as much as the normal population, but they are not associated with polyps in the colon [65–75].

FAP syndrome progresses with colonic and extracolonic findings. The presence of hundreds of adenomatous polyps in the colon is typical for classic FAP. Abdominal pain, diarrhea, and gastrointestinal bleeding may occur. These symptoms are usually signs of colorectal cancer development. The diagnosis is usually made between the ages of 20 and 40. The fact that when an individual with FAP is diagnosed in his family, the awareness that occurs with access to genetic tests and the increase in the number of families receiving genetic counseling brings the age of diagnosis to the early asymptomatic period [76].

(a) *Classical FAP*: The mean age of adenoma in an individual carrying the germline pathogenic variant in the APC gene is 16 years. Adenomatous polyps are more than 100 in classical FAP cases. An adenoma is seen in 15% of cases at the age of 10 years, while 75% at 20 years old and 90% at 30 years develop FAP. In 80% of the cases, tumors are on the left. Nearly all untreated FAP patients develop CRC (mean 39 years). Therefore, in individuals at risk for

carrying pathogenic variants in the APC gene, annual colonoscopy follow-up from adolescence is important for early detection of colonic polyps and prophylactic colectomy planning [77, 78].

(b) *Attenuated FAP (AFAP)*: First defined in 1990 in a large family with varying adenoma number. Adenomas are often on the right side (proximal). It can typically be described as oligopolyposis. The number of adenomas is generally between 10 and 99 and the age of adenoma (mean 44 years) and CRC (mean 56 years) is later than classical FAP. Although the risk of CRC is lower than the classical FAP, it is approximately 80% [79, 80].

FAP variants: Gardner syndrome-Turcot syndrome (BTP2): Initially used to describe families with colon polyposis and extracolonic symptoms. Colonic polyposis was called Turcot syndrome (brain tumor polyposis 1, BTP1) when it was accompanied by a brain tumor, and Gardner syndrome when it was accompanied by other extracolonic tumors such as desmoid tumors, sebaceous or epidermoid cysts, lipomas, and osteomas. Today, we know that Gardner syndrome is caused by APC mutation and Turcot syndrome is caused by pathogenic variants in mismatch repair genes (MLH1, MSH2, MSH6, and PMS2). In addition, the pathogenic variant was detected in the APC gene in brain tumor polyposis 2 (BTP2) syndrome, which presents a similar picture of Turcot syndrome [52, 81, 82].

Individuals presenting with a classic FAP phenotype should undergo APC testing. However, since there may be syndromes with genetic heterogeneity and phenotypic overlap, multigene containing panels are often preferred in practice. Especially in patients with less than 100 colorectal adenomatous polyps, differential diagnosis with clinical features can be difficult. The differential diagnosis should include AFAP (APC gene), MAP (MUTYH gene), polymerase proofreading-associated polyposis (PPAP) (biopsy POLE and POLD1 genes), and biallelic mismatch repair deficiency (BMMRD) (MLH1, MSH2, MSH6, PMS2, and EPCAM genes). In a large study, APC germline mutation was detected in 80% of cases with adenoma numbers greater than 1000, 56% in cases with 100–999 adenoma, 10% in cases with 20–99 adenoma, and 5% in cases with 10–19 adenoma. MUTYH mutation was detected in 10% of cases with adenoma number 20–99, whereas this rate was only 2% in patients with more than 100 adenomas. It is also important to note that deletion duplication analysis of other genes, especially APC, may be required. In the APC, whole gene deletion or Promotor 1B, deletion is frequently encountered. These deletions and duplications may not be detected by sequence analysis. Although MLPA and array CGH methods are widely used in the detection of these copy number differences, kits that allow both multigenic sequence analysis and deletion duplication analysis have been introduced recently with the advances in NGS technology. If a pathogenic variant is detected in the APC gene in a patient diagnosed with FAP, it can be decided whether family members should be followed for aggressive screening by analyzing the family members at risk for that variant. The aggressive screening will be required in family members carrying the variant and follow-up will not be necessary for those who do not carry the variant. In most cases, the pathogenic variant is detected in the parents because of autosomal

dominant inheritance. However, variants are not detected in 25% of the parents. These cases are due to "de novo" mutations or germline mosaicism. It is essential to investigate the variant in siblings in these cases [83–86].

In general, genetic testing of hereditary cancers is not recommended if the data will not be used in medical supervision or follow-up in childhood. However, because of the early onset of clinical features of FAP and the need for follow-up and supervision starts in adolescence, testing in childhood may be required. It becomes particularly important if there is a known pathogenic variant in the family. This information is necessary because children with a variant should be followed up with a colonoscopy and flexible sigmoidoscopy during adolescence. In children who do not carry the variant, such follow-up is not necessary, and these children will be protected from physical and even more important psychological trauma by avoiding unnecessary screening [87].

Mutyh-Related Polyposis (MAP)

MUTYH-associated polyposis is an autosomal recessive polyposis syndrome characterized by multiple colorectal adenomas and an increased risk of colorectal cancer. MUTYH-associated polyposis (MAP) should be suspected in a family history of autosomal recessive colorectal cancer, with or without polyps, or if the following clinical findings appear [88]:

- Ten or more colorectal adenomas before age 60
- Twenty or more colorectal adenomas at any age
- Twenty or more combinations of colorectal adenoma, hyperplastic, and sessile serrated polyps
- Sessile serrated polyposis syndrome: Pattern of autosomal recessive inheritance. At least five sessile serrated polyps of 2 or more >10 mm proximal to the sigmoid colon, or sessile serrated polyps of any size greater than 20 along the colon (except hyperplastic polyps in the rectum and sigmoid colon)
- The presence of duodenal polyp and/or duodenal cancer
- Detection of pathogenic variant c.34G→T (Codon 12) in the KRAS gene in somatic tissue test with or without polyp history [89]

MUTYH is a base excision repair gene whose protein restores oxidative damage to DNA. Failure of base excision repair causes somatic GC-TA transversion in many genes, including APC and KRAS genes in somatic tissue. This transversion is recognized as a footprint of oxidative damage, and as a result, mutated target genes cause polyposis. The most common pathogenic variants in the MUTYH gene are Y179C and G396D. However, numerous pathogenic variants have been reported at different loci. Patients with MAP may be homozygous or compound heterozygous for these or other pathogenic variants in the MUTYH gene [90, 91].

The prevalence of the MUTYH pathogenic variant in a single allele in the general population is approximately 1–2% and the biallelic pathogenic variant is detected in less than 1% of individuals diagnosed with colorectal cancer. Among individuals with multiple colorectal adenomas who do not have germline mutations

in the APC gene, the prevalence of biallelic MUTYH pathogenic variant is between 7% and 42% [92–94].

MAP is typically characterized by the presence of multiple colorectal adenomas, and phenotypic differences may be observed with respect to genotype. For example, clinical findings are more severe in individuals carrying the G396D variant than those carrying Y179C, which occurs at an earlier age and has a higher risk of developing cancer. In addition, environmental and epigenetic factors may affect the MAP phenotype [95].

Cases with MAP usually develop 10–100 colorectal polyps in the fifth and sixth decades. Although adenoma type polyps are common, hyperplastic and silent serrated polyps may also be seen. Phenotype is variable. Patients with MUTYH-associated polyposis have a high risk of developing CRC, and approximately 60% of patients have CRC at admission. The risk of CRC in monoallelic MUTYH carriers has increased by 5–7% throughout life. In a meta-analysis study, there was no significant increase in CRC risk in those with monoallelic G396D variants, whereas a 1.3-fold increased CRC risk was reported in those with monoallelic Y179C variant [83, 96–98].

Individuals with MUTYH-related polyposis have an increased risk of gastric and duodenal polyps. Other rare extracolonic features reported in patients with MUTYH-related polyposis include osteomas, congenital hypertrophy of the retinal pigment epithelium, dental cysts, desmoid, sebaceous hyperplasia, and Muir-Torre phenotype with sebaceous gland tumors. In addition to CRC risk, increased risk of duodenal, ovarian, bladder, thyroid, and skin cancer is seen in MAP patients [99, 100].

The abovementioned clinical findings and autosomal recessive inheritance pattern in MUTYH-related polyposis are important signs. In order to diagnose, it is necessary to show biallelic pathogenic germline variants in the MUTYH gene. The 4.2 Mb deletion covering exons 4–16 has been shown in three separate cases from Spain, France, and Brazil, and this variant has been claimed to be the founder variant in Southern Europe. Later, another case with exon 15 deletion was reported from Italy. Sequence analysis is often sufficient for diagnosis. However, in order to show these deletions in a small group, methods such as MLPA, specially designed array, and quantitative PCR may be required [101–104].

If germline biallelic MUTYH pathogenic variants are found, genetic testing should be offered to at-risk relatives of the index case. The pathogenic variant of the KRAS gene in somatic tissue is detected in 5–10% of sporadic CRCs. When CRC is detected in MAP cases, this rate is between 60–90%. There is a biallelic pathogenic variant in the MUTYH gene in 10–25% of CRC cases with a KRAS somatic pathogenic variant. A microsatellite is stable in the vast majority of CRCs developing after MAP [89, 101, 105].

According to the American College of Gastroenterology guidelines, colorectal cancer (CRC) screening is recommended by colonoscopy every 1 or 2 years between the ages of 25 and 30. There are also guidelines recommending colonoscopy starting at age 18. Surgical resection (e.g., partial, subtotal, or total colectomy) is recommended in patients with significant polyp burden that cannot be managed effectively by CRC or colonoscopic polypectomy. After colectomy, the remaining rectum and

ileal structures should be screened annually. Since the data suggest that the pathogenic variants of MUTYH are associated with a small increase in CRC risk, colonoscopic surveillance is recommended every 5 years, starting 10 years before the earliest diagnosis in the family of these individuals. According to the American College of Gastroenterology in MAP patients, 30–35 years of upper endoscopy is recommended to undergo duodenoscopy. Since the risk of thyroid cancer increases in patients with MAP, annual thyroid screening by physical examination and ultrasound is recommended [40, 106].

Hamartomatous Polyposis Syndrome

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS) is an early-onset autosomal dominant disease with mucocutaneous pigmentation in the gastrointestinal tract characterized by melanocytic macules in the lips and perioral and buccal regions along with both hamartomatous and adenomatous multiple polyps.

Peutz-Jeghers syndrome (PJS) is rare, male to female ratio equal, and its prevalence is 1/25,000 to 1/280,000 live births. PJS is an autosomal dominant disorder resulting from germline mutations in the gene encoding a serine-threonine kinase named STK11 in the 19p13.3 region. In addition to the germline mutation, clinical symptoms of PJS occur with an acquired genetic defect of the second allele in somatic cells (89). The penetrance of PJS is over 90% by the age of 30, with a de novo mutation rate of 10–20%. STK11 is a tumor suppressor gene. AMP-activated protein kinase (AMPK) controls multiple processes such as cell polarity, metabolism, and apoptosis by regulating the activity of family members. The germline mutations detected in the STK11 gene are nonsense, missense, frameshift variants, splice site variants, and large deletions. Mutations in STK11 are detected in only 50–80% of PJS families, suggesting a second PJS gene locus. A strong genotype-phenotype correlation relationship could not be established. About 85% of the detected variants are in the kinase domain of the expressed protein. The detection rate of a large deletion in the STK11 gene may increase by up to 30%. Therefore, in addition to sequence analysis, deletion duplication analyses are very important. In a study of 297 patients with PJS, it was shown that the type or location of STK11 pathogenic variants does not affect cancer risk. In patients with premature truncation mutation in the STK11 gene, the age at which the polyps were first seen and the age of polypectomy was significantly earlier than those with missense mutations. In patients with early-onset age, the number of polyps, the number of surgeries, and the risk of developing melanoma have been reported to be significantly higher in premature truncation mutations than other pathogenic variants. The risk of gastrointestinal polyp dysplasia in pathogenic variants affecting protein kinase domain XI (90%) has been shown to be significantly higher than variants affecting other domains of the protein (11.8%). It has been reported that pathogenic variants in the substrate recognition region are riskier in terms of cancer development than variants in ATP binding region and premature truncated mutations are riskier in terms of breast cancer [107–113].

Two characteristic signs of Peutz-Jeghers syndrome (PJS) are pigmented mucocutaneous macules and multiple hamartomatous gastrointestinal polyps. Individuals with PJS are at an increased risk for both gastrointestinal and extra-intestinal cancers. Mucocutaneous pigmentation – mucocutaneous pigmented macules (melanin stains) are found in more than 95% of individuals with PJS, caused by pigment-laden macrophages in the dermis. Typically, flat, blue-gray to brown spots are from 1 to 5 mm in size. Malignant transformation is very rare. Hamartomatous polyps—gastrointestinal hamartomatous polyps are found in most patients with PJS. Although polyps occur most frequently in the small intestine (60–90%) and in the jejunum, ileum, and duodenum, respectively, they can be found anywhere in the gastrointestinal tract, including the stomach (15–30%) and the colon (50–64%). Gastrointestinal polyps develop in the first decade of life and most patients become symptomatic between 10 and 30 years of age. Hamartomatous polyps may also occur outside the gastrointestinal tract, including the renal pelvis, urinary bladder, lungs, and nasopharynx. Although 50% of patients are asymptomatic at the time of diagnosis, they may present with signs of obstruction due to polyp intensification or obstruction of the gastrointestinal lumen, abdominal pain caused by infarction, and anemia caused by acute or chronic bleeding. Up to 69% of patients experience intensification in the small intestine during their lifetime. Although polyps are not endoscopically differentiating, their histological findings are characteristic of hamartomas with smooth muscle proliferation extending to the lamina propria in an arborization-like manner. The mean age of malignancy is 42 years. In a review of 20 studies in 2010, the lifetime risk of cancer ranged from 37% to 93%. The most common areas for malignancy are colorectal, followed by breast, stomach, small intestine, and pancreas. For example, the cumulative risk of breast cancer is estimated to be 32–54% and 21% for ovarian cancer. It is estimated that the risk of pancreatic cancer is 100 times higher than the general population. The estimated lifetime risk of gastrointestinal cancer in PJS is between 38% and 66%. This gastrointestinal cancer group mainly consists of CRC (39%), gastric cancer (29%), small intestine cancer (13%) and pancreatic cancer (11–36%). Other gastrointestinal tumors associated with PJS include gallbladder and esophageal cancers. In women with PJS, in addition to breast and ovarian cancer, cervical adenoma malignum, a rare and very aggressive adenocarcinoma of the cervix, may be seen. In addition, while women with PJS develop benign annular ovarian sex cord tumors, men have a predisposition to the development of Sertoli cell testicular tumors. Although these two types of tumors are not malignant, they may cause symptoms such as gynecomastia and advanced bone age due to increased estrogen production [109, 114–116].

The clinical diagnosis of PJS can be made by the presence of any of the following:

- Two or more Peutz-Jeghers-type hamartomatous polyps of the gastrointestinal tract
- Mucocutaneous hyperpigmentation of the mouth, lips, nose, eyes, genital organs, or fingers
- PJS in family history

Those who meet the clinical criteria for PJS should undergo genetic testing for a germline mutation in the STK11 gene. If a person who meets the clinical criteria for PJS does not have a pathogenic STK11 mutation and does not have a known PJS mutation in the family, this does not exclude the diagnosis of PJS. These cases and their relatives at risk still require frequent endoscopic surveillance for removal of polyps throughout the gastrointestinal tract and screening for extraintestinal cancers. If a genetic test is performed and a mutation is found in an affected person, the genetic test of relatives at risk will provide true positive or negative test results. Members at risk who receive true negative test results have a cancer risk similar to the general population. Risky relatives with pathogenic variants should follow the surveillance guidelines for individuals with PJS. In addition, esophagogastroduodenoscopy, video capsule endoscopy (VCE), and colonoscopy should be performed as baseline endoscopic screening in the intestinal tract since the age of 8 due to increased risk of cancer. If polyps are detected during baseline screening, they should be repeated every 2–3 years. If no polyps are detected and no symptoms are seen, it is recommended to repeat at age 18. In the meantime, if symptoms begin, new screening and, if a polyp is detected, a re-screening should be performed every 2–3 years. To reduce the risk of polyp-related complications, endoscopic polypectomy should be performed for polyps larger than 0.5–1 cm in size. Cases should also be included in the follow-up program for testicular tumors, cervical cancer, ovarian and endometrial cancer, breast cancer, and pancreatic cancer. PJS is an autosomal dominant disease, and if a pathogenic variant is detected in the STK11 gene, the probability of transmission to the next generation is 50%. Molecular analysis and clinical follow-up of persons at risk in families with pathogenic variants are very important. Since clinical findings cannot be detected until the age of 8, predictive molecular testing should be considered. The result of the test will guide clinical follow-up. Those carrying pathogenic variants should be informed about the preimplantation genetic diagnosis (PGD) when they want to have children. In large series studies, PJS was found to be 60–78% familial and 17–40% isolated. Isolated cases with pathogenic variants in the STK11 gene are called “de novo.” However, the data on this subject is not reliable enough, as the possibility of a faint clinical trial in their parents has not been fully investigated. In addition, the possibility of germline mosaicism should be considered. In addition, in a series of 300 cases, somatic mosaicism was detected by Sanger sequence and MLPA analysis in three cases. The risk of a sibling is associated with the presence or absence of pathogenic variants in their parents. If the parents have a pathogenic variant, the risk is 50%, or else the germline mosaicism is slightly higher than the normal population. The proband with the pathogenic variant in the STK11 gene has a 50% risk in each child. If there is germline mosaicism in the band, the risk is as much as the possibility of transferring the pathogenic variant, i.e., the degree of mosaicism is important. There is no family history of the tape, and the pathogenic variant cannot be detected in the STK11 gene [70, 117–127].

Juvenile Polyposis Syndrome

Juvenile polyposis syndrome (JPS) is a rare autosomal dominant syndrome characterized by multiple hamartomatous polyps throughout the gastrointestinal tract, with a primary onset of childhood and early adulthood. The estimated incidence is about 1/100,000–160,000. People with JPS are at high risk for colorectal and gastric cancer. JPS, diarrhea, GI system bleeding, and protein-losing enteropathy may occur with. In the diagnosis of JPS, it is important that it is a typical hamartomatous polyp called a juvenile polyp, not histopathologically. Solitary sporadic polyps can be seen in infantile and childhood in colon and rectum, but this is not related to JPS. These polyps occur in 2% of children under 10 years of age and are usually unique and not associated with cancer risk. There should be one or more of the following for the clinical diagnosis of JPS [128–131].

- Five or more juvenile polyps in the colon or rectum
- Juvenile polyps in other parts of the gastrointestinal tract
- Any number of juvenile polyps and family history of JPS

JPS is the result of germline mutations in SMAD4 (MADH4) (15–60%) or bone morphogenic protein receptor type 1A (BMPR1A) (25–40%) genes associated with the transforming growth factor-beta (TGF-beta) signaling pathway. Mutations in SMAD4 or BMPR1A are detected in approximately 60% of JPS patients. Approximately 25% of patients have a de novo mutation. The SMAD4 gene is located on chromosome 18q21.1 and encodes a protein that is a component of the transforming growth factor (TGF)-beta signaling pathway that mediates growth inhibitory signals from the cell surface to the nucleus. The germline pathogenic variants in the SMAD4 gene are present in 6 of the 11 exons and cause the risk of juvenile polyps and cancer. The risk of extracolonic gastrointestinal cancer, such as gastric polyp and gastric cancer, is also increased in cases with a pathogenic variant of SMAD4. The relationship between JAD due to SMAD4 mutations and hereditary hemorrhagic telangiectasia (HHT) has also been described. Therefore, HHT clinical findings such as arteriovenous malformations (AVM), mucocutaneous telangiectasias, digital clubbing, osteoarthropathy, hepatic arteriovenous malformations, and cerebellar cavernous hemangioma are also observed in patients with JPS with pathogenic variant detected in the SMAD gene. When a patient is clinically found to have both JPS and HHT properties, the pathogenic variant will generally be in the SMAD4 gene. The majority of patients with isolated HHT will have a pathogenic variant in the activin receptor-like kinase 1 (ALK1) gene or endoglin (ENG) gene. Pathogenic variants of SMAD4 have been reported in only 1% of isolated HHT cases. Heart valve anomalies can be found in 12% of JPS cases, and all pathogenic variants detected in these cases have been found in the SMAD4 gene [107, 132–136].

The BMPR1A (ALK3) gene is located on chromosome 10q22–23 and encodes a serine/threonine kinase receptor protein that is also involved in the TGF-beta

signaling pathway. Upon activation, BMPR1A phosphorylates the SMAD family of proteins. The BMPR1A gene was first identified by linkage analysis in families with JPS without detectable pathogenic variants in SMAD4. The variants described in BMPR1A are nonsense, frameshift, missense, and splice site variants. Those with SMAD4 mutations have higher polyposis and higher cancer risk in the upper gastrointestinal tract than those with BMPR1A mutation. Large deletions of both SMAD4 and BMPR1 genes have been demonstrated in patients with JPS by the MLPA method [134, 137, 138].

A serious form of JPS in which polyposis develops in the first few years of life is called infantile JPS. It is usually caused by microdeletions of chromosome 10q22–23, a region containing BMPR1A and PTEN. The phenotype is usually associated with macrocephaly and growth retardation as a result of the loss of PTEN function. Polyps can be seen in both the upper and lower gastrointestinal tract. Recurrent GI bleeding, diarrhea, exudative enteropathy, and growth retardation are associated with very high morbidity and mortality rates in these infants, so the inheritance of such cases is limited [139].

Polyps usually begin to appear in the first decade of life and occur predominantly in the colorectum (98%), but may occur in the stomach (14%), duodenum (7%), jejunum, and ileum (7%). Rectal bleeding is the most common presenting symptom in more than half of the patients. Other symptoms include prolapse polyps, melena, pain, iron deficiency anemia, and diarrhea. Juvenile polyps are characterized by dilated glands that can be microscopically edematous and contain inflammatory cells, forming abundant lamina propria and mucin-filled cysts. Although JPS is a hamartomatous polyp syndrome, adenomatous changes are also thought to play a role in the development of malignancy. In JPS, adenomatous changes have been shown in 50% of offspring polyps. Individuals with JPS are at high risk for colorectal cancer and stomach cancer. The cumulative colorectal cancer risk in JPS is 17–22% at age 35% and 68% at age 60. The estimated lifetime risk for gastric cancer in JPS patients is 20–30%, and the average age at diagnosis is 58 [130, 140].

Those with a pathogenic germline mutation in the BMPR1A and SMAD4 genes and who have not been genetically tested or whose genetic test results are uncertain should be screened for JPS symptoms. The patients with pathogenic mutations in SMAD4 should be evaluated for hereditary hemorrhagic telangiectasia (HHT). If SMAD4 mutation is known in a family, genetic testing should be performed within 6 months of birth due to the risk of HHT [141, 142].

Colorectal cancer screening with colonoscopy should be performed every 3 years starting from the age of 12 years in patients presenting with symptoms. If polyps are found, a colonoscopy should be repeated annually; otherwise, the colonoscopy intervals maybe 1–3 years. Beginning at age 12, the upper gastrointestinal tract should be investigated by upper endoscopy. If polyps are detected, upper endoscopy should be repeated annually. An upper endoscopy can be performed every 2–3 years in the absence of upper gastrointestinal system polyps. It includes a baseline examination starting from puberty and periodically repeated according to signs or symptoms, including anemia or protein-losing enteropathy. Small bowel enteroscopy can be evaluated using wireless capsule endoscopy or small bowel imaging [142].

Pten Hamartoma Tumor Syndromes (PHTS)

The germline mutations in the phosphatase and tensin homologous (PTEN) gene have been described in several rare syndromes with different clinical manifestations known collectively as PTEN hamartoma tumor syndromes (PHTS). The defining clinical feature of PHTS is the presence of hamartomatous tumors. The term PHTS refers to the presence of a pathogenic variant in the PTEN gene in any patient, not phenotypic features. PHTS is inherited as autosomal dominant [143].

1. *Cowden syndrome* (also known as Cowden's disease or multiple hamartoma syndrome): The most well-defined phenotype in PHTS. In addition to multiple hamartomas in various tissues, patients have characteristic dermatological symptoms such as trichilemmomas, oral fibromas, and punctate palmoplantar keratoses and an increased risk of breast, endometrial, thyroid, kidney, and colorectal cancer [144].
2. *Bannayan-Riley-Ruvalcaba syndrome* (BRRS): It is a rare form. In addition to hamartomas, these patients have a large number of subcutaneous lipomas, macrocephaly, and penile lentigines [143].

The presence of a similar mutation spectrum in the PTEN gene in all PHTSs suggests that it is an allelic disease [145].

- *Adult Lhermitte-Duclos disease*: Cerebellar dysplastic gangliocytoma is characterized by the growth of hamartomatous lesions and has been associated with PTEN mutations. This syndrome may occur with or without Cowden's syndrome and no other symptoms of PHTS. Although there are no hamartomas of segmental overgrowth, lipomatosis, arteriovenous malformation, and epidermal nevus (SOLAMEN) syndrome, macrocephaly, and autism spectrum disorders, which are Proteus-like syndromes, the loss of heterozygosity or germline mutation in PTEN alleles should be included in the definition of PHTS [146–148].

Clinical diagnostic criteria (PTEN hamartoma tumor syndrome clinical diagnostic criteria). The diagnostic criteria for PTHS were proposed systematically by Pilarski et al. with a review of the literature and were accepted by the NCCN [144].

Major	Minor
Breast cancer	Autism spectrum disorder
Epithelial endometrial cancer	Colon cancer
GI tract hamartomas	Esophageal glycogenic acanthosis (≥3)
Adult Lhermitte-Duclos disease	Lipomas (≥3)
Macrocephaly	Mental retardation (i.e., IQ ≤75)
Macular pigmentation of the glans penis	Renal cell carcinoma
Multiple mucocutaneous lesions	Testicular lipomatosis
Multiple trichilemmomas (≥3, at least one biopsy-proven)	Thyroid cancer (a papillary or follicular variant of papillary)
Acral keratoses (≥3 palmoplantar keratotic pits and/or acral hyperkeratotic papules)	Thyroid structural lesions (e.g., adenoma, multinodular goiter)
Mucocutaneous neuromas (≥3)	Vascular anomalies (including multiple intracranial developmental venous anomalies)
Oral papillomas (particularly on tongue and gingiva), multiple (≥3)	
OR biopsy-proven OR dermatologist diagnosed	

For the diagnosis of PTEN hamartoma tumor syndrome, the patient should have three or more major criteria (including macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas) or two major and three minor criteria.

For the operative diagnosis in a family where one meets individual PTEN hamartoma tumor syndrome, the individual should have any two major criteria with or without minor criteria; or one major and two minor criteria; or three minor criteria.

A clinical calculator has been developed for both adult and pediatric age groups considering the above diagnostic criteria. This calculator is available online. The use of this calculator is a low-cost method to determine whether the patient will receive a PTEN mutation test. However, it needs independent validation. The adult prediction model considers demographic data such as gender and age, personal cancer history, and dermatological, neurological, breast, gynecological, gastrointestinal, endocrine, and genitourinary symptoms. Pediatric criteria are macrocephaly and autism or developmental delay, dermatological findings, vascular anomalies, and gastrointestinal polyps [149].

Cowden Syndrome

The pathogenic variant in the PTEN gene has been reported in 85% of the cases diagnosed with Cowden syndrome. Such high rates of germline pathogenic variants reported in previous studies may be due to the fact that they are studied in a highly selected group because the frequency of germline pathogenic variants in more recent studies is between 20 and 34%. The autosomal dominant inheritance and de novo mutation rate are between 10% and 30%. Its prevalence is estimated to be between 200,000 and 250,000. In fact, it may be more common because some of its features are common in the community, but mostly it is not investigated in terms of Cowden syndrome [143, 150–153].

Phosphatase and tensin homologous (PTEN) gene located on chromosome 10q23, negative for phosphoinositide-3-kinase (PI3K)–AKT and MTOR (mechanistic Target Of Rapamycin) signaling pathways, which are critical for cell proliferation, cell cycle progression, and apoptosis, is a tumor suppressor gene that acts as a regulator. Loss of function of this gene contributes to oncogenesis, and somatic mutations are often identified in various malignancies. PTEN acts as a phosphatase that removes phosphate groups from tyrosine, serine, and threonine. Pathogenic variants of PTEN are varied, including nonsense, missense, frameshift, and splice site variants. Forty-percentage of pathogenic variants are found in exon 5 encoding the phosphatase core motif. Most pathogenic variants are family-specific. In the PTEN gene, more organ systems are involved in pathogenic variants between the catalytic phosphatase nuclei in exon [154–156].

Although some of the patients with Cowden and Cowden-like syndrome do not have germline pathogenic variants, large structural rearrangements, deletions, and pathogenic variants in the promoter region of the gene may cause clinical formation by decreasing PTEN expression. Hypermethylation of the promoter region leading to decreased expression of the CLLN gene has been described in some cases

without PTEN mutation. The KLLN gene on chromosome 10q23, which acts as a p53-regulated DNA synthesis inhibitor, shares the same transcription site as the PTEN gene [157].

Mutations of succinate dehydrogenase (SDH) gene, B and D subunits, have been reported in some patients. In another study, the pathogenic variant was detected in PIK3CA and AKT1 genes. In a family pathogenic variant was detected in the SEC23B gene. In a case with Lhermitte-Duclos disease, the pathogenic variant was determined by the exome sequence in the EGFR gene [158–161].

The prevalence of thyroid cancer in patients with pathogenic variants of the SDH gene appears to be higher than those with PTEN mutation-positive disease. In addition, the risk of breast cancer is higher in patients with a pathogenic variant in the PTEN gene and in the SDH gene, in which the pathogenic variant is detected. The risk of breast and kidney cancer is higher in patients with hypermethylation of the KLLN gene promoter region than those detected in the pathogenic variant of PTEN [162].

The prevalence of colon polyps among PTEN mutation carriers is 93% of colonoscopy. Hamartomatous and inflammatory polyps are the most common, but ganglioneuroma, adenomas, leiomyomas, lipomas, and hyperplastic polyps can also be found. Early detection of increased risk of early-onset colorectal cancer in patients with Cowden syndrome has been realized rather late. In PTEN mutation carriers, colorectal adenocarcinoma was found in 13% of patients undergoing colonoscopy, and all were under the age of 50. In a group of 368 positive patients with PTEN mutation, the risk of lifelong colorectal cancer was found to be ten times higher than the general population and 9%. In another group of 156 patients with positive PTEN mutation, the risk of developing colorectal cancer was found to be 18% until the age of 60. It remains unclear whether colonic malignancy originates from adenomatous polyps or hamartomatous polyps. Therefore, guidelines recommend routine endoscopic surveillance of PTEN mutation carriers. Sequence analysis and deletion/duplication analysis of the entire coding region of the PTEN gene should be performed. The majority of PTEN mutations are detected by sequence analysis, and any mutations have been reported, including missense, nonsense, splice site, insertions, and deletions. Mutations in the PTEN promoter region have also been reported. Although the clinical use and applicability of potential outcomes is still unclear, molecular testing may be performed for other genes associated with a Cowden-like clinic, including AKT1, KLLN, PIK3CA, and SDH. Cowden syndrome/PHTS has an impact on almost all organ systems and requires a multidisciplinary treatment team with specific genetic counseling. Cases with pathogenic variant detected in the PTEN gene or no pathogenic variant that meet the clinical diagnostic criteria should follow a regular follow-up program for this disease affecting many organ systems. Follow-up for colorectal cancer is a 35-year-old colonoscopy followed by an increase in the frequency of follow-up every 5 years or if the patient is symptomatic or if a polyp is seen [153, 163–165].

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Pediatric Surgical Perspective to Colon Polyps and Colorectal Carcinomas

25

Mustafa Onur Oztan

Anatomy of the Colon in the Pediatric Population

Children cannot be considered as little adults because every age has its own variables; therefore, there are differences between children and adults in the meaning of colonic anatomy. The length of the colon among adults has been well described, but data on pediatric colon length are limited [1]. There are few studies reporting postmortem values, whereas some are measuring intestinal length intraoperatively, with computerized tomography (CT) scan or air-contrast enema [2–4]. The colon length (CL) has been reported to be 180–190 cm in adults, but it differs according to the age, weight, or height at the time of the surgery in children [4, 5]. Struijs et al. measured the colon length using a silk suture on the antimesenteric border and found that CL increased from a mean of 56.8 cm at 0–6 months of age to 122.4 cm in 49–60 months of age [4]. Mirjalili et al. mentioned in their report that determining the length with CT scan may reveal better results, because intraoperative measurements may be not quite accurate because of the stretching of the bowel. The colonic lengths were found 52.3 cm in 0- to 2-year-old children, 72.9 cm in 4- to 6-year-old children, and 95.1 in 9- to 11-year-old children [2]. According to these results and the review of the literature, the practitioner must have to evaluate the pediatric patient on a personal basis to perform a successful colonoscopy.

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Colonoscopy in Children: Indications, Preparation, Procedure, and Complications

Colonoscopy is the gold standard for the evaluation of the large bowel. Endoscopic applications in pediatric patients have evolved significantly due to the technical improvements in this field. The practitioner should select the appropriate endoscope based on the child's weight. Currently, there are several colonoscopes in the market with variable insertion tube lengths (1330–1700 mm), shaft diameters (9.8–11.8 mm), and channel sizes (2.8–3.8 mm), which may be selected according to the child's weight. The American Society for Gastrointestinal Endoscopy Technology Committee recommended ≤6-mm gastroscope for patients weighing <2.5 kg, ≤6-mm gastroscope or standard adult gastroscope for patients weighing 2.5–10 kg, and 11- to 11.6-mm pediatric colonoscope or adult colonoscope for patients weighing more than 10 kg [5].

The indications for diagnostic or therapveutic colonoscopy in children are basically similar as in adults. The most common indications for pediatric colonoscopy include rectal bleeding/bloody stool, diarrhea (without blood), repetitive intussusception, investigation of lower abdominal pain, unexplained failure to thrive, anemia resistant to iron therapy, perianal lesions (fistula, abscess), inflammatory bowel disease, and familial polyposis syndromes [6, 7]. In the studies of Nambu et al. and Williams et al., disease distribution of diagnostic colonoscopies revealed polyps or polyposis syndromes 14% and 10.4%, respectively [6, 8]. The European Society of Gastrointestinal Endoscopy and European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESGE/ESPGHAN) do not recommend colonoscopy in patients with toxic megacolon or who have a colonic perforation prior to 28 days or recent intestinal resection in 7 days [9].

Abdominal discomfort and pain are the most common problems after the colonoscopy preceding to 63% of the patients as in a report of Homan et al. [10]. The incidence of complications after colonoscopy in the pediatric population is low as 1% and has been reported in a few reports [11]. Colonic perforation after colonoscopy is the most dangerous complication which is usually related to polypectomy and may be seen in 0.01% of the patients. It requires prompt diagnosis and operative intervention to decrease the extent of intraperitoneal contamination. The bleeding after colonoscopy may be seen usually after mucosal biopsy or polypectomy in 0.3–2.5% of patients [12]. It is usually in small volumes and does not alter the hemodynamic stability. Complications reported in adults like appendicitis, cholecystitis, splenic rupture, and superior rectal artery injury are extremely rare in children [13].

Good bowel preparation before colonoscopy in children assures a successful procedure: a complete investigation of the colon, visualization of all of the lesions, shorter sedation time, increased patient safety, and decreased need for the re-evaluation in a shorter interval [14, 15]. Many protocols were compared in several reviews and randomized controlled, but none of these has been found superior to another [9]. The best way to choose a regimen for bowel preparation is therefore to find the best for the patients' comfort. According to the study of Di Nardo et al.,

nasogastric tube placement need is less frequent in low-volume regimens, and therefore these regimens were better tolerated by the patients [16]. In the studies, polyethylene glycol 3350 1.5 g/kg/day over 4 days, two doses of 5-mg bisacodyl on the day before and two enemas, two doses of 10-mg†bisacodyl over 2 days and an enema midnight, polyethylene glycol electrolyte lavage solution 40 mL/kg/h, or two doses of Picolax were used with over 90% success rate (good cleansing rate) [17–21]. In many studies, clear fluids are recommended for 24 hours before the procedure [17, 19, 21].

Colonic Polyps, Polyposis Syndromes, and Colorectal Cancers in the Pediatric Age Group

Colonic polyps are the most common tumors of the colon in children. The incidence of gastrointestinal (GI) polyps in preschool and school-aged children is up to 1–2% [22]. The most common symptom observed is painless rectal bleeding. Other complaints include crampy abdominal pain due to the intussusception of the polyp or intraluminal obstruction of a large polyp and prolapse of the polyp from the anus. Multiple polyps in the colon may cause anemia due to continued blood loss, protein-losing enteropathy and consequent hypoalbuminemia, and diarrhea [23]. During the routine evaluation for other indications or during the screening for a polyposis syndrome, polyps may be discovered in asymptomatic children [24].

The diagnosis can be made by seeing the protruding polyp from the anus or palpation of a soft and mobile mass with the rectal examination in nearly 20% of the patients. In the remaining cases, ultrasonography, air-contrast barium enema, intravenous contrast-enhanced CT, and colonoscopy may reveal the diagnosis of colonic polyps. Barium enema was the primary screening method in a few decades ago, which is yet not the first choice in many institutions because of its low detection rate (76%) [25]. In the study of Hosokawa et al., they found that ultrasonography is a very reliable diagnostic method with 95% sensitivity in 288 pediatric patients with colonic polyps [26]. Intravenous contrast use during CT increases the detection ability of the polyps which are submerged in the fecal matter. With this diagnostic method, per-polyp sensitivity rates have been reported as high as 89% and 94%, but the radiation exposure still remains a challenging issue [27, 28]. Magnetic resonance (MR) colonoscopy is a radiation-free imaging modality, but its sensitivity remains very low for polyps <5 mm [29]. Full colonoscopy after an effective bowel cleansing is the precise diagnostic and also treatment method of colorectal polyps [30].

Based on microscopic appearance, colorectal polyps may be hamartomas or adenomas. Hamartomas are usually nonneoplastic and benign with a very low frequency to become dysplastic. On the contrary, adenomas are dysplastic with a high association of polyposis syndromes and have higher transformation potential to colon cancers [31].

Juvenile Polyps

Solitary Juvenile Polyps

Solitary (isolated) juvenile polyps (SJP) are the most commonly encountered polyps of all polyps in children (90%) [32]. They have a peak age between 2 and 5 years and are diagnosed mainly in the first 10 years of age [33]. Two-thirds of the polyps are single, but they cannot be classified when there are more than five polyps at the same time [34]. In the report of Wei et al. of 487 pediatric cases, they found that 84% of the polyps were in the rectosigmoid region [23]. Polyps are generally 1–3 cm in size and 90% are pedunculated (Fig. 25.1). Histologically, they have mucin-filled dilated cysts and inflammatory cell infiltration. These polyps carry almost no risk of subsequent cancer development, but children with more than five polyps, polyps with adenomatous changes, and right-sided polyps carry more risk to another [32].

Management of SJP is a snare polypectomy with colonoscopy for histological evaluation (Figs. 25.2 and 25.3). For SJP, no control colonoscopy is recommended, but the family must be warned to return if any new symptom arises. In patients with a family history of multiple polyps, the risk of a juvenile polyposis syndrome (JPS) is increased, and further evaluation is needed [35].

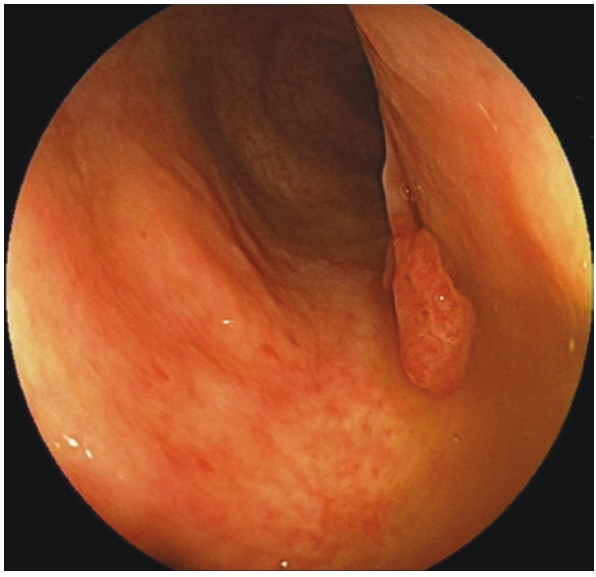

Fig. 25.1 A solitary, pedunculated polyp in the sigmoid colon

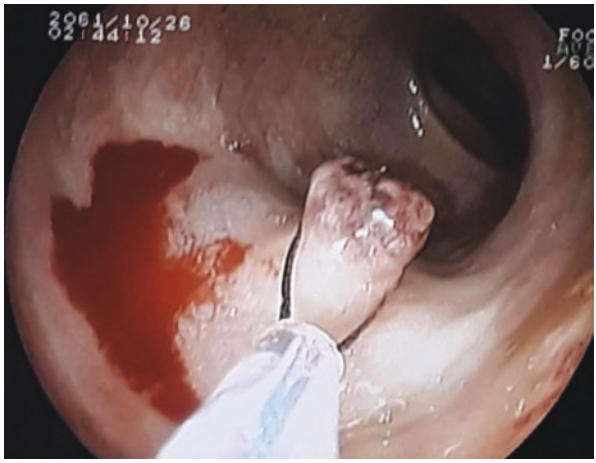

Fig. 25.2 The snare is placed around the polyp stalk for polypectomy

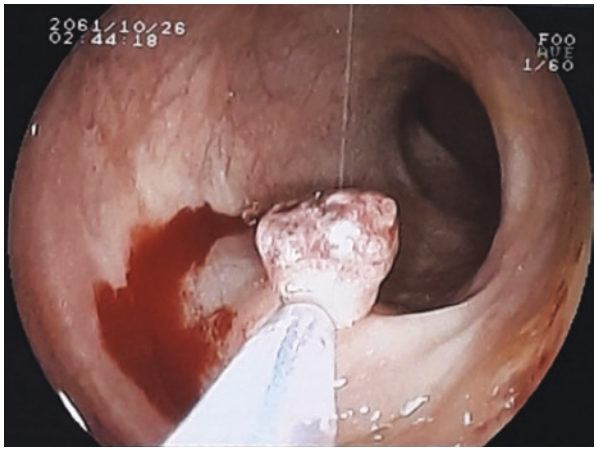

Fig. 25.3 The snare is closed tightly until the polyp is transected

Juvenile Polyposis Syndromes

JPS is an autosomal dominant inherited disease with multiple hamartomatous polyps; germline mutations against SMAD4 (18q21), BMPR1A (10q23.2), and ENG; extracolonic hamartomatous polyps; and extraintestinal manifestations. The incidence of JPS is rare (1/100,000–160,000), but it is associated with a lifetime risk of malignancy [36, 37]. The age at diagnosis is usually older (mean age of 9 years) and anemia is more likely to be seen. The extraintestinal findings in patients with JPS are cardiac (mitral valve prolapse, ventricular septal defect with pulmonary stenosis bicuspid aortic valve), vascular/skin (telangiectasia, pigmented nevi, splenic artery aneurysm, bilateral iliac artery aneurysm, pulmonary arteriovenous malformation), cranial/skeletal (macrocephaly, hydrocephalus, cleft palate, polydactyly, hypertelorism), and thyroid disease, attention deficit hyperactivity disorder/autism, epilepsy, undescended testes, and ocular abnormalities [38].

JPS has three types of presentation: juvenile polyposis of infancy (severe rectal bleeding, diarrhea, protein-losing enteropathy), juvenile polyposis coli (only colonic polyps), and generalized juvenile polyposis (polyps in the entire gastrointestinal system, in the stomach more than the small intestine) (Figs. 25.4 and 25.5). The treatment of JPS must be chosen according to these types. Colectomy is the first choice in patients with too many polyps, which is not manageable by polypectomy alone, and diarrhea and persistent blood loss causing hypoalbuminemia and anemia. In other cases, endoscopic polypectomy and long-term follow-up are suggested [39].

JPS is associated with an increased risk of colorectal cancer (CRC) and gastric cancer (GC) in adults. Brosens et al. reported a cumulative risk of CRC as 39% and the incidence of CRC almost 20% at mean 43.9 ± 10.4 years of age [40]. The ESPGHAN Polyposis Working Group recommends routine colonoscopic

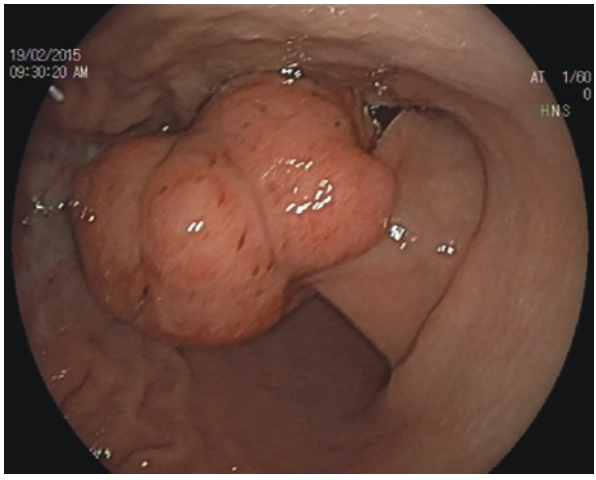

Fig. 25.4 Prepyloric antral polyp in the stomach causing mild obstructive symptoms

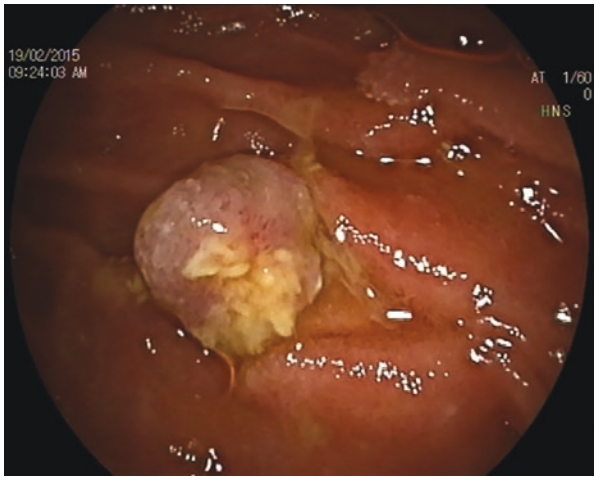

Fig. 25.5 Jejunal polyp without a stalk in an 8-year-old boy

surveillance and genetic testing between 12 and 15 years, but earlier if symptomatic. Polyps >10 mm should be removed, and colonoscopy must be repeated every year until all polyps >10 mm have been resected. Following endoscopies may be in 1–5 years ordinally. Genetic testing must be offered to first-degree family members of children with a specific gene mutation. If no genetic gene mutation was detected, the family members must be referred for screening colonoscopy at the age 12–15 years [39].

Peutz–Jeghers Syndrome

Peutz–Jeghers syndrome (PJS) is a rare autosomal dominant disorder with an incidence of 1 in 200,000 live births [41]. It is associated with gastrointestinal hamartomatous polyps and mucocutaneous pigmentation. The PJS polyps have unique characteristics like elongated epithelium and smooth muscle hyperplasia with cystic gland dilatation [33].

Mucocutaneous pigmentation is seen as hyperpigmented macules at the vermillion border of the lips, nostrils, perianal area, hands, and feet. They may start in the first years of life, but also may fade after puberty. This finding is the most characteristic feature of the PJS, but the polyps in the entire GI tract may cause bleeding, anemia, abdominal pain, and small bowel intussusception and obstruction (Figs. 25.6 and 25.7). Polyps are with the highest frequency in the small intestines and then in the stomach, colon, and extraintestinal regions like the gallbladder, bronchi, bladder, and ureter. The patients become symptomatic in the early twenties, but a child with the following findings should be investigated to have PJS:

1. Histologically confirmed PJS polyps more than one
2. Any number of PJS polyps with a family history in close relatives

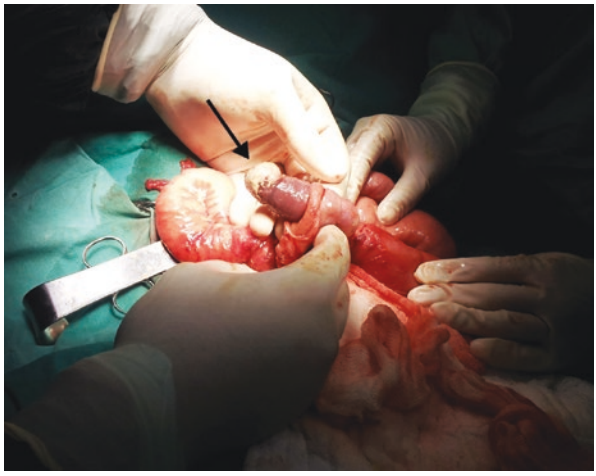

Fig. 25.6 Small bowel polyp leading to intussusception revealed in enterotomy

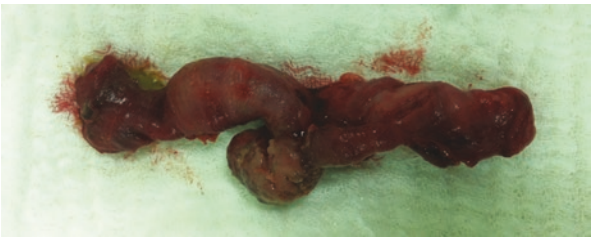

Fig. 25.7 Ileal specimen shows a huge polyp filling almost the entire lumen of the bowel

3. Characteristic mucocutaneous pigmentation with a family history in close relatives
4. Characteristic mucocutaneous pigmentation with any number of PJS polyps [42]

Predictive genetic testing on the SKT11/LKB1 gene for an asymptomatic but at-risk child should be done after age 3 and earlier in a symptomatic child [43]. GI surveillance should start before age 8 with upper endoscopy and colonoscopy, MR enterography, or video capsule endoscopy (VCE) or earlier if symptomatic. In the presence of polyps <10 mm, VCE should be repeated at least every 3 years according to the symptoms of the patient. During this period, the parents should be informed about the risk of intussusception and its symptoms. In the patients with small bowel polyps between 1.5 and 2 cm in size, prophylactic polypectomy should be performed to prevent intussusception with endoscopy, laparoscopy, or laparotomy on a case-by-case basis according to the location of the polyp [44].

It is accepted that patients with PJS have an increased lifetime risk of cancer with a rapid increase after the age of 50. Hearle et al. reported a cancer risk of 31% at age 50 but 60% at age 60 [45]. Breast cancers in females are as high as GI cancers, followed by sex cord tumors (SCTs) of the ovaries and pancreatic cancers. Although cancer is extremely rare in children with PJS, all children and adolescents should be routinely examined to have SCT because of the several reports of SCTs affecting children [42].

Adenomatous Polyps

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease with an incidence of 1–3:100,000 live births. Most children evaluated for FAP were diagnosed because of family history. Although there are hundreds to thousands of adenomatous polyps in the colon starting to develop by the age of 15 years, they are not symptomatic until the third decade of life (CRC at 39 years of age on average) [33].

The adenomatous polyposis coli (APC) gene is located on chromosome 5q21 and produces APC protein, which has a tumor-suppressor activity with its role in apoptosis. In 20–30% of patients, the condition is caused by spontaneous mutation

without a family history. Extraintestinal tumors like hepatoblastoma, congenital hypertrophy of the retinal pigment epithelium, thyroid and adrenal gland carcinomas, desmoid tumors, dental abnormalities, and bone tumors (osteomas, mandibular and maxillary) may be apparent in childhood because of this mutated, inactive APC protein [46]. The genetic site of the mutation within the gene is correlated with the severity of the clinical course. Mutations near the middle of the gene are associated with an unfavorable phenotype, whereas the mutations at the extreme ends are associated with an attenuated FAP with lesser polyps in the GI tract and later presentation [47]. Predictive genetic testing is recommended at age 12–14 at children with family history, but earlier if symptomatic (bloody stools and/or anemia) [48].

The development of CRC is inevitable without surgical intervention, and therefore clinical surveillance in FAP is very important. In patients who are gene positive or if the testing is not possible, screening colonoscopy should commence age 12–14 years. The adolescents who do not have the family mutation may be discharged because it is predicted that they will not develop FAP [46].

Colonic adenomas identified at colonoscopy confirm the diagnosis of FAB in a patient with a gene mutation. Predictive genetic testing should be offered to other first-degree family members. The interval between the colonoscopies recommended as 1–3 years, because the risk to have a CRC in the teenage years is very low (0.2%) [49]. Adenomatous duodenal polyps are found nearly in all patients with FAP, but to develop an invasive cancer is very slow with a rate approaching 3–5% in adulthood. Therefore, no upper GI surveillance is recommended in childhood, but it must be advised to the patients to have an endoscopy at 25–30 years of age as a start [50].

Cyclooxygenase-2 inhibitors and sulindac were administered to decrease polyp burden in adults, but although the number of polyps were decreased in the short term, the progression to CRC was not prevented [51]. The use of sulindac and celecoxib are studied in two placebo-controlled trials, but no significant effect on slowing the progression or development of adenomas has been shown [52, 53]. Therefore, the use of these chemopreventive agents is not recommended in children with FAP [46].

Removal of the colon is necessary to prevent CRC in FAP patients. The timing of colectomy is controversial, and no association has been revealed regarding the polyp size or polyp burden. The type of colectomy is also not clear in the literature and most recommendations are arbitrary. Most authors are recommending colectomy in patients with many polyps >10 mm and polyps more than 500 or carpeting the entire colon [54]. Low-grade dysplasia is also an indication for colectomy because waiting puts the patient in the risk of developing CRC. Therefore, if there is any concern of dysplasia, an increase in polyp size and number, or advanced changes, the patient should be advised for colectomy [46].

There are two options for colectomy: ileorectal anastomosis (IRA) and ileal pouch–anal anastomosis (IPAA). Total colectomy with a permanent ileal stoma is not the first-line option in children, because having a stoma for a lifelong period has its own disadvantages, both medically and psychologically. The surgical choice between IRA and IPAA depends on several factors: rectal and colonic adenoma burden, site of mutation, risk or presence of desmoid tumors, risk of impact on

fertility in females, long-term function, and the surgeons' preference. Both methods have their own advantages and disadvantages. IRA can be done laparoscopically with a shorter hospital stay, good cosmetic healing, and preservation of bowel function and continence, but the remaining rectal mucosa has always the risk of polyp recurrence. Therefore, it is recommended that patients with a few rectal adenomas (<20) or infrequent colonic polyps should be referred for IRA whereas patients with more rectal adenomas or a total colonic burden or adenomas more than 500 should be referred for IPAA [49]. After IRA, rectal surveillance is necessary for every 6–12 months. IPAA is a more complex surgery with a higher perioperative morbidity (anastomotic leak, pouchitis, pelvic abscess, sepsis) and a need for a temporary ileostomy. After IPAA operations, there is a reported reduction in female fertility and rare erectile and ejaculate function in males [55]. Compared with IRA operation, IPAA is associated with lower defecation frequency and impaired continence but with similar functional outcomes in further years [55]. In summary, the reports investigating the quality of life after both operations revealed variable results, indicating the best surgical choice must be individualized [56].

Hereditary Nonpolyposis Colorectal Cancer (HNPCC)/ Lynch Syndrome

HPNCC is an autosomal dominant inherited genetic disease and is due to a mutation in the DNA mismatch repair system. Patients with this disease have a markedly increased lifetime risk of CRC and endometrium, ovarian, and other cancers. The prevalence is 1:500 in the general population, and it causes 2–3% of all CRCs [57]. Because adenoma–carcinoma sequence is more rapid in patients with HNPCC, Järvinen et al. removed colorectal adenomas for primary prevention and reported the carcinoma rate in HNPCC patients has reduced [58]. According to the guideline of ACG, the patients may require colectomy with IRA eventually. Therefore, it is important to refer the children and siblings of a genetic carrier for genetic counseling to investigate whether they carry the same mutation. If there is evidence of familial mutation, the relative should undergo diagnostic screening [59].

Conclusion

Pediatric colonic polyps are generally solitary and most of them are benign with no malignant potential. A small proportion of children with multiple polyps, adenomatous polyps, and polyps other than the colorectal region or family history should be evaluated for a polyposis syndrome. The challenge is to identify the patients at risk to develop CRC and also manage the extraintestinal malignancies. Therefore, genetic testing, endoscopic surveillance, and prophylactic colectomy should be applied in accordance with clinical guidelines.

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Surgical Anatomy of the Liver and Biliary Tree

26

Goksever Akpinar and Alper Uguz

General Anatomy

The liver is the largest organ in the human body [1], weighing approximately 1200–1800 g, and accounts for approximately 3% of adult total body weight [2, 3]. The major anatomical points that determine the topographic anatomy of the liver are falciform ligaments, umbilical fissures, gallbladder fossa, and transverse hilar fissures [4]. These anatomical points divide the liver into four different lobe areas: left, right, quadrate, and caudate. The liver is connected to the duodenum, stomach, diaphragm, and anterior abdominal wall by peritoneal folds that also form the Glisson's capsule on the liver [5]. The liver (Fig. 26.1) consists of two lobes which are generally described in two ways, by morphological anatomy and by functional anatomy (Fig. 26.2). It is located in the right upper quadrant of the abdomen, beneath the diaphragm, and is encased by the ribs. The liver maintains its position in the abdomen by attaching to the surrounding tissues with ligamentous attachments consisting of avascular peritoneal folds. These ligaments are in continuity with the Glisson's capsule of the liver.

Liver Ligaments

The liver is attached to the anterior abdominal wall and diaphragm by the falciform ligament, a peritoneal fold that extends from the anterior abdominal wall to the anterior superior surface of the liver at the level of the umbilicus and is in continuity with the umbilical fissure (Fig. 26.3). It is suspended from the diaphragm superiorly by the coronary ligament, which continues outward to form the right and left triangular

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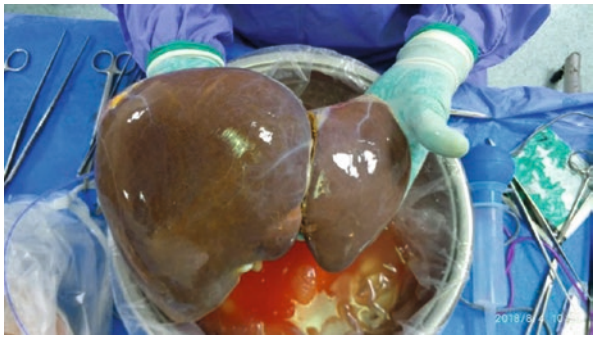

Fig. 26.1 Split recipient hepatectomy specimen

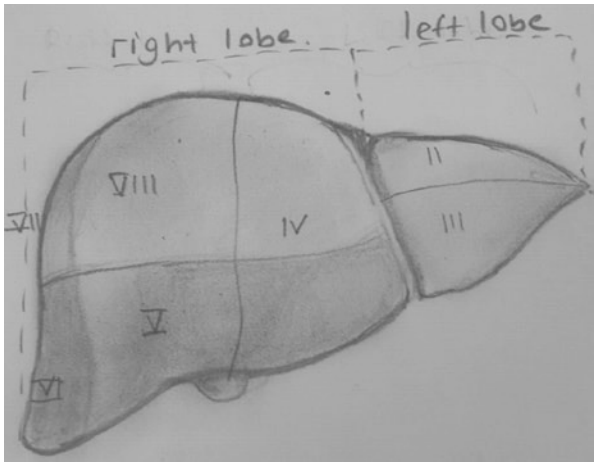

Fig. 26.2 Liver anatomy

ligaments, and anteriorly by the falciform ligament and at the porta hepatis by the gastrohepatic and hepatoduodenal ligaments. The hepatoduodenal ligament envelops the porta hepatis including the hepatic artery, portal vein, and extrahepatic bile ducts [6].

Within the lower border of the falciform ligament is the ligamentum teres hepatis, a remnant of the obliterated umbilical vein (ductus venosus) that runs from the umbilicus in the umbilical fissure where it is in continuity with the ligamentum venosum as it joins the portal vein. Ligamentum venosum carries the oxygenated blood coming from the placenta by the umbilical vein to the inferior vena cava during fetal life. This connection is important because the recanalized ligamentum leads to varicose portosystemic collaterals known as caput medusa on the abdominal skin surface in case of portal hypertension. Behind the upper part of the liver, the falciform ligament is divided into two to form the right and left anterior coronary ligaments. These ligaments combine posteriorly with the right and left posterior coronary ligaments, which are the reflections of the diaphragmatic peritoneum, defining the borders of the bare area. The bare area is the surface of the liver, devoid

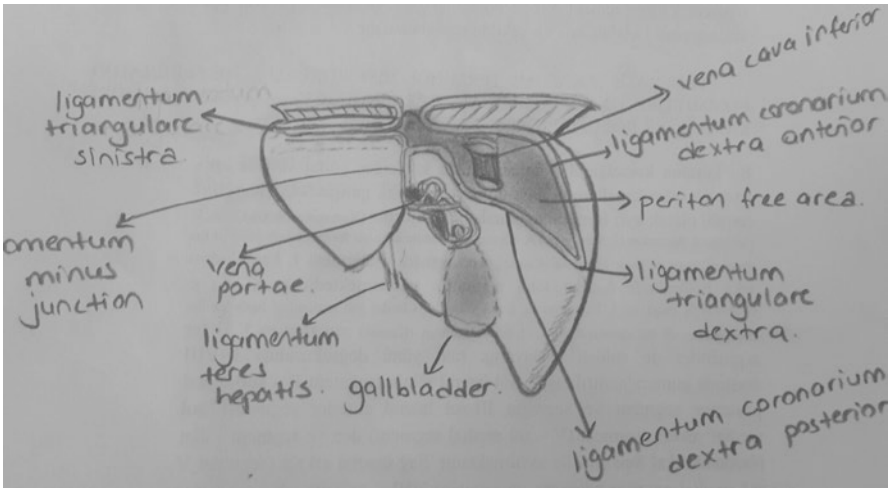

Fig. 26.3 Liver ligaments

of peritoneum, and is attached to the diaphragm by loose fibroareolar tissue. Coronary ligaments unite to form the right and left triangular ligaments on the right and left sides. These ligaments play a role to fixate the liver by attaching the liver to retroperitoneal tissues and surrounding tissues [7]. Of surgical importance, there are hepatic veins which drain into the inferior vena cava at the base of the falciform ligament. There may be a conception that falciform ligament divides the liver into the left and right lobes which is not a functionally correct approach.

The liver is also in contact with surrounding gastrointestinal organs. The left posterior coronary ligament courses toward the posterior-inferior of the liver, joining ligamentum teres hepatis, and extends toward the stomach and forms the gastrohepatic ligament that runs between the liver and the lesser curvature of the stomach and also forms the superior aspect of the lesser omentum. The gastrohepatic ligament connects the left lobe of the liver and the lesser curvature of the stomach from the level of the ligamentum venosum, while the hepatoduodenal ligament which extends from the onset of the first and second portions of the duodenum to the porta hepatis is formed at the free edge of the gastrohepatic ligament. The portion of the vagus nerve that provides hepatic innervation travels in this ligament. In some cases, the aberrant left hepatic artery can also be found in the gastrohepatic ligament. On the right, the posterior coronary ligament courses along the lower border of the right posterior hepatic surface and reflects onto the cranial pole of the right kidney, forming the hepatorenal ligament. The right posterior coronary ligament continues toward the hepatic flexure of the colon to form the hepatocolic ligament. The colon may be in close proximity with the right lobe of the liver at the hepatic flexure or may be adherent. In liver surgeries, it is necessary to divide the hepatocolic ligament, hepatorenal ligament, the right triangular ligament, the right anterior coronary ligament, and the right posterior coronary ligament to mobilize the right liver. In 1954, Claude Couinaud described the segmental

anatomy of the liver based on the distribution of the hepatic veins and the portal vein [8]. This definition is a definition that basically uses the distribution of the branches of the portal vein. Couinaud stated that the hepatic artery and bile ducts follow the portal vein. In 1957, Goldsmith and Woodburne divided the liver into four segments, lateral, medial, anterior, and posterior, using the distribution of portal vein and hepatic artery, and then divided the four segments into four separate subsegments as superior and inferior [1]. Bismuth divided the liver by three fissures, including the hepatic veins and the horizontal plane passing through the right and left portal veins. Bismuth named the caudate lobe as segment 1 [8]. While the confusion in the anatomical description of the liver was ongoing, the liver anatomical description proposed by Healey and Schroy was accepted at the International Anatomy Congress in 1965. By 1998, the International Hepato-Pancreato-Biliary Association (IHPBA) was established to provide a consensus in defining the liver anatomy. This committee presented their recommendations on terminology in Brisbane in 2000.

It will be appropriate to take a look at the topographic anatomy of the liver before details about the current definitions of the segmental anatomy of the liver. The liver occupies the right hypochondrium adjacent to the left part of the diaphragm and the anterior aspect of the stomach and extends toward the epigastrium and the left hypochondrium [2]. The liver has three surfaces: anterosuperior surface, posterior surface, and inferior surface [8].

The posterior surface is adjacent to the diaphragm, retrohepatic part of the vena cava inferior, the right adrenal gland, the upper pole of the right kidney, and T10-T11 vertebrae. A certain area of the posterior surface is devoid of any peritoneum. This is referred to as the bare area which is separated from the right lung and costophrenic angle by the diaphragm. The anterosuperior surface of the liver is in contact with the diaphragm dome, the pericardium, and the lower segments of the right and left lung. This surface is adjacent to the thoracic wall between the fifth and tenth ribs on the right. From this level, it extends obliquely to the epigastric region, covers the anterior aspect of the stomach, and is attached to the diaphragm at the sixth costal level on the left. Looking at the inferior surface, it is in contact with distal esophagus, stomach, the first and second portion of the duodenum, pancreatic head, proximal part of the pancreatic neck, common bile duct, portal vein, proper hepatic artery, gallbladder, hepatic colonic flexure, the right kidney, VCI, and the right adrenal gland. Morison's pouch is located in the right inferior of this surface [6–8].

Functional Anatomy of Liver

The first definition of the functional anatomy of the liver was the definition of Hugo Rex in 1888, in which he divided the liver into two lobes, the right and left lobes, by an imaginary line which runs from the point where the gallbladder bed ends inferiorly to the VCI (vena cava inferior) part which is below the diaphragm, passing through the liver surface [8]. Although the same line was defined by James Cantlie in 1897 and Bradley in 1909, broader recognition was accompanied by an understanding of the functional anatomy of the liver [8, 9]. Today, it is assumed that the

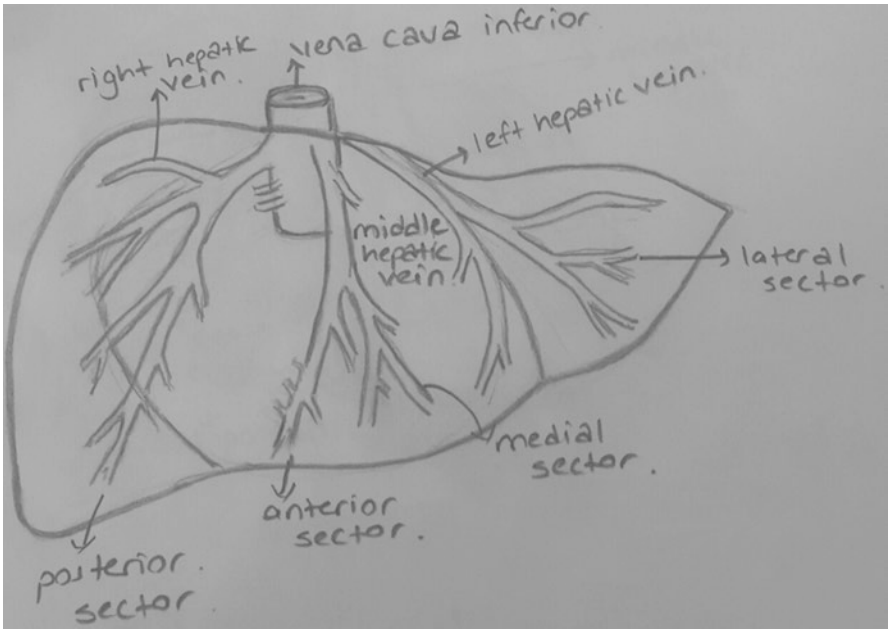

Fig. 26.4 Hepatic scissures

liver is divided into functional lobes and segments based on the distribution of hepatic artery branches, portal vein branches, and bile ducts and the drainage of the hepatic veins. Now, the most widely accepted and most commonly used liver segmentation is the liver segmentation proposed by Couinaud in 1954 [8].

In the description of the functional anatomy of the liver, the distribution of hepatic veins and portal veins in the liver is defined as scissura and the functional anatomy of the liver is defined based on the anatomical location of these scissure. According to Couinaud, Bismuth, and FCAT, the liver is divided into sectors by portal scissure containing hepatic veins, and these sectors are divided into segments by hepatic scissure, each of which containing portal veins [10] (Fig. 26.4).

Right Portal Scissura

This scissura starts from the right border of the VCI and follows the attachment site of the right anterior coronary ligament to the liver. It is, then, inclined anteriorly. This point where the scissura is inclined is on the line connecting the right border of the liver with the gallbladder fossa. Scissura crosses the caudate lobe [8], traveling in a line parallel to the gallbladder fossa to reach the VCI posteriorly. According to the liver segmentation of Couinaud, the right portal scissura divides the right liver into the right lateral sector (segment VI, VII) [8, 10, 11], lying posterolateral, and paramedian sector (segment V, VIII) lying anteromedial.

Main Portal Scissura (Cantlie's Line)

In 1897, Sir James Cantlie noticed patients with atrophic right liver during autopsy studies. He revealed that this atrophy, which was in the right lobe of the liver, was not in the right half of the falciform ligament, but on the right half of the Cantlie's line, which he later described, and showed the true anatomical distinction of the right and left liver [12].

Cantlie's line or main portal scissura refers to a line running from the middle of the gallbladder fossa to the left side of the VCI and extending from the gallbladder to the liver pedicle and to the retrohepatic VCI posterior inferiorly [1]. The main portal scissura divides the liver into two parts: the right (segment V, VI, VII, VIII) and left hemilivers (segments II, III, IV) based on the liver segmentation of Couinaud [8, 10, 11].

Left Portal Scissura

This scissura extends from the left side of the VCI to a point between the dorsal one-third and the ventral two-thirds of the left border of the liver. The left portal scissura runs to the origin of the ligamentum venosum [8]. The left portal scissura divides the left liver into two sectors called the left lateral sector (segment II) and the left paramedian sector (segment III, IV), based on the liver segmentation of Couinaud [8, 10, 11].

Portoumbilical Scissura

This scissura is located superficially at the point where the falciform ligament, which contains ligamentum teres hepatis at the inferior border, joins the liver [8]. It joins with the inferior border of the liver at an angle of about 50°. The left hepatic vein lies right next to the portoumbilical scissura. In his anatomical and organogenesis studies, couinaud claimed that portoumbilical scissura is the hepatic scissura located between segments II and III. According to Healey and Schroy, portoumbilical scissura was considered to be a line of biliary tract branching between the medial and lateral segments of the left liver lobe [8]

Lobes and Segments of the Liver

Anatomical Liver Lobes

Considering the external appearance of the liver, it is anatomically divided into four lobes: the right lobe, the left lobe, the quadrate lobe, and the caudate lobe [2, 3]. The separation point of the right and left lobes was considered to be the attachment place of the falciform ligament on the anterosuperior surface. On the visceral surface of the liver, this border is formed by scissure containing ligamentum venosum and ligamentum teres. The quadrate lobe is bounded by the gallbladder fossa,

portoumbilical scissura, and porta hepatis on the visceral surface [2]. The caudate lobe is bounded by the groove for the VCI and fissure for the ligamentum venosum [2, 10]. The right part of the caudate lobe is in continuity with the caudate process of the right lobe, which forms the upper border of the foramen epiploica [2]. In the anatomical description, the quadrate lobe was defined to be a subdivision of the anatomical right lobe [2].

Healey and Schroy: According to Healey and Schroy, hepatic segmentation was based on the intrahepatic distribution of hepatic artery and biliary duct, and portal vein branches followed this distribution later [8, 9]. As specified by this segmentation, the liver is divided into two as the right and left liver by a plane (median scissura, Rex line, Cantlie's line) passing from the left side of the gallbladder fossa to the left side of the VCI. The left lobe is divided into medial and lateral segments by a plane defined by the falciform ligament and portoumbilical scissura, and the right lobe is divided into anterior and posterior segments by the right scissura. Then, these resultant segments are further divided into a superior and inferior subsegment by a horizontal plane passing through the ninth ribs. Also, in this segmentation, the caudate lobe was not defined as a separate lobe. Later, Sexana et al. reported that the quadrate lobe and the greater part of the caudate belong functionally to the left lobe of the liver and this claim was accepted in the studies of Hjortsjo, Mizumato, and Suzuki [13]. Topographically, the quadrate lobe was described to be a portion of the inferior half of the medial segment of the left lobe. The caudate lobe was reported to be located in the medial segment of the left lobe, continuing into the right lobe. The caudate lobe was divided by the median scissura into the right and left subsegments. The bile ducts, arteries, and portal vein of this lobe arise from both right and left main branches. The caudate lobe is drained by two small hepatic veins that empty directly into the VCI [8].

Couinaud: The Couinaud segmentation system is based on the distribution of both the portal vein and the hepatic veins in the liver [8, 9, 11]. Three portal scissures containing hepatic veins divide the liver into four sectors: right paramedian, right lateral, left paramedian, and left lateral. These segments are also divided into eight segments by hepatic scissure containing portal pedicles. According to this, the left lateral sector is divided into segment II, left paramedian sector into segments III and IV, the right lateral sector into segments VI and VII, and the right paramedian sector into segments V and VIII. The caudate lobe is called segment I. These segments correspond to the subsegments of Healey and Schroy (Fig. 26.5).

Bismuth: Bismuth divided the liver into segments by three scissure including the hepatic veins and the horizontal plane passing through the right and left portal veins [8, 9, 11]. Bismuth first divided the liver into two hemilivers by main portal scissura. The right liver was divided into anteromedial and posterolateral sectors by the right portal scissura and the left liver into anterior and posterior sectors by the left portal scissura. After this division, they were divided into two segments by hepatic scissure containing portal pedicle. Accordingly, the left posterior sector contains only segment II, and the left anterior sector is divided into segment III and segment IV by the left hepatic scissura. Likewise, the right anteromedial sector is divided into segment V and segment VIII and the right posterolateral sector into segment VI and segment VII. Bismuth described the caudate lobe as a separate segment I.

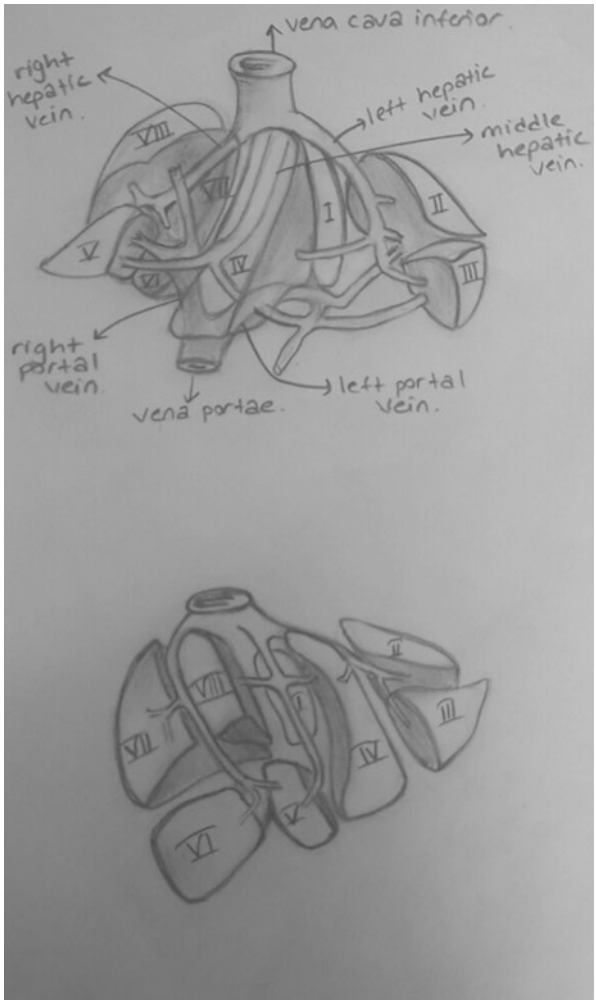

Fig. 26.5 Liver segments

Hepatic Segmentation of the Federative Committee on Anatomical Terminology (FCAT)

In the hepatic segmentation of this committee, the liver was divided as developmental, functional, and surgically separable units based on the distribution of portal vein, hepatic arteries, and the biliary ducts [9]. The segment I corresponded to the caudate lobe in the posterior part of the liver [9, 14]. The other segments were numbered from II to VIII clockwise, starting from the left. The left lateral sector (segment II, left lateral posterior segment; and segment III, left lateral anterior segment) is separated from the left medial sector (segment IV, left medial segment) and from the segment I by the portoumbilical scissura. The right medial sector (segment V, right medial anterior segment; and segment VIII, right medial posterior segment) is

separated from the right lateral sector (segment VI, right lateral anterior segment; and segment VII, right lateral posterior segment) by the right portal scissura. There is another important point to be remembered when discussing liver segmentation. For many years, it was believed that there are very few and unclear anastomoses between the right and left lobes, except for the caudate lobe [15–19]. Mays et al., however, have shown that the left lobe was supplied with the blood from the right lobe after the ligation of the left hepatic artery, and vice versa [19–22]. However, these anastomoses could not be observed in the cadaveric studies.

In today's practice, the taxonomy reached by the changes made by the Brisbane committee and Bismuth based on the hepatic anatomy described by Couinaud is used for the segmental anatomy of the liver [23]. In this taxonomy, the liver is divided into two parts as right and left and then into sectors and segments. The right and left liver are separated by Cantlie's line. Hepatic sectors are separated by two hepatic veins or one hepatic vein and an edge of the liver. A liver segment is a region of parenchyma with independent vascular inflow, outflow, and biliary drainage. Thus, the liver is divided into right and left hemilivers at Cantlie's line corresponding to the bifurcation of the portal vein, aligned roughly with the middle hepatic vein. It is then subdivided from lateral to medial by the right and middle hepatic veins to form the right posterior, right anterior, and left liver sectors. In Couinaud's system, the left liver was divided into a medial and lateral sector by the ligamentum teres and is still commonly referenced as such. Recently, a single left sector with three segments was proposed to replace the two-sector left hemiliver [24].

Hepatic Arteries

The liver is a highly vascularized organ (Fig. 26.6), receiving approximately 25% of cardiac output. Unlike any other organ, the liver provides oxygenated blood from two different sources. Hepatic artery provides 25–30% of blood flow

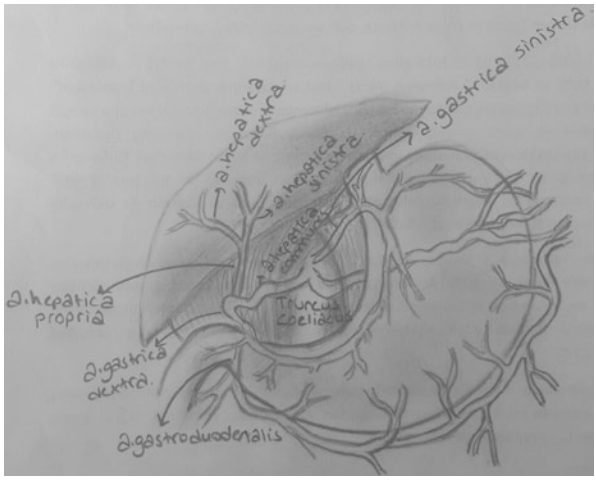

Fig. 26.6 Vascularization of the liver

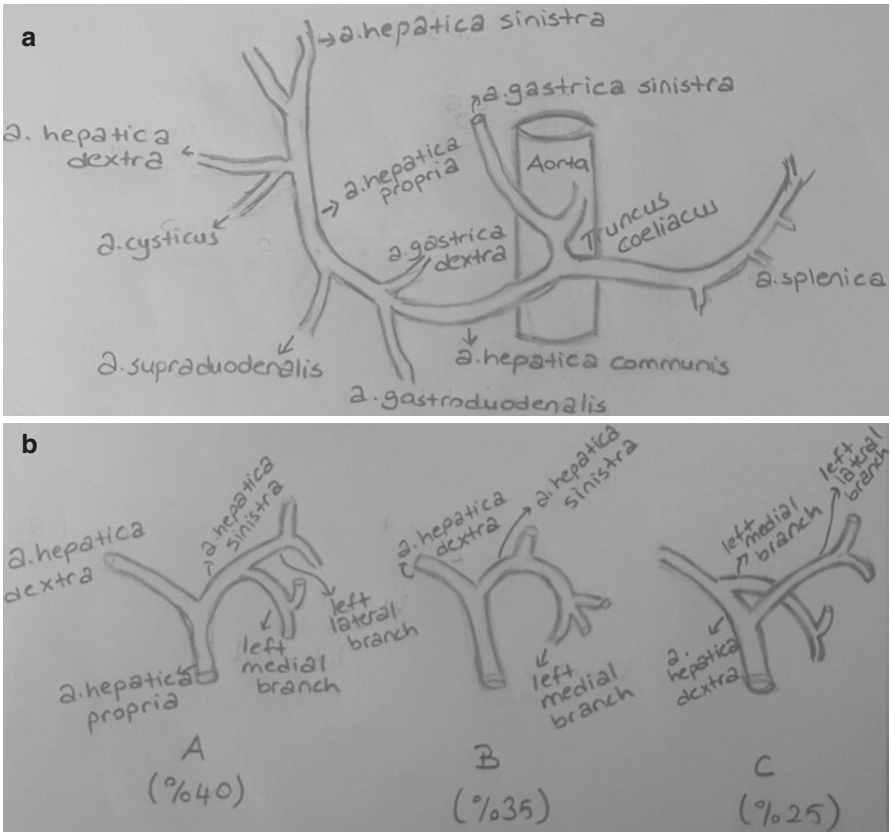

Fig. 26.7 (**a**) Normal artery. (**b**) Artery variation

and 30–50% of oxygen [3, 8]. The hepatic artery enters the liver via the portal pedicle, surrounded by a fibrous cover (Glisson's sheath), along with the portal vein and the common bile duct. Anatomical studies showed that so-called normal hepatic artery anatomy could be observed in only 55–60% of people (Fig. 26.7a) [2, 25, 26]. The common hepatic artery normally arises from the celiac trunk and gives off two branches, right and left. The definition of the "aberrant hepatic artery" refers to the artery that originates from another source other than the celiac trunk and arrives the liver with a different course [8]. If such an aberrant artery supplies a segment of the liver that also receives blood supply from a normal hepatic artery, it is called an "accessory artery" [8]. It is a replaced artery if it is the only blood supply to such lobe or segment [8]. Different variations on the arterial circulation of the liver are combined in the Michels' classification (Fig. 26.7b).

Common Hepatic Artery

The common hepatic artery originates from the celiac trunk by 86%, superior mesenteric artery (SMA) by 2.9%, aorta by 1.1%, and less frequently from the left gastric artery. This artery courses along the upper border of the head of the pancreas covered by the peritoneum after arising from the celiac trunk. As the artery runs, it branches off the gastroduodenal artery behind the duodenum. After the origin of this artery, it becomes the hepatic artery proper. Hepatic artery proper turns upward to ascend in the lesser omentum and enters the hepatoduodenal ligament in the front of the epiploic foramen (foramen Winslow). It branches to give rise to the right gastric artery within the hepatoduodenal ligament. Within the hepatoduodenal ligament, it generally lies to the left of the common hepatic duct and anterior to the portal vein. Then, it is divided into the right and left hepatic artery. These arteries are distributed to different segments in the liver, similar to the distribution of the portal vein [26, 27].

Left Hepatic Artery

The left hepatic artery arises from the common hepatic artery above the portal vein bifurcation. Then, before entering the liver at the level of portoumbilical fissure, it courses extrahepatically along the inferior surface of segment IV with the left hepatic duct and the left portal vein. Meanwhile, it lies anterosuperior to the left portal vein. While this artery courses extrahepatically, it gives off branches that supply segment IV. In some cases, the main branch to segment IV may arise from the left hepatic artery at the level of the portoumbilical scissura near the origin of the left hepatic artery. After giving off the arteries to medial segment IV and lateral segment, the left hepatic artery gives origin to the branches to segment II and segment III. This anatomical course of the left hepatic artery is observed at a rate of 40%. While the artery to segment IV originates from the artery to segment III in 35% of cases, the segment IV artery originates from the right hepatic artery in 25% of cases and reaches segment IV after passing the median scissura [8, 27].

The left hepatic artery originates from the left gastric artery in 25–30% of people and supplies the segments II and III. This artery branches from the left hepatic artery in the lesser curvature of the stomach and goes to the segment III by passing through the gastrohepatic ligament. This anatomical variation may be the replaced main branch that principally supplies the segments II and III, as well as the accessory arteries supplying the segments [25, 27].

Right Hepatic Artery

The right hepatic artery is anterior to the portal vein and posterior to the common hepatic duct (85–95%) after it branches from the common hepatic artery. It should be taken into account that in some cases it can be in the front of the bile duct

(5–15%) [26, 27]. Before entering the liver, it gives rise to the cystic artery in the Calot's triangle (formed by the common hepatic duct, cystic duct, and the inferior edge of the liver) and enters the liver. There are branches of less than 1 mm in diameter from the right hepatic artery to segment IV. These branches may be the main artery originating from the right hepatic artery and supplying segment IV in the form of an artery with a large diameter in 25% of cases [25, 27]. Therefore, careful dissection of the right hepatic artery in the lateral of the common hepatic duct is important to avoid damage to these arteries and to prevent ischemia of segment IV [27]. The right hepatic artery is divided into anterior and posterior sector (segment) arteries intrahepatically or sometimes extrahepatically which in turn divide into superior and inferior segmental (subsegmental) arteries [8]. There are arteries to the caudate lobe from the right hepatic artery. These arteries are found under the bile ducts of the caudate lobe. Sometimes an accessory right hepatic artery originating from the a. hepatica propria extrahepatically leaves before entering the right liver parenchyma and contributes to the arterial supply of the inferior parts of segments V and VI. Renz et al. found this condition in 5% of cases [27].

The right hepatic artery stems from SMA in 17% of cases and provides the arterial supply of the right liver in 12% of the cases [2, 3, 8]. After this artery branches from SMA, it enters the hepatoduodenal ligament in the right lateral of the portal vein and runs to the right liver in the same localization. Intrahepatic distribution of hepatic artery generally follows the distribution of the portal vein. As the arterial branches travel toward the distal, they surround the portal vein branches. Unlike portal vein, the right and left hepatic artery are in contact with small branches in the Glisson's capsule in the falciform ligament groove. There are various arterial branches originating from phrenic artery and gastroduodenal artery. These branches may supply the liver by the collateral circulation if the common hepatic arterial blood flow is interrupted. In case of ligation of the right hepatic artery or the left hepatic artery, arterial flow can be restored on the side where the artery is ligated thanks to intrahepatic collateral blood flow. This collateral blood flow has been shown to occur within 24 h. However, when the common hepatic artery or the right hepatic artery is ligated, cholecystectomy should be performed as the circulation in the gallbladder will be impaired [28].

Portal Vein

The portal vein carries about 75% of liver blood flow and offers 50–70% of liver oxygen need [2, 3, 8]. There are no valves in the portal vein [3]. This provides a high blood flow with low pressure due to the low resistance. The absence of valves in the portal vein ensures that the portal venous pressure is the same throughout the portal system, and therefore, pressure can be measured from anywhere in the portal vein. Portal vein measures 7–10 cm in length and has a diameter of 0.8–1.4 cm.

The portal vein is formed by the confluence of the superior mesenteric vein (SMV) and splenic vein behind the pancreas (Fig. 26.8). In 25% of cases, the inferior mesenteric vein (IMV) merges with SMV, slightly distal to the junction of the SMV and the

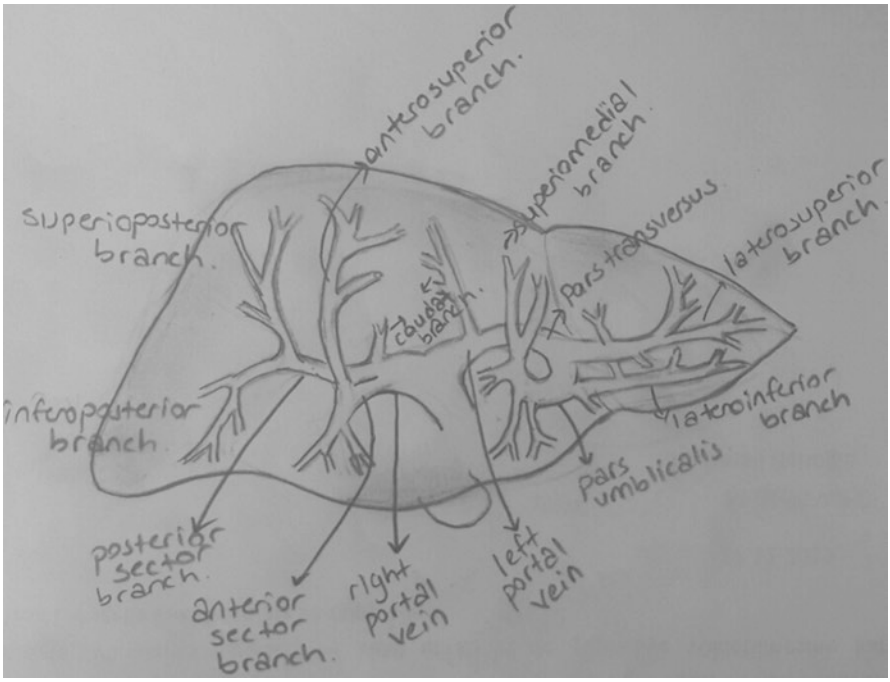

Fig. 26.8 Portal vein and tributaries

splenic vein. The portal vein, then, ascends behind the first part of the duodenum, posterior to the hepatoduodenal ligament. In the hepatoduodenal ligament, a. hepatica propria lies anterior to the portal vein. Normally, there are no tributaries on the anterior and posterior surface of the extrahepatic portal vein. However, sometimes accessory pancreatic veins may drain into the anterior surface near the duodenum. In some cases, pyloric, pancreatic venules, and duodenal vein may merge with the portal vein at the lower border of the portal vein. In 25% of cases, the coronary vein (left gastric vein) may join the portal vein in front of the hepatoduodenal ligament. Normally, this vein drains into the portal vein just above the junction of the SMV and the splenic vein. No branches drain into the portal vein near porta hepatis. This feature makes this area the most suitable place for portal vein dissection. However, the location where the cystic vein drains into the portal vein at porta hepatis should be considered. The portal vein gives off two separate branches at the porta hepatis level at an angle of about 90° [8]. The right portal vein is wider and shorter, and the left portal vein is narrower and longer. The right portal vein lies anterior to the segment I and gives off a branch to segment I where it leaves the portal vein. The right portal vein is divided into anterior and posterior branches in the liver parenchyma. The posterior branch gives origin to superior and inferior branches, while the shorter anterior branch is divided into superior, inferior, medial, and lateral branches. The left portal vein runs horizontally and extends from the porta hepatis to the portoumbilical scissura. After giving branches to segment 1 during this course, it takes an abrupt turn anteriorly at the level

of portoumbilical scissura and courses to the ligamentum teres hepatis and ends proximal to the inferior border of the liver. It merges with the ligamentum teres hepatis near this termination site. The left portal vein is divided into left medial and left lateral branches during this course. The left medial branch splits into superior and inferior branches to segment IV, and the left lateral branch is divided into superior to segment II and inferior to segment III [2, 3, 8].

In 10–15% of cases, the right portal vein immediately divides into two branches. Rarely, portal branches to segments V and VIII may originate from the left portal vein. In some cases [10, 25], the portal branches to the right posterior sector originate from the portal vein before the portal vein divides into two [10, 25]. Another rare anomaly is the absence of the left portal vein. In such cases, the portal vein is undivided as it enters the liver. It gives off the right posterior and then the right anterior sectorial branch when it enters the liver. After then, it continues as the left portal vein, crossing the portoumbilical scissura and splits into medial and lateral sectors.

The portal vein can sometimes enter the hepatoduodenal ligament, passing anterior to the duodenum and the neck of the pancreas [10, 25]. A very rare anomaly occurs when the portal vein drains directly into the VCI [10, 25].

Hepatic Veins

The venous drainage of the liver comprises three main hepatic veins and accessory hepatic veins, ranging in number from 10 to 50, that drain into the suprahepatic part of the VCI [2, 3, 8, 10, 25] (Fig. 26.9).

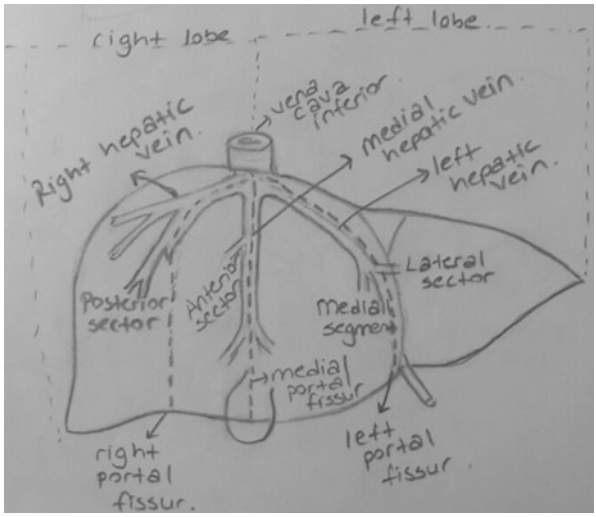

Fig. 26.9 Hepatic veins tributaries

The hepatic artery and portal vein deliver the blood to the hepatic sinusoids. Between these two vascular systems are presinusoidal arteriovenous anastomoses. Each liver lobule has radially arranged structures. The blood in the sinusoids drains into the central vein located in the center of each lobule. These central veins coalesce to form sublobular veins, which in turn form the collecting veins. A various number of collecting veins merge to form hepatic veins [2, 3]. The hepatic veins course in intersegmental planes formed by portal vein branches. The diameters of the hepatic veins where they drain into VCI are between 0.8 and 2 cm [2, 3].

Right Hepatic Vein

The right hepatic vein is the largest vein among the hepatic veins in diameter. It runs in the right scissura which is between the anterior and posterior sectors of the right liver. It is single in 94% of cases. Its main trunk mainly consists of the union of the anterior branch draining segments V and VI and the posterior branch draining segment VII. Other than this, it also drains part of segment VIII [3, 8, 10].

Middle Hepatic Vein

The middle hepatic vein runs at the median scissura. In 60–85% of cases, the middle hepatic vein joins the left hepatic vein before draining into VCI. It mainly drains segment V and segment IV. However, it contributes to the venous drainage of part of segment VIII. In 70% of cases, the middle hepatic vein drains segment IV, segment V, and segment VIII in approximately equal amounts. It is the only vein that drains segments IV, V, and VIII in 20% of cases [27]. In the remaining 10% of cases, it has a very large structure and drains the entire anterior and anterolateral aspect of the right hemiliver [27]. In other words, in addition to segment VIII and segment IV drainage, the main venous drainage of segment V and segment VI drains into the middle hepatic vein.

Left Hepatic Vein

The left hepatic vein lies in the upper part of the left scissura. It is formed by the union of the transverse branch draining segment II and the branches draining segment III [27]. The left hepatic vein also drains the superior section of segment IV.

There are three different anatomical variations of the left hepatic vein. In 73% of cases, the veins of segments II and III join in the portoumbilical scissura and form the left hepatic vein. In this anatomical structure, the veins draining the posterior of

segment IV drain into the left hepatic vein where the left portal vein approaches the VCI. In 14% of cases, separate venous branches providing the posterior venous flow of segments II, III, and IV join to form the left hepatic vein at a point close to VCI. Each of these veins also receives branches from the posterior of segment IV. The third anatomical variation was detected in 13% of cases. In this variation, the veins that provide the venous flow of segments II and III become a single resultant in the medial of the portoumbilical scissura in the parenchyma of segments II and III and drain directly into VCI without receiving any tributaries from segment IV [27].

Accessory hepatic veins are discussed in two sections as the right and left accessory veins. In most of the cases, there are two short accessory (dorsal) veins on the right side that contribute to the venous drainage of segments VI and VII and drain directly into retrohepatic VCI. While the vein on the upper side was found in half of the cases, the vein on the lower side was detected in 86% of the cases [8]. The veins on the left are the draining veins of segment I. The segment I is drained directly into VCI via a single vein in 50% of cases and via two or three veins in 50% of cases. In addition, approximately 20 venules have been shown to contribute to venous drainage from segment I to VCI.

The study of Nakamura and Tsuzuki in 1981 to reveal the patterns of the ramifications of the hepatic veins showed that the size of the right hepatic vein was important in determining the number and diameter of the accessory hepatic veins [25]. As the drainage of the posterior sector will be largely derived by this vein in the presence of a large right hepatic vein, there is only one or sometimes no accessory hepatic vein. If the right hepatic vein is medium-sized, there may be a single posterior or posteroinferior vein with a diameter of 0.5–1 cm, and it may drain segment VI separate from the right hepatic vein. In the presence of a short and small right hepatic vein, this vein drains only segment VII, while a posterior or posteroinferior accessory vein drains segment VI. In such circumstances, the anterior sector is drained solely into the middle hepatic vein.

In some cases, veins originating from segment III or segment IVa may empty directly into the VCI near the junction of the left hepatic vein and middle hepatic vein. This condition is not observed in the right half of the liver. While the area between segment IV and the left lateral sector is drained by a tributary of the left hepatic vein that runs across the falciform ligament in 60% of cases, it is equally drained by the left hepatic vein and middle hepatic vein in 30% of cases. In 10% of cases, this area is drained only by middle hepatic vein [8, 25, 27].

Biliary Tract

The intrahepatic biliary tracts show different variations at the portal hilum level, lobar, and sectoral levels. Therefore, bile duct anatomy, which we can call “normal anatomical structure,” is seen only in 50% of the cases (Fig. 26.10) [25].

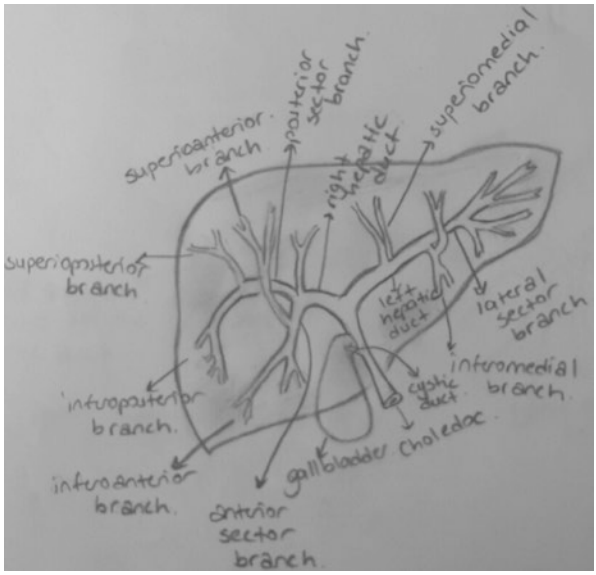

Fig. 26.10 Intrahepatic biliary tract

Intrahepatic Biliary Tracts

Bile canaliculi are formed by the combination of the parts of the membrane of adjacent parenchymal cells, and they are isolated from the perisinusoidal space. Bile flows are delivered from the canaliculi to the interlobular bile ducts found in portal pedicles through ductules (canals of Hering). These segmental and sectorial pedicles are surrounded by the Glisson's sheath. The bile ducts are located on the upper side, while portal vein and hepatic artery branches are located below. Biliary segmentation is identical to portal vein segmentation. Unlike portal vein branches, no relation is observed between bile ducts [8].

Right Hepatic Duct

The right hepatic duct has a length of approximately 0.9 cm and is formed by the intraparenchymal fusion of the anterior and posterior branches close to the portal hilum at a variable point. Each of the anterior and posterior branches was generated by the confluence of the superior and inferior branches in 72% of the cases in the studies of Healey and Schroy [8]. In the remaining cases, the posterior branch or, rarely, the anterior branch crosses the segmental scissura to empty into the left hepatic duct or one of its tributaries. In these cases, the right hepatic duct is absent.

Left Hepatic Duct

Medial and lateral branches join to form the left hepatic duct, which has an average length of 1.7 cm. The left hepatic duct drains segment II, segment III, and segment IV. According to Healey and Schroy, this anatomical structure is observed in 67% of cases [8]. The medial and lateral branches coalesce in the left portal scissura in 50% of cases, to the right of the left portal scissura in 42% of cases, and to the left of the left portal scissura in 8% of the patients.

The biliary drainage of segment I is provided by both the right and the left hepatic ductal systems in 80% of individuals, while it is drained only into the left hepatic duct system in 15% of cases. It is drained into the right hepatic duct system alone in 5% of cases [8].

Six subtypes of the biliary tract have been identified in the study of Smadja and Blumgart [25]:

- Type A (57%): This type is normal anatomy. The anterior and posterior branches unite to form the right hepatic duct in the right liver and the medial and lateral branches form the left hepatic duct in the left liver. These ducts combine to form the common hepatic duct.
- Type B (12%): In this type, there is a triple confluence of the right anterior, the right posterior, and the left hepatic duct to form a common hepatic duct.
- Type C (20%): In this type, there is aberrant drainage of the right anterior and posterior ducts into the common hepatic duct. In the C1 subtype (16%), the posterior duct passes behind the anterior duct and drains into the common hepatic duct. In the C2 subtype (4%), the anterior duct first joins the left hepatic duct, and then, the right posterior duct joins the resultant duct and forms the common hepatic duct.
- Type D (6%): In this type, there is aberrant drainage of the right anterior and posterior ducts into the left hepatic duct. In the D1 subtype (5%), the right posterior duct passes behind the anterior duct, joining the left hepatic duct at a higher level than that is seen in the type C1. In the D2 subtype (1%), the anterior duct joins the left hepatic duct.
- Type E (3%): In this type, there is no confluence of the right hepatic duct and the left hepatic duct forming the common hepatic duct. There is a union of two or more ducts from either hemiliver to form the common hepatic duct. E1 is seen at a rate of 2% and E2 at a rate of 1%.
- Type F (2%): In this type, there is an absence of the right hepatic duct with aberrant drainage of the right posterior duct into the cystic duct. Variations in the intrahepatic bile ducts are commonly seen (Fig. 26.11) [10]. The incidence rate of the right intrahepatic bile duct variations is 9% in segment V, 14% in segment VI, and 20% in segment VIII. Subvesical duct was identified in 20–50% of cases. This duct sometimes lies deeply embedded in the cystic plate and joins either the common hepatic duct or the right hepatic duct. This duct does not drain any specific liver territory and is never in contact with the gallbladder. No hepatic artery and portal vein branch travel along with this duct. In 67% of patients, a classical distribution of the left intrahepatic biliary ductal system exists. The variation of intrahepatic bile ducts in the left liver is represented by the union of the bile ducts of segments III and IV in 25% of cases. The bile ducts of segment IV join the common hepatic duct independently in 2% of cases.

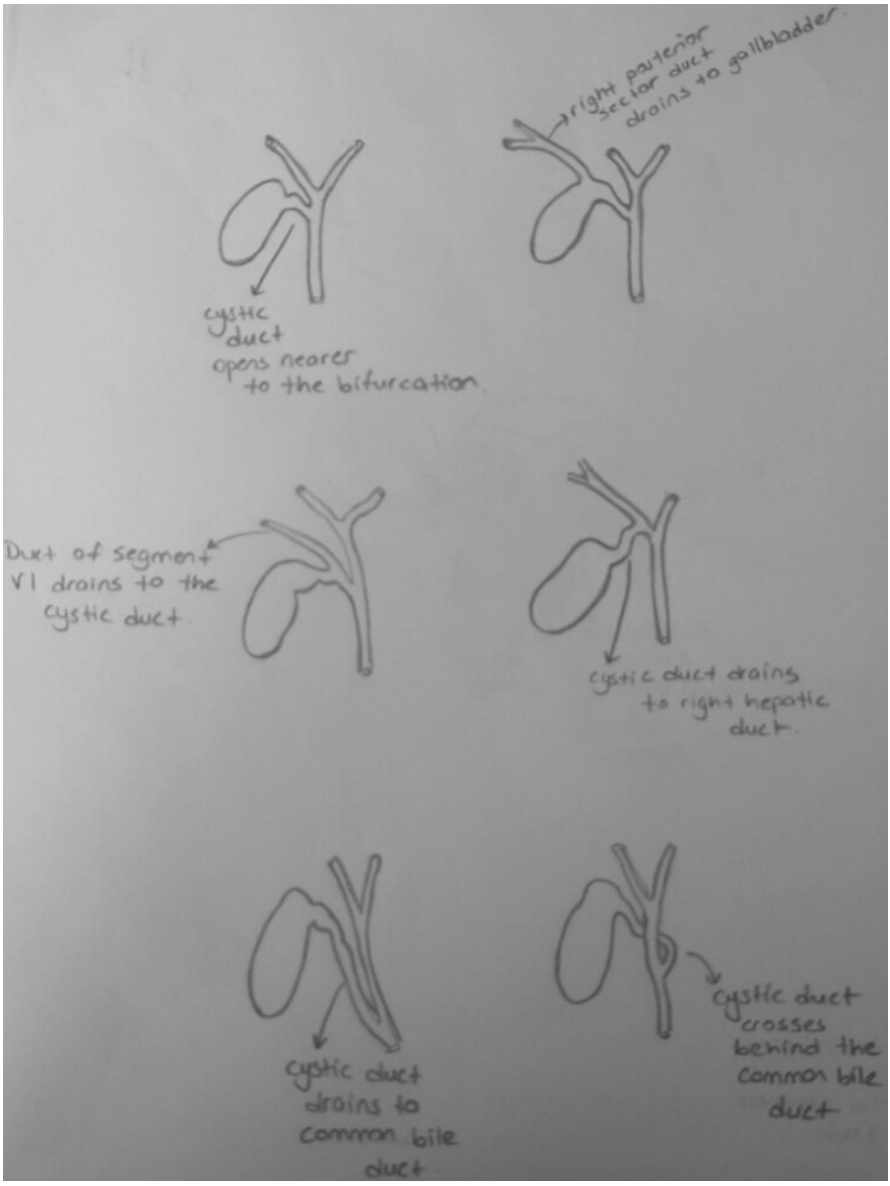

Fig. 26.11 Variations of bile ducts

The Gallbladder

The gallbladder is an expandable bile reservoir with a capacity of approximately 30–50 ml which resides in the cystic fossa on the inferior surface of the right hemiliver. The superior or hepatic surface of the gallbladder attaches to the cystic fossa by connective tissue. Fundus, inferior, and lateral surfaces are covered with a peritoneum

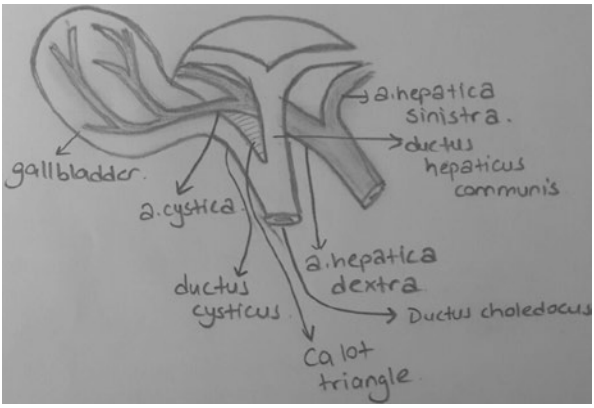

Fig. 26.12 The confluence of the cystic duct with the common bile duct

that is continuous with the peritoneum covering the liver. In some cases, the gallbladder is completely covered with peritoneum and attached to a cystic fossa by a mesentery. In rare cases, the gallbladder is completely embedded within the liver parenchyma (intrahepatic gallbladder).The gallbladder consists of fundus, body, infundibulum, and neck. A diverticulum called Hartmann's pouch occurs as a result of the expansion of the infundibulum or neck. The fundus is usually in contact with the anterior abdominal wall anteriorly and the transverse colon posteriorly. While the superior portion of the body is attached to the cystic fossa by connective tissue, the inferior portion is in juxtaposition to the transverse colon and duodenum. The infundibulum is located between the body and neck portions. The neck occupies the deepest part of the cystic fossa and lies in the free portion of the hepatoduodenal ligament [8, 10].

The cystic duct connects the gallbladder to the common bile duct. Its length varies from 1 to 5 cm. The confluence of the cystic duct with the common bile duct has different variations (Fig. 26.12) [10]. Sometimes it may be absent at all. In some cases, it drains into the right hepatic duct or the retroduodenal common bile duct. The lumen of the cystic duct contains a variable number of mucosal folds called Heister valves. These valves lie spirally and do not have a true valvular function.

The cystic artery, which provides arterial blood to the gallbladder, usually stems from the right hepatic artery. However, it may also branch from the left hepatic artery, the common hepatic artery, gastroduodenal artery, or SMA. After arising from the right hepatic artery, the cystic artery runs parallel to the cystic duct and lies within the hepatocystic triangle which is medial to the cystic duct or forms the superior border of the Calot's triangle. When the cystic artery approaches the gallbladder, it is divided into two branches: deep branch which runs to the cystic fossa and superficial branch which lies on the anterior surface of the gallbladder [10, 11].

The venous blood of the hepatic surface of the gallbladder drains into the branches of the hepatic vein. Venous blood from other surfaces drains into the portal vein. After the lymphatic drainage of the gallbladder reaches the cystic duct lymph node located at the junction of the cystic duct and the common bile duct, it mainly empties into the liver lymphatic tract. The lymphatic drainage of the gallbladder surfaces adjacent to the liver is associated with the lymphatic pathways in the liver.

The sympathetic and parasympathetic nerves of the gallbladder arise from the celiac plexus fibers that travel along the hepatic artery. The hepatic branch of the left vagus nerve provides parasympathetic innervation to the gallbladder. Sympathetic fibers are delivered by the T5-T9 spinal nerves to the celiac ganglion through the greater splanchnic nerve. Postganglionic sympathetic fibers reach the gallbladder, biliary tract, and liver, traveling along the hepatic artery. Visceral afferent fibers originating from the gallbladder run to the dorsal roots of the medulla spinalis at T5-9 levels via the greater splanchnic nerve. The sensory fibers of the gallbladder receive fibers from the right phrenic nerve. There is also a rich neural network between the celiac plexus and phrenic plexus. Therefore, pain may be felt on the right scapula in gallbladder pathologies [8, 10, 11].

Common Bile Duct

The common bile duct is formed by the union of the cystic duct and the common hepatic duct (Fig. 26.12). It is approximately 8 cm in length, with an average diameter of 4–9 mm. The upper 1/3 section or supraduodenal portion lies anterior to the portal vein and to the right of the hepatic artery proper within the hepatoduodenal ligament. Its middle 1/3 portion resides behind the first part of the duodenum (retroduodenal part). This portion is lateral to the portal vein and anterior to the VCI. The lower 1/3 portion runs horizontally behind the pancreas before it usually joins the main pancreatic duct (intrapancreatic part). Then, it courses intramurally within the second part of the duodenum and opens into the duodenum with the ampulla of Vater (intramural or intraduodenal part). The common bile duct is in relation to the main pancreatic duct in different forms. In 85% of the cases, the common bile duct and the main pancreatic duct coalesce within one duct to open on the ampulla of Vater, or they fail to coalesce and open into the duodenum separately. In 10–13% of cases, the common bile duct drains alone into the duodenum [8, 11].

Arterial Supply of Biliary Tract

The blood supply of the right hepatic duct, the left hepatic duct, and the upper part of the common hepatic duct arises from the cystic artery, the right hepatic artery, and the left hepatic artery (Fig. 26.12) [10, 25]. Common bile duct is supplied by cystic artery, posterior superior pancreaticoduodenal artery retroduodenal artery, and the right hepatic artery. The most important arteries of the supraduodenal biliary tract are located at 3 o'clock and 9 o'clock parallel to the bile duct. The arterial blood supply of the supraduodenal biliary tract arises from inferior by posterior superior pancreaticoduodenal artery and retroduodenal artery by 60% and from superior by cystic artery and the right hepatic artery by 38% [10, 25]. Injury in this axial arterial system causes ischemic biliary stricture. Only 2% of the arterial blood supply to the supraduodenal biliary tract is segmental, not axial. This blood supply is provided through a. hepatica propria. The source of blood supply to the

retroduodenal and intrapancreatic bile ducts is from the retroduodenal artery and the anterior and posterior pancreaticoduodenal artery. The venous blood of the intrahepatic bile ducts drains into the branches of the hepatic veins within the liver. The venous blood of the more distal parts of the biliary tract drains into the portal vein.

Lymphatic Drainage of Biliary Tracts

Lymphatic vessels from the intrahepatic and extrahepatic upper bile ducts drain into hepatic lymph nodes and reach the celiac lymph nodes via the hepatic artery. The lymphatic drainage from the distal bile ducts is into the hepatic and upper pancreatic lymphatics [8, 10, 25].

Neural Supply of Biliary Tract

The biliary tract receives the sympathetic and parasympathetic nerve fibers that are derived from the celiac plexus and course along the hepatic artery [10, 25].

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Management of Colorectal Liver Metastases

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Overview

According to the world health organization, 18.1 million new cancer cases were detected in 2018, while the number of people who died from cancer was 9.6 million. Cancers of the lung, female breast, and colorectal are the top three cancer types in terms of incidence. However, lung cancer is the first and colorectal cancer (CRC) is the second leading cause of mortality [1]. As the liver acts as a filter in the portal circulation, it is the first organ that is frequently exposed to metastatic dissemination in gastrointestinal neoplasms. The development of liver metastasis mainly depends on the location of the primary tumor. Colorectal adenocarcinoma and gut-associated neuroendocrine tumors may metastasize via portal venous drainage and intra-abdominal lymphatic ducts. In colorectal and gut-associated non-neuroendocrine tumors, metastasis occurs through the systemic circulation. In recent years, a multidisciplinary approach, more effective utilization of new chemotherapeutic agents, improvements in surgical techniques, and strengthening of perioperative management have increased the chances of CRLM surgical treatment. Although the surgery of hepatic metastatic lesions has not yet been generally accepted, the use of perioperative ultrasound and technological advances that make the parenchyma and the anatomical structures of the liver visible has made surgical treatment of liver metastases more reliable and resulting in less mortality. The mortality of complex liver surgery performed in reference centers experienced in liver surgery is about 5% [2, 3]. Treatment of CRLM requires a multidisciplinary approach. The treatment team should include colorectal surgeon, liver surgeon, medical oncologist, radiation oncologist, and abdominal radiologist. Known guidelines recommend preoperative thorax,

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abdomen, and pelvic computed tomography (CT). CT is often sufficient to determine the resectability of liver metastases. The sensitivity of CT and magnetic resonance imaging (MRI) used in preoperative CRLM resection planning is almost the same (91% and 94%). Approximately 50% of CRC patients develop liver metastasis at the time of diagnosis or during the treatment. Surgical treatment is almost the only alternative that offers a chance of cure and long-term survival. The overall survival time of these patients is limited to months with conventional chemotherapy. The 5- and 10-year survival rates after liver resection are around 40% and 25%, respectively. Advances in the surgical treatment of liver metastases, low mortality rates, and the contribution of surgery to the overall survival brought the option of surgery in CRLM into the forefront [4]. Most patients with multiple liver metastases cannot benefit from surgery. Palliative chemotherapy is the standard treatment. While expected life expectancy is 5 months or less depending on the size of the lesion, the overall 5-year survival expectation is below 10%. Although it is known to be contraindicated for this group of patients, liver transplantation may be a treatment option in the selected patient groups with a liver-only tumor in recent years. There are a few studies showing increased life expectancy after liver transplantation [5]. Approximately two-thirds of CRLMs are resectable at the time of diagnosis and may be treated with curative surgery. However, local and distant metastases may be seen in 25–30% of patients. Major metastases develop in the liver but can also develop in the anastomosis line and in the lungs. Metachronous liver metastases may be observed by 15% within 5 years after curative colorectal surgery. Early detection of local and distant metastases, especially in asymptomatic patients, is associated with increased survival. Therefore, early detection of metastatic lesions is of vital importance during postoperative follow-up. Although there is no general consensus for the postoperative follow-up, guidelines recommend a minimum of two thoracic, abdominal, and pelvic CT scans within the first 3 years in the patient who underwent curative colorectal surgery. Liver ultrasonography may be used alternately with CT scanning at 6-month intervals during the first 3 years. The usage time and order of these tests may vary according to the treating physician. Ultrasonography plays a role in the early detection of liver metastases and may increase the chance of resectability [6]. In this section, the surgical treatment of CRLMs will be discussed in light of current guidelines and literature. Radiological examinations used in the diagnosis of metastases and their diagnostic values will be discussed. Examining the morbidity and mortality of CRLM resections and their contribution to the overall survival of patients, the choice of imaging modality which will be used during post-resection follow-up is an important issue regarding the overall survival of the patients. Surgical timing and strategy such as the resection order of primary tumor and liver metastases, diagnostic laparoscopy, chemotherapy, targeted therapies in colorectal cancer patients with synchronous liver metastasis, and opposing views will be argued. Liver transplantation, a recent treatment option for patients who had multiple metastases or underwent multiple resections and had a low chance of surgery, will be discussed as a final treatment option, although it is known to be contraindicated.

Mechanism of Colorectal Cancer Liver Metastasis

The "seed and soil hypothesis" still remains valid for distant metastases. Certain tumor cells (seed) choose the organs (soil) where they can provide metastatic growth most efficiently [7]. Most cancer-related deaths are caused by metastasis. Metastatic dissemination is the main step in the transition from a local tumor to metastatic foci that will result in fatal causes. An invasive colorectal cancer spreads to the lymph nodes through regional lymphatic ducts and reaches systemic circulation by lymphatic spread after the ducts. Thus, local and distant metastases occur. Colorectal cancers can reach the liver directly through the portal venous circulation, as the hepatic blood flow is mostly derived from the portal vein. Therefore, the liver is the most common site of metastasis and is the organ most frequently exposed to tumoral spread. During this spread, the location of primary colorectal cancer is important for the metastasis to the liver and prognosis. Based on the National Cancer Registry in the Netherlands between 1989 and 2014, Brouwer et al. found that the location of the primary tumor was statistically different and significant for metastasis in their study of 36,297 patients with colorectal cancer who had only synchronous metastasis. In the study, the patients were divided into three groups depending on the location of the primary colon tumor: right colon (proximal to the splenic flexure), left colon (splenic flexure to rectum), and rectum. According to these data, rectal cancer has a higher metastatic rate to the lung (28%), followed by the left colon cancer (17%) and the right colon cancer (14%). While the liver metastases are most commonly seen in the left colon cancer, the right colon cancer has the worst prognosis. Liver metastases are found by 43%, 54%, and 52% in the right colon cancer, left colon cancer, and rectal cancer patients, respectively ($p < 0.001$). The right colon cancer with synchronous metastasis has a 1-year survival of 40% compared with 51% for the left colon cancer and 54% for rectal cancer. For subjects with liver-only metastases, 1-year survival is 43%, 57%, and 60% for the right colon cancer, left colon cancer, and rectal cancer, respectively. The main reason for the poor prognosis of right colon cancer is the histopathological origin. Mucinous and signet-ring adenocarcinoma are most common in the right colon by 16% and 3%, respectively, versus 10% and 1% in the left colon, and 6% and 1% in the rectum. Among the patients with isolated CRLM, the patients with the lowest chance of metastasectomy and survival compared to patients with left colon and rectum cancer are patients with right colon cancer [8]. CRC can spread to local lymph or develop distant metastases nodes via the lymphatic and portal circulation. It was investigated whether the circumferential tumor location has an effect on the spread and 5-year survival in the clinical study of Boni et al., and they were able to distinguish whether the tumor was located on the mesenteric or antimesenteric sides in 45% of 461 patients who underwent curative colorectal surgery. The tumor was located on the mesenteric side in 160 patients and on the antimesenteric side in 47 patients. The patients mostly have T3 tumors. 62% of tumors located on the mesenteric side and 51% of tumors located on the antimesenteric side were in the T3 stage. A statistically significant difference was detected in terms of N status among the patients. It was positive in 51% of tumors with mesenteric location and 30% of tumors with antimesenteric location ($p = 0.003949$). Considering the T3N+ patient

group, the 5-year survival study revealed that patients with tumors located on the antimesenteric side had statistically significantly worse survival than patients with tumors located on the mesenteric side. It was reported that patients with mesenteric CRC were more likely to have N+ but better 5-year survival than patients with antimesenteric CRC. A possible explanation for such results might be dense vascular and lymphatic networks on the mesenteric side and the different patterns of diffusion of cancer cells. In experimental studies with rats, the colon was observed to be tended to spread to the locoregional lymph nodes in tumor injections to the mesenteric side. The incidence of peritoneal diffusion was found to be higher in tumor injections on the antimesenteric side [9]. In the study of Kamocki et al., right and left colon cancers were compared for the prognostic values of tumor location and mesenteric-antimesenteric locations. Of 191 patients, 82 presented with right-sided colon cancer, whereas 109 presented with left-sided colon cancer. Lymph node metastases were observed in 100 patients, including 44 patients with synchronous liver metastases, 24 of whom underwent synchronous metastasectomy. Twenty of them were patients with non-resectable metastasis. It was found that having a right or left-sided colon cancer was not statistically significant for lymph node or distant metastasis development. It was statistically determined that tumors with mesenteric location are associated with a higher incidence of lymph node metastases than those with antimesenteric location ($p = 0.04$). Besides, it was found that tumors with antimesenteric location are more likely to develop liver metastasis than those with mesenteric location ($p = 0.044$). In addition, it has been determined that the histological type and the degree of nuclear/cellular polymorphism of colon tumors are not very valuable as predictors of metastasis. In the study, it was stated that the location of the tumor within the right or left colon has no significance for metastatic processes; however, the prognosis of the right colon tumors may be worse as a result of the late detection due to the fact that right colon tumors usually have a flat morphology and may be missed in endoscopy. Besides, the circumferential tumor location was also stated to be significant for tumor spread. While colon tumors with mesenteric location are predisposed to lymphatic spread, tumors with antimesenteric location spread via hematogenous/peritoneal route. Therefore, it has been underlined that caution should be exercised with antimesenteric tumors for the development of liver metastasis. Particular attention should be paid during the follow-up of antimesenteric tumors [10]. Theoretically, circulating tumor cells should be more common in the portal vein than in systemic circulation in patients with gastrointestinal cancer. However, the liver is the first organ where tumor cells can reach through the portal vein and proliferate easily. The chance of a hematogenous pulmonary metastasis without liver metastasis is very low. However, pulmonary metastasis may somewhat develop without liver metastasis in 2–4% of patients who underwent curative resection for CRC. Tien et al. obtained samples from the portal vein by the catheter they inserted into the portal vein through the right gastroepiploic vein during CRC surgery and obtained samples from the systemic circulation and tumor tissue, concurrently. CEA and cytokeratin 20 (CK 20) mRNA are widely used for the detection of circulating tumor cells. However, CEA and CK 20 may also be observed at certain levels in healthy individuals without cancer. Therefore, guanylyl cyclase C (GCC) mRNA,

which can be detected very rarely in healthy individuals, was detected and employed in the samples by PCR method. Based on the results of the study, colorectal epithelial cells were found to be higher in the portal vein than in systemic circulation in samples from those with Dukes' stage B disease obtained before CRC mobilization. However, in patients with stage C and D disease, while tumor cells were detected in the systemic circulation, no cells were observed in the portal vein before and during mobilization. Dukes' stage C and D primary colorectal tumors are associated with lymph node and liver metastases. At this point, it was emphasized that the lymph nodes inhibit tumor cells and that the tumor cells in the lymph node may enter into the systemic circulation without passing through the portal vein via capillary alternative ways [11].

Radiological Examination and Diagnosis in Liver Metastases

New advances in radiology have increased the chance of imaging distant and especially liver metastases of CRC at the early stage. Thoracic and whole abdominal CTs are the first standard imaging modalities used in the diagnosis and staging of patients with CRC. The radiological methods used in the diagnostic stage at the treatment centers may differ significantly. Evidence shows that CT and MRI are the two most effective methods of showing CRLM. Some centers perform CT imaging combined with ultrasonography during follow-ups to reduce the radiation exposure, considering high-dose radiation that patients will receive during repeated CT scans. CT, MRI, and contrast-enhanced ultrasonography may be used to detect liver metastasis of CRC. MRI is a much more sensitive method than CT for detecting lesions smaller than 10 mm. Lesions may be detected with a higher accuracy rate by hepatobiliary MRI performed using specific contrast agents (gadoxetate). Positron emission tomography (PET) and computed tomography (PET/CT) may be used to detect local recurrences and extrahepatic metastases after the first colorectal surgery. PET/CT may provide additional information, particularly in demonstrating extrahepatic disease, but there is no general consensus on the use of PET/CT in all patients [12]. Granata et al. investigated which imaging method should be performed for the preresection detection of CRC hepatic metastases and they compared two main imaging methods to standardize this. They retrospectively analyzed the radiological detection of 512 established liver metastatic lesions of 128 patients with CRLM who underwent liver resection and registered at the National Cancer Institute of Naples, and liver metastasis of all patients was histopathologically verified. All patients underwent both multidetector computed tomography and gadoxetic acid (Gd-EOB)-enhanced liver MRI within a month. There was less than 1 month between radiological and pathological diagnosis. There were images of resected specimens. MRI detected 489 metastases while multidetector CT found 384 liver metastases. MRI showed a statistically significantly higher performance ($p < 0.001$). MRI could not detect 19 subcapsular metastatic lesions. This is because these lesions were in the extra-parenchymal area and Gd-EOB contrast cannot reach high contrast gradient in this area. In patients who develop hepatic steatosis after

chemotherapy, CT cannot differentiate the density of metastatic lesions from liver density. In contrast, Gd-EOB MRI is superior to CT in detecting these lesions [13]. Although transabdominal ultrasonography is the readily available and most cost-effective imaging modality, it has the lowest sensitivity in showing liver metastases. This modality cannot show approximately 50% of hepatic lesions because of its subjective nature and its decreased imaging ability due to anatomical factors such as gas disposition. Hepatic steatosis developing after chemotherapy further reduces the imaging ability of ultrasonography. It is very useful in imaging biliary obstruction developed due to neoplastic causes. On the other hand, the use of perioperative ultrasonography has a high-resolution rate in imaging the liver and vascular structures and may easily detect hepatic lesions. Using intraoperative ultrasonography may also be very helpful for surgical decision-making. It is especially useful in the detection of deeply located and non-palpable liver lesions. The sensitivity of using intraoperative ultrasonography is between 85% and 95% depending on the ability of the operator. Intraoperative ultrasonography success also depends on the size, depth, and echogenicity of the lesion. Multidetector CT (MDCT) is the standard examination used in post-diagnostic staging and surgical planning. Liver metastases may be best seen on CT during the portal-venous phase. If the size of the liver lesions is 10 mm and less, the ability of CT to detect these lesions decreases considerably. Technical advances in MRI examination brought diffusion-weighted imaging (DWI)-MRI use together. DWI-MRI has greatly facilitated the detection and characterization of liver lesions. DWI-MRI is superior to MDCT and T2-weighted conventional MRI in detecting lesions less than 1 cm in size. PET/CT is not used in every patient due to its high cost and accessibility challenges. In addition, there is no general consensus on its use in each patient. FDG/PET is superior to CT, which has a sensitivity of 65–95%, with a sensitivity of 78–95% in detecting liver metastases. However, it has a low sensitivity of 36% for detecting metastases of 1 cm and less [14].

Staging with Diagnostic Laparoscopy

Hepatic resection is performed for curative intent in patients with CRC. Systemic chemotherapy and targeted agents are usually used after resection. Laparotomies that cannot provide a cure in unresectable liver metastases may cause delays in the administration of systemic treatments. While unnecessary laparotomies significantly increase the morbidity of the patients, they can also lead to the prolonged hospital stay and increased costs. Herein, a diagnostic laparoscopic examination before surgery may prevent unnecessary laparotomies and eliminate all these negative factors. Jarnagin et al. examined 103 patients with potentially resectable tumors in this way and performed resection in 77 of them. Diagnostic laparoscopy identified 14 of 26 patients with unresectable disease, ten of whom were spared an unnecessary laparotomy. Diagnostic laparoscopy shortens hospital stay in patients with unresectable liver metastasis and reduces hospital costs by 55%. Clinical risk score (CRS), which entered into practice recently, has been shown to be associated with

unresectable disease. The likelihood of unresectable disease is 12% especially in those with a score of ≤2 but increased to 42% in those with a score of >2. Patients with a CRS value above 2 are more likely to benefit from diagnostic laparoscopy [15]. Grobmyer et al. performed a diagnostic laparoscopy for 264 patients with CRLM scheduled for surgery and 12 patients with CRLM scheduled for hepatic arterial infusion pump placement, and only 168 patients had a complete laparoscopic examination. Other patients had incomplete laparoscopic examination due to adhesions from prior surgery. Twenty-six of 264 patients were spared an unnecessary laparotomy. Of these patients, 15 patients were found to have unsuspected liver lesions and 11 to have extrahepatic metastases. Non-therapeutic laparotomy was performed in 22 (8.3%) patients. They had undergone non-therapeutic laparotomy for reasons that were missed at laparoscopy. Of these patients, 11 had perihepatic lymph nodes, five peritoneal disease, and six unsuspected additional hepatic metastases. Diagnostic laparoscopy reduced the unnecessary laparoscopy rate from 18% to 8%. In the study, 4 of 12 patients scheduled for hepatic arterial infusion pump placement prior to the study were spared unnecessary laparotomy due to the detection of extrahepatic disease. Diagnostic laparoscopy does not need to be performed in every patient scheduled for partial hepatic resection. It will be more appropriate to perform in patients with a high CRS who are considered to have an unresectable liver tumor and suspected to have the extrahepatic peritoneal disease [16]. Diagnostic laparoscopy was performed in 1047 patients in a meta-analysis of 1107 patients by Hariharan et al. 870 patients were found to be laparoscopically resectable, but 748 had a resection. 177 patients were identified as unresectable based on the diagnostic laparoscopy, and 71 of them had extrahepatic and 72 had extensive liver involvement. In the presence of peritoneal disease and in patients with a high CRS value, diagnostic laparoscopy may be more useful to avoid unnecessary laparotomies [17].

Liver Transplantation for Unresectable Liver Tumors

Liver transplantation for cancer patients has been on the agenda more often over the years. Hepatocellular cancer is still the primary indication. Understanding of tumor biology, improvements in preoperative treatment options and appropriate patient selection have contributed to optimizing long-term outcomes after transplantation. The 5-year survival has reached 75% in liver transplantation for hepatocellular cancer. Parallel developments in the field of oncology and transplantation have recently created a new perspective for advanced cancers regarding oncological transplantation. In a prospective study of liver transplantation by Hagness et al., patients with isolated unresectable CRLM whose primary tumor was excised, and chemotherapy treatments were completed were included. A total of 21 patients underwent liver transplantation in the study. The overall survival rates at 1, 3, and 5 years were 95%, 68%, and 60%, respectively. After an average follow-up of 27 months, 33% of the patients had no evidence of disease. As expected, recurrent lesions developed in patients were generally found to be suitable for surgery or ablative treatment options. Hepatic tumor load before liver transplantation, time from primary surgery to liver

transplantation, and progressive disease on chemotherapy were identified as significant prognostic factors [18]. While the liver transplantation for unresectable CRC tumors has been performed in small series in previous years, positive results have increased transplantation studies with larger series in recent years. Liver transplantation may be considered as a regional curative treatment for removing the tumor with all liver tissue. However, long-term intensive cycles of chemotherapy may lead to severe liver dysfunction in patients with liver metastases over time. In the years during which modern chemotherapy and immunosuppression agents were not yet in use, Mülbacher et al. started their first studies with a small series of 25 patients in Austria and achieved a 5-year survival rate of 12% in their first studies. In their second study consisting of 55 patients, they achieved the 1- and 5-year survival rates of 62% and 18%, respectively. A decade after this study, a randomized controlled liver transplantation study (SECA Trial) was initiated in CRC patients with liver metastases in Norway, which had a large donor pool and was highly developed in surgical oncology and transplantation. Hagness et al. announced the results of the SECA trial in 2013, and the 1-year disease-free survival rate was 35% and the 5-year survival rate was 60%. The results of the study emphasized the importance of patient selection criteria. For example, according to Cox regression analysis, having less than 2 years between the diagnoses of primary and metastasis, a carcinoma embryonic antigen (CEA) level over 80 ng/ml and peritoneal disease during transplantation were found to be correlated with poor outcomes. Liver transplantation is on the agenda as a promising option for selected patients with unresectable liver metastases meeting eligibility criteria [19].

Liver Injury After Chemotherapy

The rate of synchronous colorectal liver metastases is 15–25%. Metastasectomy is possible in the setting of liver-only metastases. However, only 15–20% of patients are considered to be candidates for resection at the time of presentation. Systemic chemotherapy is increasingly used to improve the potential benefit of surgery and to downstage. The two most commonly used chemotherapy regimens of the patients with CRLM include FOLFOX (oxaliplatin +5-FU + leucovorin) and FOLFIRI (irinotecan +5-FU + leucovorin). Chemotherapy regimens administered before hepatic resection lead to hepatic parenchymal injury; this is a chemotherapy regimen-specific phenomenon. For example, oxaliplatin-based regimens are associated with sinusoidal injury, whereas irinotecan-based regimens are associated with hepatosteatosis. If liver injury due to chemotherapy develops during surgeries performed after chemotherapy, the risks of intra- and postoperative complications and postoperative liver failure are increased. This is associated with residual functional liver tissue [20]. Sinusoidal obstruction syndrome (SOS), previously termed veno-occlusive disease, is caused by various toxic agents affecting sinusoidal endothelial cells and is mostly associated with the use of oxaliplatin-based systemic chemotherapy. Histologically, SOS is characterized by dilated sinusoids with congestion. The incidence of oxaliplatin (OX)-induced SOS has been reported to be between

8.3% and 54% in the literature. Patients with CRLC who develop OX-induced SOS have significantly reduced hepatic reserve and increased blood transfusions. The standard chemotherapy in the first-line treatment has gradually been shifting from FOLFIRI to FOLFOX during the last decade. SOS resulting from increased use of OX-based regimens and parenchymal injury has become more recognized. SOS may be diagnosed based on the histopathological parameters such as CD34/SMA/GS and may present clinically with symptoms such as weight loss, hyperbilirubinemia, acid, and hepatomegaly. Stevenson et al. emphasize the importance of generating a sinusoidal injury index based on all these parameters. SOS is associated with an increased need for intraoperative blood transfusions, increased duration of hospitalization after surgery, and decreased response to chemotherapy and characterized by early recurrence and decreased overall survival after resection due to liver failure. Both hepatosteatosis due to the use of irinotecan and SOS related to the use of oxaliplatin increase postoperative morbidity. However, long-term chemotherapy regimens administered preoperatively may cause significant injury to healthy liver tissue that does not contain tumor tissue due to the chemotherapeutic agents used on the liver [21].

Hepatic Arterial Infusion Pump Chemotherapy

Unlike normal liver tissue, metastatic liver lesions receive the majority of their blood supply via the hepatic artery instead of the portal vein. The chemotherapy pump placed in the hepatic artery is not used in every center. This approach is preferred in some experienced and high-volume centers. In CRLCs, adjuvant chemotherapy may be used to downstage initially unresectable metastases to resectable status. The administration of chemotherapeutic agents directly into the hepatic artery is a more specific treatment option, increasing the delivery of certain cytotoxic agents to the metastatic foci while minimizing systemic side effects. 5-FU-deoxyuridine (FUDR), the analog of 5-FU which is the main antineoplastic agent, is used in CRC and liver metastasis. FUDR is 400-fold more effective than systemic therapy with a 95% first-pass extraction rate. Considering ten randomized controlled trials comparing the systemic treatment and the hepatic arterial pump chemotherapy in patients with initially unresectable colorectal liver metastasis, treatment via the hepatic artery has been shown to provide a dramatically higher tumor response rate than systemic therapy (43% vs. 18%, $p < 0.001$) [22]. Very little FUDR treatment, which is administered through the hepatic artery, reaches the systemic circulation. In the absence of systemic chemotherapy, the possibility of developing occult extrahepatic metastases increases. A limited number of phase 1 and 2 trials have been conducted on this combined therapy. The study of Kemeny et al. from Memorial Sloan Kettering Cancer Center found a response rate of 74% with hepatic arterial infusion pump chemotherapy in combination with systemic irinotecan and a response rate of 88% in combination with systemic oxaliplatin with minimal toxicity in both combinations [23]. Based on the successful results reported, chemotherapy via the hepatic artery is administered in many centers in combination

with systemic chemotherapy. The complication rate related to the pump is about 20%, even in centers experienced in the chemotherapy pump placement technique. However, many pumps having problems may be salvaged in these centers, allowing chemotherapy to be infused in 90% of patients. There are many surgical techniques for the placement of the pump. The pump placement appears to have a challenging learning curve. Studies have shown that it is possible for the surgeon to gain experience in this matter and to place and be able to use the pump during perfusion with reasonable complication rates after placing at least 25 chemotherapy pumps [24]. Chemotherapy perfusion technique via hepatic arterial chemotherapy pump needs a multidisciplinary approach that includes expertise in hepatobiliary surgery, medical oncology, interventional radiology, and nuclear medicine. Total hepatic arterial infusion pump (HAIP) cases and results from experienced centers confirmed that this method is safe and is associated with excellent tumor response rates. In the first-line setting for initially unresectable CRC liver metastasis, data from the randomized phase 3 trials of HAIP alone suggest an overall tumor response rate of approximately 40–50%. The response rates from the phase 1/2 trials of HAIP in combination with modern systemic chemotherapy are far higher, ranging from 64% to 100%. In patients who have received prior chemotherapy, modern chemotherapy combined with biologic agents produces response rates between 20% and 35%. HAIP in combination with systemic therapy in patients who have progressed on systemic therapy alone achieves tumor response rates ranging from 62% to 85%. Although at low rates, HAIP may downstage the initially unresectable tumors, creating a chance of resection. Resection of colorectal cancer liver metastases prolongs survival and is the only chance that offers a cure. However, 80% of patients on long-term follow-up may develop disease recurrence after liver resection. Approximately one-third of the patients may develop recurrence in the liver alone. Adjuvant HAIP offers the potential to reduce the hepatic recurrence rate after resection of colorectal liver metastases [25, 26].

According to the consensus statements announced by Karoliconas et al. after their meeting in Toronto with the participation of representatives from experienced centers in Canada and the United States [27];

(a) Hepatic arterial infusion pump chemotherapy is recommended to be given in combination with systemic chemotherapy.
(b) HAIP chemotherapy should be offered in experienced centers with the multidisciplinary program that includes expertise in hepatobiliary surgery, medical oncology, interventional radiology, nursing, and nuclear medicine.
(c) HAIP chemotherapy in combination with systemic therapy should be considered in patients with initially unresectable CRLMs who have progressed on the first-line systemic treatment. In addition, HAIP chemotherapy may be used as the first-line treatment in patients with initially unresectable CRLMs.
(d) HAIP chemotherapy is not recommended in the setting of extrahepatic disease.
(e) HAIP chemotherapy in combination with systemic therapy is an option for selected patients with resected CRLMs [27].

Medical Treatment in Colorectal Liver Metastasis

Until the early 2000s, there were limited treatment regimens for advanced colorectal cancer. Until these years, 5-fluorouracil (5-FU) was used alone or in combination with other agents as the main treatment agent for patients with advanced CRC. 5-FU is a fluorinated pyrimidine and acts by inhibiting thymidylate synthase, which plays a role in the production of thymidine nucleotides essential for DNA synthesis. 5-FU is often used with leucovorin (LV). LV increases the binding of 5-FU to thymidylate synthase. Besides, it increases inhibition of DNA synthesis and the antitumoral effect of 5-FU. The treatment combination of 5-FU and LV is associated with improved tumor response rates compared with 5-FU alone (23% vs. 11%, respectively) with median survival of 11.5 months versus 11 months, respectively. While this combination of treatment increased tumor response rates, it did not contribute significantly to median survival [28]. Continuous intravenous infusion administration of 5-FU has been developed to enhance its effect. This way of administration significantly increased the tumor response rate to 22% and resulted in a modest increase in the median survival with over a year [29]. Irinotecan, a topoisomerase I inhibitor, offers a mechanism of action different from 5-FU in the treatment of CRC. Topoisomerase I is an enzyme required for the unwinding of DNA during replication. Irinotecan binds to the DNA/topoisomerase-1 complex and leads to DNA strand breaks and tumor cell death [30]. Irinotecan was used as the first-line treatment alone or as the second-line treatment in patient groups after the failure of the first-line treatment with 5-FU. Phase-3 studies were conducted upon the success it achieved. These studies showed that its use combined with 5-FU-based infusion in patients after the failure of the first-line 5-FU-based regimen provided a survival advantage. The success rate of irinotecan treatment in 5-FU-resistant patients with untreated CRC led to its use in combination with 5-FU/LV treatment. The triple combination of 5-FU, LV, and irinotecan has become the first-line treatment in patients with stage IV colorectal cancer [31, 32]. In a multicenter, large-scale controlled, randomized study conducted by Saltz et al., three main treatment regimens were compared with each other. Treatment protocols using bolus 5-FU/LV, irinotecan/bolus 5-FU/LV, and irinotecan alone were examined. The tumor response rate in the irinotecan/5-FU/LV treatment group was observed to be almost twice that of the 5FU/LV treatment group with the median survival of 13.3 months versus 15.9 months for 5FU/ LV versus irinotecan/5-FU/LV. The risk of death at any time during the treatment of irinotecan/5-FU/LV decreased statistically significantly by 21% compared to the 5-FU/LV treatment alone ($p = 0.003$). Using irinotecan in combination with 5-FU/LV resulted in a reduction in tumor size and regression, as well as a suppressive effect on long-term tumor growth. Based on the results of studies, the combination regimen of irinotecan/5-FU/LV (FOLFIRI) has been accepted as the standard first-line treatment in initially unresectable CRLM cases [33]. Oxaliplatin, a cytotoxic agent belonging to the diaminocyclohexane platinum family, produces a synergistic effect when added to 5-FU/LV treatment in metastatic CRC treatment. In their study combining oxaliplatin with 5-FU/LV, De Gramont et al. have found that the oxaliplatin/5-FU/LV combination yielded a

tumor response rate which was twice that of the use of 5-FU/LV alone. It was found that while 5-FU/LV produced a tumor response rate of 23.6%, this rate was 54.4% in the combination of oxaliplatin and 5-FU/LV in patients with isolated CRLM. This high response rate increased the likelihood of curative liver resection. Oxaliplatin/5-FU/LV combination (FOLFOX) has taken its place as the standard approach in the first-line treatment due to this success rate [34]. In a randomized, controlled phase-3 study conducted by Colucci et al., previously untreated patients with advanced CRC were divided into two groups to receive FOLFIRI and FOLFOX4 treatments. While 178 patients received the FOLFIRI regimen, 182 patients received the FOLFOX4 regimen. 72% of patients in the FOLFIRI treatment group and 73% of the FOLFOX4 treatment group had primary colon cancer with liver metastasis. The 1-year survival rate was 55% and 62% in FOLFIRI and FOLFOX4 groups, respectively. The median survival was 14 and 15 months for patients in FOLFIRI and FOLFOX4 groups, respectively. There was no statistically significant difference. However, no difference was observed in the response rate. The significant difference between the two groups was seen in the toxicity. Thrombocytopenia and neurological toxicity were more common in the FOLFOX group. As neurological toxicity, mainly cold-sensitive dysesthesia or paresthesia was observed. Both treatment protocols were found to be equally effective regarding overall survival and tumor response rates and were considered to be a standard approach for the first-line treatment [35]. Hsu et al. conducted a study comparing postoperative chemotherapy regimens in patients with synchronous CRLM. Only patients who underwent curative resection of primary CRC and liver metastasis were included in this study. 5-FU/LV was administered in group 1, FOLFIRI in group 2, and FOLFOX in group 3 following R0 resection. At the end of the study, the median disease-free survival rate was found to be 14.5, 20.8, and 18.9 months in the 5-FU/LV group, FOLFIRI group, and FOLFOX group, respectively. It was underlined that irinotecan and oxaliplatin-based chemotherapy regimens were beneficial for patients with synchronous CRLM after R0 resection [36]. R0 resection is the treatment modality that provides a survival advantage most in CRLMs. There are three ways to follow during this surgical treatment. These may be classified as classical colorectal-first approach, simultaneous-combined approach, or reverse approach-liver first approach. The surgical approach at this point is related to the area which is at the forefront oncologically and symptomatically and the condition of the patient. If possible, performing surgery in the first plan avoids giving excessive chemotherapy. Irinotecan and oxaliplatin-based chemotherapy regimens and FOLFIRI and FOLFOX contribute significantly to survival. However, irinotecan-based therapy is associated with hepatosteatosis at higher rates, especially if the patient has obesity and diabetes mellitus, and oxaliplatin-based therapy is associated with vascular injury (sinusoidal obstruction, microvascular injury, nodular degenerative hyperplasia, long-term fibrosis). The injury of normal liver tissue which is caused by chemotherapeutic agents used postoperatively and preoperatively may also lead to manifestation such as postoperative liver failure [37]. Fluoropyrimidine-based hepatic arterial infusion chemotherapy results in higher tumor response rates in liver metastases and does not have toxic effects on

extrahepatic organs compared to systemic chemotherapy. Besides, it protects the healthy parenchyma of the liver. The portal vein and hepatic arteries provide the blood supply of the liver. Liver metastases derive most of their blood supply from the hepatic artery, whereas normal liver tissue is primarily supplied by the portal vein. This condition leads to the cytotoxic effect on metastases during the locoregional chemotherapy performed via the hepatic artery while sparing normal liver tissue. As such, the toxic effects of systemic irinotecan and oxaliplatin-based regimens on the liver may be reduced [38]. 5-FU-based chemotherapy has been shown to increase survival in patients with synchronous colorectal liver metastasis. Liu et al. compared patients who received FOLFOX and FOLFIRI treatment after liver resection with the group receiving 5-FU/LV-based chemotherapy in patients with metachronous liver metastasis. Disease-free survival was found to be 34.3 months in FOLFOX and FOLFIRI group and 14.2 months in the 5-FU/LV group ($p = 0.022$). The median survival was 54% in the FOLFOX/FOLFIRI group compared to 34.6% in the 5-FU/LV group. FOLFOX and FOLFIRI chemotherapy protocols following surgery of metachronous liver metastasis provide significant benefit in disease-free survival and median survival than 5-FU/LV chemotherapy [39]. Options for targeted small molecular and antibody therapies have recently been raised in the treatment of CRC. Autophosphorylation of epidermal growth factor receptors (EGFR) causes activation in the cellular pathways. Thus, while cancer cells proliferate, the apoptosis mechanism stops, and invasion and metastasis are activated, neovascularization is increased. Cetuximab is an IgG1 monoclonal antibody. It targets specifically EGFR and binds competitively to EGFR receptors and other ligands. Thus, it inhibits cellular pathways of tumor cells trying to induce angiogenesis and metastasis and prevents them from stimulating cell proliferation [40]. Garufi et al. used chronomodulated irinotecan, 5-fluorouracil, leucovorin, and oxaliplatin (chrono-IFLO) plus cetuximab in their prospective phase-2 study (POCHER) that they carried out for CRCMs. A high tumor response rate was obtained. Based on the data, liver resection was performed in 60% of the patients with this treatment option. The addition of targeted therapies to conventional chemotherapy regimens increases the chance of resection for initially unresectable liver metastases [41]. In their CELIM study, Folprecht et al. added cetuximab to FOLFIRI and FOLFOX regimens to increase neoadjuvant chemotherapy efficacy for patients with initially unresectable liver metastases. Patients with ≥5 colorectal liver-only metastases who do not have any extrahepatic spread and were considered unresectable were enrolled in the study. Seventy patients had K-RAS codon 12/13/61 wild-type tumors and 29 patients had tumors with K-RAS mutations. The patients were divided into two separate groups. FOLFIRI/cetuximab group and FOLFOX6/cetuximab group consisted of 53 patients. The chances of liver resection were found to be almost the same in both groups. The R0 resection rate was 38% in the FOLFOX6/cetuximab group and 30% in the FOLFIRI/cetuximab group. The rate of patients in both groups that may be treated with R0/R1 resection and radiofrequency ablation method was 46%. The combination of chemotherapy with cetuximab yielded a higher rate of tumor responses than conventional chemotherapy regimens and increased the chance of liver resection. The disease-free survival was 9.9 months and the median 5-year

survival was 46.2% for R0 resected patients. The addition of cetuximab to both FOLFOX/FOLFIRI regimens creates the chance of resection in initially unresectable patients who are not suitable for surgery and improves overall survival. Both treatment protocols appear to be appropriate regimens for patients with K-RAS wild-type mutations, as this patient group had a better response rate [42, 43]. Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF). Its concomitant use with 5-FU-based chemotherapy options has recently become one of the treatment options. Gruenberger et al. examined the patients with initially unresectable colorectal cancer liver metastases, whom they divided into two groups, by adding bevacizumab in addition to 5-fluorouracil/folinic acid, oxaliplatin (FOLFOX-6) or 5-fluorouracil/folinic acid, oxaliplatin, and irinotecan (FOLFOXIRI) treatments in the OLIVIA study. The overall tumor response rates were 81% in the bevacizumab-FOLFOXIRI group and 62% in the bevacizumab-mFOLFOX-6 group after the treatment. The overall resection rate was 61%, and the R0 resection rate was 49% in the bevacizumab-FOLFOXIRI group. The overall resection rate was 49% and the R0 resection rate was 23% in the bevacizumab-mFOLFOX-6 group. The median progression-free survival was 18.5 months in the bevacizumab-FOLFOXIRI group and 11.5 months in the other group. The treatment combination of bevacizumab-FOLFOXIRI had a higher tumor response rate, resection rate, and disease-free survival time compared to the bevacizumab-mFOLFOX-6 combination [44]. NCCN and ESMO guidelines recommend the most effective treatment with concomitant targeted agents (bevacizumab/cetuximab for patients with K-RAS wild-type) and combined chemotherapy administration. The chance of resection is increased for initially unresectable liver metastases after the use of targeted agents in combination with chemotherapy agents. However, median survival and disease-free survival rates are increased [45, 46].

Predictive Factors and Clinical Risk Scores

Surgery is the most effective treatment modality for patients with isolated CRC liver metastases. Liver resection is safe and remains the only curative treatment option. The expected life expectancy in the natural course of the disease without hepatic resection is 6–12 months. Life expectancy with chemotherapy treatment is only 12–18 months. These anticipated short survival times emphasize the importance of hepatic resection. Fong et al. identified risk factors for recurrence based on the data obtained by liver resection and subsequent follow-up of 1001 patients with CRLM in their study. The median 1-year survival rate after liver resection was 89%, 3-year 57%, 5-year 37%, and 10-year 22%. They identified seven poor predictive factors that increased the likelihood of recurrence after liver resection: positive surgical margin ($p = 0.004$), extrahepatic disease ($p = 0.003$), node-positive primary tumor ($p = 0.02$), disease-free interval from primary tumor to the diagnosis of liver metastasis <12 months ($p = 0.03$), number of liver metastases >1 ($p = 0.0004$), largest metastasis >5 cm ($p = 0.01$), and carcinoembryonic antigen (CEA) level >200 ng/ml ($p = 0.01$). The last five criteria may be determined in the preoperative period.

The risk score may be found by assigning one point to each criterion. The total score is highly predictive ($p < 0.0001$). Favorable outcomes may be expected in patients with a score of up to 2. Alternative treatments may be considered in patients with a score of 3 or above [47]. The clinical risk score (CRS) developed by Fong et al. was defined in 1999, and the modern chemotherapeutic agents and targeted therapies which are being used today were not being used at that time when patients were treated. Owing to today's technological developments, more advanced liver resections may be performed and longer disease-free time, and prolonged survival time may be achieved with current neoadjuvant/adjuvant medical regimens. According to the results from the MIROX study which was conducted in France, the 5-year overall survival was 67.11% and the 5-year disease-free survival was 35.4%. Considering CRS, the survival rates with the current chemotherapy regimens were found to be higher compared to the rates of Fong. CRS criteria of Fong are still used effectively today, but the MIROX study showed that CRS has a poor correlation with overall survival. Identifying strong prognostic scores will help to determine the patients with isolated CRC liver metastasis that will benefit from resection [48].

Liver Surgery

About half of the patients with CRC develop synchronous or metachronous metastasis. Most of them are liver metastases. The majority of CRC patients who develop liver metastasis are deemed to be unresectable due to intrahepatic and/or extrahepatic extensive disease. Only 20% of CRLMs are suitable for resection. The mortality rate is less than 5% during the hospital stay, including major resections, in experienced centers. The 5-year survival of CRLM patients may increase from 40% to 50–60% with modern surgical and oncological approach owing to the advanced technology and surgical techniques [49, 50].

The decision of resectability of liver metastasis can be made by examining three main subjects: technical, physiological, and medical. Technically, it is crucial to reach the R0 level with microscopically negative surgical margins and preserve sufficient liver parenchyma that can be regenerated in the meanwhile. The future remnant liver should include two adjacent segments with preserved vascular circulation and biliary drainage. A clear distinction must be made between the resectability of the tumor and the operability of the patient. The operability is that the patient may undergo major abdominal surgery and overcome the healing process physiologically and medically. From an oncological perspective, liver-only metastatic lesions and lesions that already exist but show minimal growth while on perioperative treatment should be resected. However, patients with controllable extrahepatic spread (such as portal lymph nodes, small lung metastases) should also be operated, but it should be kept in mind that these patients have a higher chance of recurrence and should take chemotherapy during the postoperative period. In these patients, if the tumor is still anatomically within the resection margin, a chance of resection should be given. Patients who develop new liver metastases on treatment or who have extrahepatic metastasis during the interval period should not be operated until the systemic disease is under control [37] (Fig. 27.1).

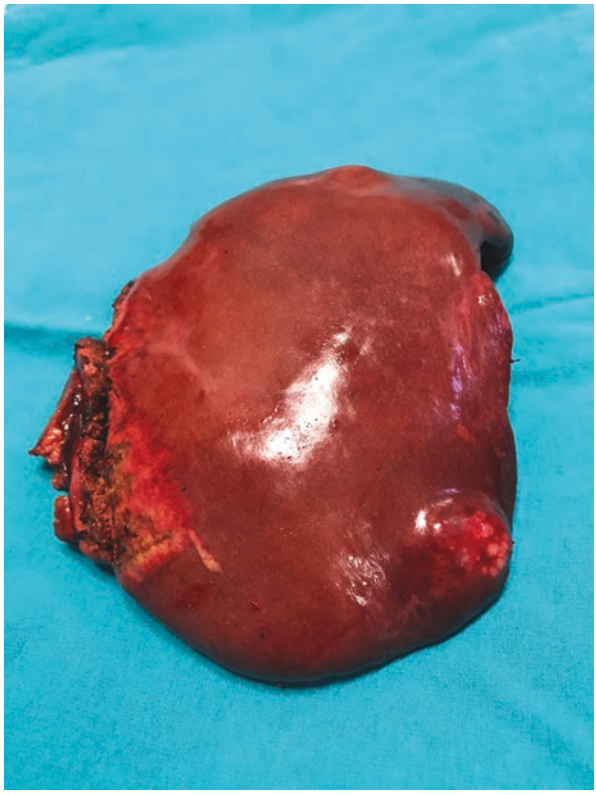

Fig. 27.1 Macroscopic view of the right hepatectomy material of a patient with multiple metastases in the right lobe of the liver

Colorectal Cancer with Synchronous Liver Metastasis

Patients with CRLM present with advanced stage disease at the time of diagnosis and only receive systemic chemotherapy. Surgical resection should be performed to provide a cure in patients with an adequate tumor response. There are three main approaches in patients with liver-only metastatic CRC: colorectal-first, combined or simultaneous colorectal, and liver-first surgery. The colorectal-first surgery is the classical approach. The two-stage approach is applied in patients with newly diagnosed colorectal cancer and synchronous resectable liver metastases. First, the colorectal surgery is performed and the primary disease is eliminated, and then, delayed liver resection is performed by administering intermediate chemotherapy. The colorectal-first approach is the standard method that precludes simultaneous resection and reverse approach applied in similar situations. When CRC with synchronous liver metastasis is detected in case of emergency, if there is obstruction or perforation, simultaneous resection should not be performed by assessing potential complication risks. With this classical approach, patients will be under less physical stress than simultaneous combined resection. Patients can be expected to have less mortality and morbidity with a two-stage colorectal-first approach [51].

Nevertheless, Chen et al. compared the results of two groups of patients treated with a total of 2204 simultaneous and two-stage resections in many centers using the following parameters in a study [52];

(a) Operative Factors: Operation time in minutes, blood loss in millimeters, hospitalization time in days.
(b) Postoperative Complications: Wound infection, hemorrhage, anastomosis leakage, pulmonary infection, pleural effusion, biliary leak, respiratory complications.
(c) Survival: Overall survival has been defined until death or last follow-up.

As a result of the study, it has been shown that the surgery time of simultaneous resection was almost the same as that of staged resection and there was no significant difference between the blood losses in both procedures. However, it was observed that the hospitalization time was shorter in the simultaneous group compared to the group with staged resection. While a total of 301 complications were experienced in 768 patients who had simultaneous resection, 419 complications occurred in 973 patients undergoing staged resection. In this way, it has been demonstrated that the complication rates in the group who had simultaneous resection were lower than that of the group who had staged resection (OR, 0.71; 95% CI, 0.57–0.88, $p = 0.002$; heterogeneity $p = 0.34$). When both groups were compared regarding overall survival, there was no statistically significant difference, 1-year (OR, 0.77; 95% CI, 0.51–1.16, $p = 0.21$; heterogeneity $p = 0.84$), 3-year (OR, 1.12; 95% CI, 0.85–1.47, $p = 0.43$; heterogeneity $p = 0.38$), and 5-year (OR, 1.14; 95% CI, 0.86–1.50, $p = 0.37$; heterogeneity $p = 0.53$). The benefit of liver resection in patients with CRLM is known. The timing of liver resection is controversial. Performing either simultaneous or staged resection depends on the symptoms, location, and extent of the disease, the performance status, and comorbidities of the patient. The treatment strategy may be made by considering all these parameters [51, 52]. Li et al. performed simultaneous resection in 1116 patients and staged resection in 1608 patients in 19 non-randomized controlled trials involving a total of 2724 patients with synchronous CRLM. Meta-analysis showed that shorter hospital stays and lower total complication rates were observed in patients undergoing simultaneous resection compared to the patients undergoing staged resection ($p < 0.001$). There was no statistically significant difference in other parameters such as wound infection, leakage of bile, pleural effusion, perihepatic abscess, and liver failure. There was no statistically significant difference regarding the 1-, 3-, and 5-year overall survival rates, as well as the 1-, 3-, and 5-year disease-free survival rates between both groups. Simultaneous resection is safe and efficient and may be the reason for the preference for avoiding a second laparotomy [53]. Feng et al. compared simultaneous resection and staged resection in an examination including 22 studies with a total of 4494 patients. It was pointed out that the morbidity rates increase as the number of liver metastases increase. The morbidity rate was 13.8% in the staged resection group and 17.2% in the simultaneous resection group in patients with ≤ 3 metastases. This difference was not statistically

significant. The morbidity rate was 50.9% in the staged liver resection group and 49.4% in the simultaneous resection group with >3 metastases. Both groups were almost the same in morbidity [54]. Mentha et al. have published a prospective study involving the reverse approach which consists of systemic chemotherapy followed by liver resection prior to resection of the primary colorectal cancer in patients with synchronous liver metastasis. The rationale behind their studies was to be able to act without fear of progression in liver metastasis, while neoadjuvant radiotherapy was given especially in advanced rectal cancers. They treated 16 patients with synchronous colorectal liver metastases with a morbidity rate of 19% by the liver-first approach. The overall survival rates at 1, 2, 3, and 4 years were 85%, 79%, 71%, and 56%, respectively [55]. In another prospective study they conducted, 30 of 36 patients were treated with R0 resection. In this study, the 1-, 2-, 3-, 4-, and 5-year overall survival rates were reported to be 100%, 89%, 60%, 44%, and 31%, respectively. The median survival rate was 44 months. Based on the results of the study, they reported that the liver-first approach was safe and feasible [56]. Brouquet et al. also treated 72 patients with the classical method, 27 with the reverse approach, and 43 with the combined approach and have found that all methods were associated with similar outcomes in terms of postoperative mortality, morbidity rates, and 3- and 5-year overall survival rates. The liver-first approach may be an option for patients without intestinal symptoms. However, studies on this approach are few and have been carried out with groups with a small number of patients. The treatment option in patients with synchronous colorectal cancer liver metastasis depends on the patient's symptoms, condition, and comorbidities. The surgeon may opt between these methods, taking into account his/her own experience and the conditions of the center where he/she works. The outcomes of all these treatment options are almost similar [51, 57].

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Liver Resections in Metastatic Colorectal Cancer

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Features of Tumor Spreading in Colorectal Cancer

The colonic cancers do metastasis similar to that of other cancers. The cancer focus gets grown-up by direct invasion. Then, entering the lymphatic ducts, cancer cells metastasize to the regional lymph nodes. Cancer cells continue through the lymphatic ways to make distant lymph node metastasis. For hematogenous spread, cancer cells must access into the lumens of venous vessels. After gaining entry into the lumen, cancer cells reach the organs on the venous drainage system and settle in the lumen of capillaries of the target organ, making organ metastasis [1–3].

The venous drainage of the colon is joined the portal vein through superior and inferior mesenteric veins. As the venous drainage of the colon first passes through the capillary bed of the liver, the most frequently seen metastases are the liver metastases in colon cancers. However, the situation is different for rectal cancers. In the rectum, the superior rectal vein is drained by the inferior mesenteric vein, thus, portal vein. But, middle and inferior rectal veins are drained by the internal iliac veins, thus systemic venous system. However, in the rectum, there are shunts between these two. Therefore, the cancer cells pass to the systemic venous circulation through the middle and inferior rectal veins, reaches to the right atrium and ventricle and the capillary bed of the lungs, making the lung metastasis. As a result, the cancer of the rectal parts drained by the middle and inferior rectal veins most frequently metastasizes to the lungs. But, there are collaterals between the superior rectal vein with middle and inferior rectal veins and cancer cells might use these collaterals. Therefore, as well as the cancer of upper rectum might metastasize to

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the lungs via hematogenous way, middle and lower rectum tumors might metastasize to the liver [1, 4, 5].

Colon cancer exceeds the colon wall by growing up and invades the surrounding tissues. This process might result in two events: either invade the neighbor organs or peritoneal seeding occurs. Ureter, uterus and/or vagina might be invaded by direct invasion of colorectal cancer. The treatment approaches in the presence of these situations will be discussed in urology and gynecology chapters. The colorectal cancers might also spread to the other parts of the intestines by direct invasion. Intraperitoneal seeding might result in metastatic foci at anywhere within the intraperitoneal cavity, omentum, intestinal surface, or anterior abdominal wall. These metastatic lesions might cause mechanical intestinal obstruction which might occur in one part of the intestinal segment or more [6–8].

Ways to Occur Liver Metastases

Metastatic liver cancer occurs because of the metastasis of a primary tumor of another organ to the liver. The colorectal cancers most frequently metastasize via the portal vein to the liver by the hematogenous route. Plenty of primary tumors of other organs might metastasize to the liver, too. Lung cancer mostly metastasizes to the liver via a systemic route. The locally advanced cancers of the neighbor organs like gastric and gallbladder cancers might metastasize to the liver by direct invasion [9–12].

Clinical Features of Metastatic Liver Cancer

The secondary liver cancer term is also used for metastatic liver cancer. More than 50% of colon cancer patients develop liver metastases during clinical progress. The risk for liver metastasis development is reported to be related to the stage of colorectal cancer. For example, the risk for stage 3 colorectal cancer is sevenfold more than that of the stage 1 disease. In the beginning, symptoms are obscure or the patient is asymptomatic. During the asymptomatic period, the diagnosis can be made using periodic US, CT imaging, or measuring the CEA (carcinoembryonic antigen) levels on follow-up [13–16].

The liver metastases of the colorectal cancers have a growth tendency by time. The doubling time is the term for the time during which the tumor grows up twofold. While the doubling time is 86 (30–192) days for the occult metastases, it was reported to be 155 (48–321) days for the overt metastases. Weakness, weight loss, right upper quadrant abdominal pain, abdominal distention, jaundice, and darkening of the urine because of jaundice are among the symptoms [13, 17, 18].

Diagnosis in Metastatic Liver Cancer

The diagnosis of the liver metastasis might be made incidentally during the screening for other diseases or, in symptomatic patients, with radiological imaging. Ultrasound (US) is one of the most frequently used noninvasive imaging methods.

The US can give the information about the location, size, and formation of the liver mass and whether it is homogenous or heterogeneous, cystic or solid. US imaging depends on the experience of the radiologist. The contrast computed tomography (CT) reveals well-quality images, but kidney functions must be assessed by measuring the creatinine level before contrast use. If the creatinine level is high, the contrast agent might damage the kidneys. Also, as the contrast agent involves iodine, it might cause a thyroid storm in hyperthyroid patients. Thus, the order of thyroid function test is suggested. CT images are objective and can be interpreted by different physicians. Magnetic resonance imaging (MRI) is another method to image liver metastases. It can give more detailed information on the metastases. Positron emission computed tomography (PET/CT) is also used for searching metastatic foci, and it can show missed metastases in the body. Tumor markers are used in the diagnosis of secondary liver metastasis of the colorectal cancers. CEA and CA-19-9 are among these tumor markers. The localization, size, and number of the metastases are important in treatment. As the treatment approaches to the metastases gathered in the one segment or scattering diffusely on the liver are different, the detailed information on the metastases must be known [19–21].

Management of Colorectal Liver Metastases

The gold standard for liver metastases of the colorectal cancers is standard surgical resection. Radiofrequency ablation therapy is another option. Neoadjuvant chemotherapy can be used for micrometastases or downsizing unresectable metastases to resectable ones. Adjuvant chemotherapy is used for the treatment of residual microscopic disease. If the patients have colorectal metastases confined to the liver only, the patients can benefit from selective internal radiation therapy [22]. The information of interventional radiologic procedures are given related chapters of the book.

Surgical Treatment Options in Liver Metastases

Resection is accepted as the standard treatment of the colorectal cancer liver metastases. Advancements in operative techniques for liver resection, downsizing of the metastases using chemotherapy, providing liver hypertrophy before resection, and presence of various ablation techniques expanded the indications for liver surgery [23].

At least 25–30% functional liver tissue must have remained after resection for the metastases. Prognostic risk factors include the presence of plenty of metastases in number, being of the metastases in big size, being of the primary tumor in the advanced stage, and being the tumor markers (CEA, CA 19-9) at high levels [24].

The number of metastases is not a contraindication for resection. The extrahepatic disease might be intra-abdominal or intrathoracic. Today, the pulmonary metastases coexisting with colorectal liver metastases (CRLM) can be treated successfully in selected patients. Again in the selected CRLM patients with the intra-abdominal extrahepatic disease, cytoreductive surgery along with chemotherapy

has promising results. In the cases with liver pedicle lymph node invasion, aggressive surgery might be curative.

The inoperability criteria of liver lesions are presence of incurable primary tumor, intrathoracic widespread invasion, locoregional recurrence, uncontrollable peritoneal dissemination, presence of bone or central nervous system metastases, invasion of one liver pedicle along with contact with contralateral branch, invasion of portal confluence, invasion of the all portal veins, insufficient liver remnant volume after resection, and extensive nodal disease like retroperitoneal or mediastinal nodes [25–29].

In the presence of node-positive tumor, there is an increased risk of recurrence following liver resection in the following situations: If the liver metastasis has developed within less than 12 months following the diagnosis of the primary tumor, there are more than one metastases in the liver, the metastatic lesion is bigger than 5 cm, and CEA level is higher than 200 ng/mL [30].

Liver Resection for Metastases of Colorectal Cancer

The colorectal liver metastases can be excised by either anatomical or non-anatomical resection. The anatomical resections can be chosen for big and deeply located metastases. Also, the anatomical resection is the treatment of choice for situations where plenty of metastases are located in one part of the liver. Anatomic resections include segmentectomy, multi-segmentectomy, sectionectomy, lobectomy, and extended lobectomy. Non-anatomic resections involve wedge resections (Fig. 28.1) and metastasectomy (Fig. 28.2). The liver resections can be performed along with colon resection simultaneously. If so, the liver resection is performed at first and then colon resection. Following the colon resection, the hepatic cut surface is checked for bleeding and bile leak. In the two-stage approach, the colon and liver tumors are resected at different times.

Segmentectomy is the resection of the liver part supplied by a segmenter branch of the portal vein. It is important to know and understand the branching pattern of the portal vein. The most commonly used classification for understanding the segmental anatomy of the liver is Couinaud classification. The first line branches of the portal vein are left and right main branches. The second line branches are right paramedian sectoral, right lateral sectoral, left umbilical, and caudate branches. The third line branches are the segmenteric ones. Care must be taken during transection of the third branches of the right portal vein. While the right anterior portal branch gives branches to the segments 5 and 8, the right posterior portal vein gives branches to the segments 6 and 7. However, it was shown that each segment has two or more of the third branches. Moreover, there might be plenty of variations in the branching of the portal vein. Thus, for each case, portal vein anatomy must be known by using preoperative detailed imaging studies and confirmed with preoperative USG. Indications for segmentectomy are being of the metastatic tumor restricted to one segment on preoperative radiological examination and having sufficient liver functions. Criteria for a sufficient liver

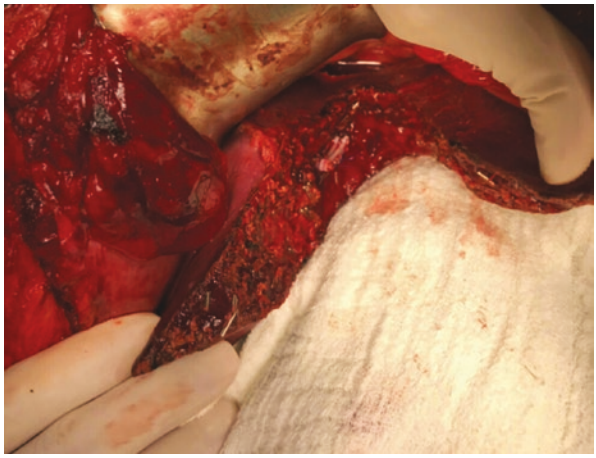

Fig. 28.1 Liver wedge resection

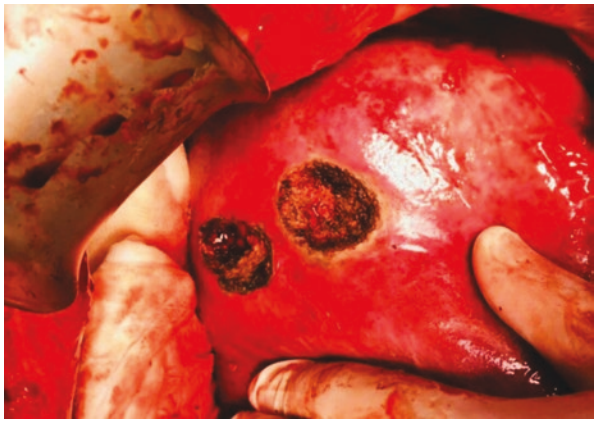

Fig. 28.2 Metastasectomy for colorectal liver metastases

function are the absence of ascites, serum total bilirubin level less than 1 mg/dL and less than 30% indocyanine green capture ratio on 15 min indocyanine (ICG-R15) test. Multi-segmentectomy is the term for the resection of two or more of the liver segments. If the metastasis invades two neighboring segments, these segments can be resected en bloc. But, there are metastases in the segments which are not neighbor between each other; anatomical resection of these segments can be performed separately. The liver has four sections named as the right posterior (segment 6 and 7), the right anterior (segment 5 and 8), the left medial (segment 4a and 4b), and the left lateral (segment 2 and 3). The anatomical resection of these each section are multi-segmentectomy and called sectionectomy. The imaginary line connecting the middle hepatic vein (the left margin of inferior vena cava in some resources) and the long axis of the gallbladder is called Cantlie line. This line divides the liver into the right and the left functional half. While the right hepatectomy (or hemihepatectomy) involves the resection of the segment 5, 6, 7, and 8, the left hepatectomy involves the resection of 2, 3, and 4. The umbilical

fissure divides the liver into anatomical right and the left lobes at the falciform ligament. The right lobectomy (extended right hepatectomy or right trisegmentectomy) involves the resections of all segments lateral to the umbilical fissure (segments 4, 5, 6, 7, 8 and sometimes segment 1 (caudate lobe)). The extended left hepatectomy (or left trisegmentectomy) involves the resection of all segments medial to the umbilical fissure (segments 2, 3,4,5 and 8). The left lobectomy, also known as the left lateral segmentectomy, involves only the resection of the segments medial to the umbilical fissure (segments 2 and 3) [31–36].

Preoperative portal vein embolization provides an increased liver remnant following the resection. This method is mostly used when extended right hepatectomy is planned. Postoperative liver failure is a serious and potentially fatal complication following the surgical resection for primary and secondary liver cancers. The mortality can be attributed to the size and function of the remnant liver parenchyma for most of the cases. Portal vein embolization (PVE) can be performed either by means of surgical or percutaneous transhepatic approach. PVE is performed successfully by using either a single agent or a combination of the agents: particles (polyvinyl alcohol (PVA) or trisacryl gelatin microspheres), n-butyl cyanoacrylate (NBCA), absorbable gelatin, ethanol, fibrin glue, and sclerosing agents (e.g., Aethoxysklerol/air foam). Embolization must be permanent and as possible as distally located. Proximally located or fluid embolization results in restriction of the liver hypertrophy by causing the formation of intraparenchymal shunts. Following the embolization with the absorbable gelatin, recanalization of the portal vein occurs within as short as 2 weeks. Madoff et al., in their series of 44 patients, found that the right portal embolization extended to as far as the segment 4 with trisacryl gelatin microspheres (100–700 μm) resulted in a more bigger hypertrophied liver remnant compared to that of PVA particles (355–1000 μm). For PVE, the endpoint for the embolization is complete stasis. Cessation of the embolization before that point might lead to insufficient embolization and vascular recanalization, which restrict hypertrophy development [37–44].

ALPPS (associating liver partition and right portal vein ligation for staged hepatectomy) method provides faster liver hypertrophy. In this method, along with the right portal vein ligation (PVL), in situ liver splitting (ISLS) is performed intraoperatively. Using this method, it was reported that hypertrophy of the remnant liver up to 40 to 80% can be obtained at the end of 14th day. Nowadays three modified ALPPS (the left, the rescue, the right ALPPS modifications) are described:

Modified left ALPPS:

Step (1): Anatomical segmentectomy or restricted resection of the right anterior and posterior sections, left PVL and ISLS between the right and left livers.

Step (2): Consists of completing the left hemihepatectomy with resection of segment 1.

Modified rescue ALPPS:

Step 1: ISLS between the right and left hemilivers along the main portal fissure. The right portal vein has already been "ligated" by radiologically.
Step 2: Completing the right hepatectomy.

Modified right ALPPS:

Step 1: Left lateral sectionectomy, ligation of the posterolateral branch of the right portal vein, few limited or anatomical resections of the left medial, right anterior sections and caudate lobe. ISLS along the right portal fissure is facilitated with a right modified hanging maneuver positioning the lower end of hanging tape between the anterior-posterior right pedicles.
Step 2: Completing the right posterior sectionectomy.

These procedures can be performed in suitable patients [45–47].

Salvage' ALPPS involves the transection along the liver parenchyma of which hypertrophy is planned. This procedure is described for the patients who have insufficient remnant liver hypertrophy following the PVE. Following the PVE and ALPPS performed consecutively, the mean remnant liver hypertrophy rate varies between 57% and 65% [48–51].

The main aim of the liver resections is R0 resection in which the surrounding tissue is clear of the tumor. In R1 resections, there is a remnant tumor on the surgical margins. In a clinical study, R1 resections were reported to have a higher hepatic and surgical margin recurrence risk without no negative effect on survival. Thus, R1 resection possibility should not be considered as a contraindication for surgery as the chemotherapy is very effective [52].

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Liver Transplantation for Non-resectable Colorectal Cancer Liver Metastasis

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Overview of Colorectal Cancer Liver Metastasis

The incidence of colorectal cancer (CRC) is gradually increasing especially in western countries. In worldwide, CRC is the second most common cancer in woman and third most common cancer in man [1]. According to the National Cancer Institute's surveillance, epidemiology, and end results program, CRC incidence was decreased 5% in the USA between 2000 and 2013, but the incidence of CRC in patients younger than 50 years was increased [2]. Increase in young patients of CRC was also observing in Asian population [3, 4]. Unfortunately, more than 50% of patients with CRC developed liver metastasis. And only 10–30% of these patients are eligible to liver resection [5]. Relapse is observed in most of the patients underwent to liver resection, and 5-year overall survival (OS) of these patients is about to 30–40% [6]. Otherwise, 5-year OS of most patients with non-respectable CRC liver metastases is only 10% [7].

Surgery can provide curative treatment approach for liver metastasis of CRC [8]. Palliative chemotherapy (CT) applications can be used for the patients with liver metastasis of CRC. The 5-year OS rates after the first-line CT is 10% [9]. Most of the disease recurrences are reported in the first 2 years [10]. Median time is gradually increasing for recurrences, especially rectal cancer [11]. Liver is the first organ, where the disease recurrences are seen most commonly, with the rate of 28–45%. The lungs follow the liver with the rate of 17–27%. Multiple recurrences are seen 28–30% of patients [12–14]. There is no difference in terms of survival between liver and lung recurrences [15, 16]. There is only one trial showing better survival results with solitary lung recurrence over solitary liver recurrences [17].

Key findings from current systematic reviews are focused on pattern, stage, and time of recurrent CRC after curative surgery [11]:

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(a) Liver metastases are seen relatively early term of disease in CRCs treated with curative surgery.
(b) Pulmonary metastases are seen relatively late term of CRCs.
(c) After curative surgery, pulmonary metastases are related rectal cancers more than colon cancers.
(d) It is shown that multiple site recurrences are related with right colon cancers.
(e) Advanced stage is significantly related with loco-regional and distant metastasis and decreased disease-free survival.

Treatment Options for Liver Metastasis of Colorectal Cancers

Standard treatment option for the patients with liver metastasis of CRC is surgical liver resection. This offers long-term disease-free survival for these patients. Additionally, surgical resection obtains curative results for some cases [18]. The developments in liver resection techniques, interventional techniques providing liver hypertrophy such as intra-arterial CT or radioactive ablations, and CT agents are the factors making both liver surgery and locally ablative techniques commonly used for liver metastasis of CRCs [18].

The first prospective randomized trial is EORTC CLOOC showing survival benefit of the usage of reception/ablation over the systemic CT alone [19]. In this trial, 119 patients with liver metastasis of CRC were selected, and they included the patients with maximum 4 cm size and up to ten liver metastasis. The comparison was done with medical treatment alone versus medical treatment with radiofrequency ablation. Radiofrequency ablation with open technique was used in most patients, and it was combined with resection. PFS rate at 3 years for combined treatment was 27.6% compared with 10.6% for systemic treatment only (hazard ratio = 0.63, 95% CI 0.42–0.95, p = 0.025). Median progression-free survival (PFS) was 16.8 months (95% CI 11.7–22.1) and 9.9 months (95% CI 9.3–13.7), respectively [19]. In this study, combined treatment approach cured approximately 30% of patients with <10 liver metastasis without extra-hepatic extension. Additionally, it was shown that resection and ablation treatment could affect OS significantly.

In CELIM study, median disease-free survival after conversion treatment and resection was 16.8 months in patients with <5 liver metastasis, but in patients with >10 liver metastasis, it was only 2.5 months. According to CELIM study, the number of liver metastasis is a poor prognostic factor for overall and disease-free survival. Resection of liver metastases provides good long-term survival benefit. When we look at the studies that are focused on factors affecting the long-term overall survival after hepatic resection in metastatic CRC, a number of hepatic metastasis >3, node positive primary, poorly differentiated primary, extra-hepatic disease, tumor diameter > or =5 cm, carcinoembryonic antigen (CEA) level >60 ng/Ml, and positive resection margin were found to be independent predictors of poor survival [20]. Lymph node metastasis, disease-free interval, and CEA level are significant prognostic factors for CRC liver patients [21].

Good long-term overall survival after liver resection of colorectal liver metastasis provocated aggressively used of procedures that increase the resectibility and new developments in this area. Portal vein embolization, portal vein and hepatic vein embolization, and ALLPS (associating liver partition and portal vein ligation for staged hepatectomy) are mostly used procedures to increase the resectibility of liver metastasis. The aim of the portal vein resection is the hypertrophy of the contralateral liver segments [22]. ALLPS procedure includes the portal vein ligation and intraoperative in situ splitting of the liver for more rapid hypertrophy of the contralateral liver segments in a short time [23]. Combination of ablation and resection of metastasis in extensive liver metastasis ensures parenchyma sparing liver resection [24].

Previous Experience for Liver Metastasis of Colorectal Cancers

Indication of the first two liver transplantations of seven liver transplantations was colorectal metastasis in 1963 and 1964 [25]. According to the European liver transplant registry between 1968 and 1995, 1- and 5-year overall survival of 58 patients underwent liver transplantation due to the colorectal liver metastasis was 62% and 18% [26, 27]. Twenty-four of those liver transplantations were performed by the Vienna group, and others were sporadic cases. Vienna group reported the perioperative mortality rate as 30% in their first learning phase of liver transplantations [28]. Most of the patients losses were in early perioperative period, and 44% of the graft losses were not associated with the tumor recurrences; this data were interpreted poor outcome for colorectal liver metastasis. And liver transplantation in patients with liver metastasis of colorectal cancer had been accepted as absolute contraindication [8]. In the same study population, patients without lymph node micrometastasis had long-term survival, and one has survived for more than 22 years after liver transplantation [29]. After this experience, in literature, several case series have reported good long-term outcomes in selected patients [30–33]. Unfortunately, although these results any prospective study focused on liver transplantation for colorectal liver metastasis has been published until Norwegian SECA study.

The Role of Liver Transplantation

Liver transplantation is standard of care for the malign liver tumors (like hepatocellular carcinoma) and liver metastasis of low-grade neuroendocrine tumors [34, 35]. Improvements of patient and graft survival in liver transplantation pushed the transplant centers to review the results of liver transplantation in patients with CRC liver metastasis. For this purpose, in Oslo, Norway, a clinical pilot study, SECA study was designed and approved in 2006 [32].

SECA study was started in Oslo University Hospital and included 21 patients with non-respectable CRC liver metastasis [32]. At first, the study had quite strict inclusion criteria in terms of rules and response to the chemotherapy. But in first

11 months, any patients were included in the study and wider inclusion criteria were approved [36]. At final, inclusion criteria of the SECA study were non-resectable CRC liver metastasis, without extrahepatic involvement and local recurrence, ECOG score 0–1, no more than 10 kg weight loss in the last 3 months, and at least one line of chemotherapy received by patients [32]. Moreover, during the liver transplantation application, chest scan of three patients was negative, and intraoperative lymph node biopsy for evaluation of metastasis was negative. The trial was conducted in 2006 and till 2011, totally 21 patients (13 males, 8 females) with median age 56 included in it. The primaries of those patients were colon for 13 patients and rectum for eight patients. Sixteen of included patients had T3 tumor and three of them were T4 stage. Median liver metastasis number was 8 (range, 2–40), and maximum tumor size was median 4.5 cm (range, 2.8–13). Under all lines of CT, six patients had progressive disease. First line CT was used for nine patients, and second and third line CTs were used for 12 patients. Median follow-up time was 27 months. Additionally, they reported that 1-, 3-, and 5-year OS rates were 96%, 70%, and 60%, respectively. Although the survival data presented good outcome, their results should be interpreted with caution. Firstly, small numbers of patients were evaluated, and they had no control arm. Secondly, tumor recurrences were seen in 90% of patients [37]. For the patients followed over 11 months, tumor recurrence rate was 100% [36]. Median time to recurrence was 6 (range, 2–24) months. Mostly recurrences were observed in lungs (17 patients). After resection of lung lesions, seven of them did not have disease in the lung again within follow-up period [8]. When they evaluated the 16 patients' outcomes, which did not have four negative prognostic factors, they reported that 6- and 7-year OS rates were 60% [38].

NORDIC VII study was phase 3, multicenter trial, and the purpose of it was to compare the application of CT with liver transplantation for the patients had non-resectable liver metastasis of CRC [39]. In this trial, 21 patients in SECA study and 47 patients applied first line CT without hepatectomy were compared. There was no any difference in terms of patients' characteristics. 5-year OS rates for first line CT arm ($n = 47$) and liver transplantation arm ($n = 21$) were 9% and 60%, respectively. Six patients recurred despite the all used standard treatments were evaluated in detail. It was seen that all these patients used 5-FU-, irinotecan- and oxaliplatin-based regimens [40]. Patients were evaluated in terms of KRAS mutation status. Three patients with KRAS mutation had progression after second line CT, and three patients with KRAS-wild type had progression after third line CT (with cetuximab). The median disease-free survival time for these six patients was 3.3 (range, 2.1–12.4) months, while their OS was quite longer than expected. Their median OS was 41 (range, 6–84) months and 5-year OS rate was 44% [40]. For the similar patient group in NORDIC VII trial, median OS was 5.6 months [40]. In NORDIC VII trial, liver transplantation results were significantly better than the KRAS mutated patients who completed second line CT [40].

In a recent retrospective cohort study reporting the experience of 12 patients with colorectal liver metastasis [33], ten of the patients had undergone liver resections and 11 of 12 patients were chemotherapy responders. Median time from resection to transplantation was 41 months (12–97 months). Median number of lesions was 9

and only two patients had tumor diameter larger than 5 cm. According to study, overall 1-, 3-, and 5-year survival was 83%, 62%, and 50%, respectively [33]. Disease-free survival rates at 1-, 3-, and 5-year were 56%, 38%, and 38%, respectively. In this study, patients were highly selected, and interval from resection to liver transplantations was long, but this study also demonstrated that disease-free survival may be obtained [41].

SECA study was designed to determine the OS and DFS after liver transplantation for 15 selected patients with non-resectable liver metastasis of CRC [42]. The inclusion criteria were as follows: (1) non-resectable liver metastasis alone was confirmed with computed tomography, magnetic resonance imaging, or positron emission tomography (PET), (2) minimum 10% CT response rate was obtained according to RECIST criteria, and (3) the time interval between diagnosis and liver transplantation was more than 1 year. After a median 36 months follow-up period, 1-, 3-, and 5-year OS rates were 100%, 83%, and 83%, respectively. The authors reported that six resections due to pulmonary metastasis were done to five patients. Median time from relapse to resection was 21.4 months. Hepatic resection was performed in one patient due to solitary liver metastasis. Resection and radiotherapy were performed in two patients due to lymph node metastasis. Additionally, two patients with oligometastatic disease were included in palliative CT program. Although more favorable patients were selected in the SECA-2 study compared to the SECA-1 study, it is still worth emphasizing in the SECA-2 study that the patients had extensive non-resectable liver metastasis [42]. Despite extensive tumor burden, it is promising that 5-year OS rates were 83%. It should be kept in mind that in patients with non-resectable CRC liver metastasis, the 5-year OS after first line CT is approximately 10% [43, 44]. In these patients, the median survival after second cycle of CT is 10–12 months [45, 46].

The Factors Affecting Long-Term Survival and Recurrence Patterns

Long-term survival-related criteria in liver transplantation in CRC colorectal liver metastases were examined with three different scoring systems [47]. In this comparison, the power of the Fong clinical risk score, total FDG uptake (metabolic tumor volume), and the OSLO score were compared to detect long-term survival. Totally 19 patients from SECA-1 ($n = 14$) and ongoing SECA-2 ($n = 5$) were evaluated. Inclusion criteria were as follows: (1) previously received CT, (2) PET taken 90 days before liver transplantation, (3) ECOG 0–1, and (4) patients with unresectable CRC metastases without extrahepatic disease. According to these comparison criteria, 1-year OS rate for 6 patients with 0–2 Fong clinical risk score (FCRS) was found 100%. Five-year OS rates for the patients with MTV <70 cm^3 ($n = 10$) and the patients with 0–2 Oslo score were 78% and 67%, respectively [47]. The best OS rates were detected for the patients with low FCRS (0–2); however only 30% of trial cohort were in this group. Determining very strict selection criteria would make in fewer patients eligible for liver transplantation.

According to the SECA study, four factors could be given as risk factors for poor survival. These are tumor size bigger than 5.5 cm, <2 year time interval between CRC resection and liver transplantation, >80 μg/L CEA level in pre-transplantation process, and having progressive disease during CT application [32]. Older than 46 years age, heavy tumor load, extrahepatic metastasis, unfavorable tumor histology type, and KRAS or BRAF gene mutations could be given as other poor prognostic factors [37, 48, 49].

In a study in which the recurrence patterns after liver transplantation of the SECA-1 study were examined in detail, recurrence was seen in 19 of 21 patients [50]. Median time to recurrence was 6 (range, 2–24) months. When recurrence pattern was examined, it was seen that there were 68% lung metastases, 11% liver and lung and 11% lymph node metastasis, and 5% liver and ovary. No liver metastasis was observed in any patient. In 13 patients, the first and only recurrence site was the lungs. No other metastases were observed in seven of them, and three of them were treated with lung resection. At the end of the follow-up, these seven patients were alive, and two had no evidence of disease. Recurrence was observed in two patients simultaneously in three patients. These recurrences were lung or ovary and the other was liver in all of them. Two of them died in 6 and 26 months.

Five-year overall survival in patients with pulmonary site recurrence was 72%. Patients with only one site recurrence, pulmonary, or other recurrences had better overall survival beside to multiple site recurrences (all had liver recurrences). Median recurrence time in seven patients with hepatic metastasis was 6 months (2–30 months). One of those patients underwent liver resection, one had stereotactic radiation, and one had stereotactic radiation and transarterial chemoembolization. At the end of the follow-up, six of seven patients died. Although, 12 patients had not liver recurrences were still alive at the end of the follow-up. This study shows that liver recurrences have poor prognosis then pulmonary recurrences. Despite pulmonary recurrences seen early and more frequently, they are relatively indolent. According to prognostic factors in Nordic VII study, pulmonary metastasis after liver transplantation even prior to transplantation are accepted relatively unimportant recurrences [39]. Backward, recurrent liver metastasis is an important factor that affects the prognosis in a bad way [39, 50].

Future Perspectives and Ongoing Trials

The main problem for liver transplantation for non-resectable colorectal liver metastasis seems to be the scarcity of suitable organs. Very short waiting time in SECA study should be kept in mind. To add a new indication for liver transplantation would prolong the long waiting times. Using the similar inclusion criteria in the USA, it is estimated to come up to 3% of all liver transplant activities performed in the USA [42]. To use the expended criteria, donors would be an option to overcome the organ shortage.

Further, RAPID concept (resection and partial liver segment 2/3 transplantation with delayed total hepatectomy) comes forward a new perspective to increase the

opportunity of liver transplantation in non-resectable colorectal liver metastasis. The RAPID concept is currently evaluated in a prospective pilot study in OSLO (clinical trials.gov: NCT02215889). Preliminary data is promising, but future role of this procedure in clinical practice is sill need large series. Beside, a new study to use living donor liver transplantation for non-resectable colorectal liver metastasis is started in Canada (clinical trials.gov: NCT 02864485) [41, 51, 52].

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Interventional Radiology in General Practice of Colorectal Cancer

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Interventional Radiology in Diagnosis

Biopsy

Initial diagnosis of colorectal cancer is done by endoscopy. Imaging helps to reveal extent of the disease. Histopathological evaluation follows diagnosis. Biopsy is required for diagnosis of primary tumor, to confirm metastatic lesions and for staging. In addition, molecular profile (e.g., micro-satellite stability, KRAS status, EGFR, BRAF) of patient evaluated by analysis of tumoral tissue obtained either from primary or metastatic tumor has become standard in treatment of colorectal carcinomas. Tissue diagnosis of primary tumor in colorectal malignancies is mostly done by examination of biopsy materials obtained during endoscopy or by examination of surgical specimen. Percutaneous biopsy is rarely required. Imaging findings are usually characteristic for metastases in patients with a previous diagnosis of colorectal tumor. Biopsy is not required in high-risk patients such as a patient with a history of CRC in the preceding 5 years who has a new elevation of carcinoembryonic antigen (CEA) and new unresectable liver lesions on imaging that are clinically suspicious. If the nature of primary tumor is suspicious (e.g., large polyps with only dysplasia) or if confirmation of tumor genotype is relevant for subsequent treatment decision, a biopsy is likely indicated [1].

Contraindications

Absolute contraindications are uncorrectable coagulopathy and absence of a safe access route. Masses with dominant cystic or necrotic component, uncooperative patients and inability to give position to patient, and severe cardiopulmonary or hemodynamic instability are the relative contraindications. A special concern for

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biopsy of metastatic lesion, especially liver metastasis, is tumor seeding along percutaneous biopsy tract. Although this condition is especially reported in biopsy of primary liver tumors and rare in colorectal liver metastasis, in some small series, rates of 6–19% have been reported after percutaneous biopsy of liver metastases [2–5].

Preparation Prior to Biopsy

Review of previous imaging studies helps to decide site of entry on skin, the needle trajectory, and the guiding imaging method. The shortest possible path to the lesion should be chosen. Medical history of patient should be evaluated. Medications patient used, especially antiaggregants and anticoagulants, should be asked. Oral anticoagulants, antiaggregant drugs, and nonsteroidal anti-inflammatory drugs should be discontinued at least 5 days prior to biopsy. If cessation of such drugs is vital for patient's medical status, a bridge therapy with low molecular weight heparin can be started and stopped 12 h before biopsy. Laboratory examinations, coagulation profile, and hemogram should be ordered. Levels should return to acceptable intervals. Antibiotic prophylaxis for percutaneous biopsy is not recommended routinely, with the exception of biopsies performed transrectally [6].

Guiding Methods

Guiding method used during biopsy is determined by the location of the lesion. Ultrasonography and computed tomography are the most commonly used methods. Ultrasonography (US) is the primary guiding method for liver masses and intra-abdominal lymphadenopathies. It can be used for thoracic lesions located on chest wall. It allows real-time imaging, and the advance of needle toward target lesion can be followed. It causes no radiation. Another advantage of US is that it can be used for bed site interventions. Limited efficacy in lesions containing air and fat is the disadvantage of US. Computed tomography (CT) is preferred in lesions hard or impossible to access under US guidance. It can also be used in lesions containing air and fat. CT is the method of guidance in lung and bone biopsies. Biopsy under CT lasts longer, and real-time imaging is not possible unless CT fluoroscopy is present [7].

Technique

Percutaneous biopsies are performed as either fine needle aspiration biopsy (FNAB) or core biopsy. Cytological samples are obtained by FNAB, whereas tissue samples are obtained by core biopsies. FNAB is used in epithelium containing tumors and metastasis, and it is not sensitive to sarcomas and lymphomas that do not contain epithelial tissue; core biopsy is obligatory for such tumors. FNAB is preferred to core biopsy in lesions close to neural and vascular structures less than 2-cm distance (because of high risk of injury with core biopsy) and in lesions less than 1-cm diameter (since there is no sufficient cutting distance for cutting needle) [8].

Skin is prepared and draped sterilely. Local anesthesia with 1% lidocaine is applied. Three- to five-millimeter incision is made superficially with a scalpel. Twenty-two guage or smaller needles are used for FNAB, whereas 20 G or larger cutting needles are used for core biopsies. Small-sized needles are preferred in possibility of transgressing bowel or pleura. Since needles less than 20 G in size have a

tendency to bend out of the needle tract, 20 G or larger needles are required for deeply located lesions. For bone lesions, special needles, Jamshidi needles, are used to pass through thick cortex [7].

Biopsy is obtained either by direct advancement of needle used for biopsy into the lesion or by coaxial technique. In direct technique the safest needle size should be used, with the least number of needle placements. In most of the biopsies, coaxial technique is preferred. A coaxial needle (a biopsy cannula) is placed into the lesion under image guidance as an introducer needle. Biopsy needle, one size smaller than the coaxial needle, is advanced through it. This technique gives opportunity to obtain multiple biopsies. Both cytological and core biopsy are possible. Anatomical structures are passed once; thus, patient discomfort and risk of complication are less. Tract embolization, if necessary, can be done after biopsy. Disadvantage of this technique is using a larger diameter needle. The needle is advanced back and forth in a rotational fashion during continuous suction in fine needle aspiration. Less suction is applied in vascular lesions. The most optimal portion of the lesion should always be targeted. During removal of the needle from the lesion, suction should be stopped to prevent aspiration of non-aimed tissues [8].

Liver biopsies are performed mostly under US guidance. In the presence of multiple liver lesions suggesting metastasis, biopsy of a single lesion is generally sufficient to confirm the diagnosis. Ascites may be a relative contraindication. Ascites drainage before biopsy will be better before biopsy. Core biopsy is performed unless there is a contraindication. Eighteen guage needle is usually enough to obtain specimen. If coaxial technique is used in liver biopsies, needle track embolization by giving gelfoam or N-butyl cyanoacrylate through the needle can be done to reduce bleeding risk. This is especially required in hypervascular tumors, in coagulopathies, and in presence of ascites. Another technique is to insert the stylet of coaxial needle halfway and leave it in place for 1–2 min. The clot formed during this time is then injected into the track by advancing the stylet forward prior to removal [9].

CT guidance is the rule in lung biopsies. US can be used for the lesions which are settled on to pleura or chest wall with a broad base. Lung biopsy is contraindicated in patients under mechanical ventilation and having severe chronic obstructive lung disease, pneumonectomy at the opposite lung, abnormal pulmonary function, and pulmonary hypertension. Both FNAB and core biopsy can be used in lung lesions. Passage of the needle through emphysematous areas and bullae increases pneumothorax risk. As the number of passed pleural surface increases, the risk of pneumothorax increases. Care should be taken not to pass fissures if possible. Vascular structures (supraaortic vessels in anterior apical access, internal mammarian artery and vein, axillary artery and vein) should be avoided [10].

Post-Biopsy Follow-Up

Following biopsy, the patient should be monitored for vital signs and be on bed rest for 4–6 h. If possible, patient should lie as the biopsy site in dependent position. This serves as a tamponade for bleeding and decreases air leakage risk in lung biopsies by better apposition of pleural layers. Hemogram follow-up can be done if required. When the patient's vital signs have stabilized and it has been confirmed

that there have not been any complications due to the procedure, patient can be discharged. Immediately following procedure, a chest X-ray or CT taken on expiration is indicated to assess for development of pneumothorax in the case of lung biopsy and if pleural passage of needle has occurred during the procedure. Heparin, low molecular weight heparin, clopidogrel, aspirin, and NSAIDs can be reintroduced 12 h after the procedure in low risk of bleeding or 24 h in high risk of bleeding. The patient should be aware of signs and symptoms of potential complications and be instructed properly on follow-up [8].

Complications

Complications from percutaneous biopsy are rare, estimated at less than 2%. The most common complication is bleeding. Liver biopsies result in hemorrhage in an estimated 0.3–3.3% of cases [11, 12]. Most are minor bleedings and self-limited. Only follow-up is enough. Major bleeding needs blood transfusion; CT angiography is required to reveal the site of bleeding.

Infection is also very rare. In rare instances, injury to adjacent viscera is possible mostly due to inappropriate imaging guidance and needle trajectory.

Pneumothorax is a common complication in lung biopsies with a mean incidence of 20% (12–60%) [11]. If not symptomatic, only follow-up is enough. Tube insertion is required for moderate and severe pneumothorax.

Interventional Radiology in Management of Complications

Drainage of Fluid

Fluid collections in patients with CRC and metastatic lesions may occur due to various reasons. The most frequent postoperative complication in all abdominal surgeries is abdominal collection. The incidence changes between 5.8% and 28% in different series [13, 14]. There may be dehiscence and leaks after anastomosis surgery. Hepatic abscess and biloma may occur after hepatic resections of metastases. Perforation of the primary tumor may cause contained fluid accumulations and abscess formation [15]. Liver and peritoneal metastases may cause malignant ascites formation.

Image-guided catheter drainage has become the treatment of choice for patients with intra-abdominal abscess who do not have other indications for surgery. The vast majority of collections or abscesses can be managed with an appropriately sized and positioned catheter. Percutaneous drainage success rate is between 80% and 100% [16].

Indications

Indications of aspiration or drainage of collections are fluid characterization, treatment, and alleviation of symptoms. The character of a collection as an abscess, biloma, hematoma, lymphocele, or urinoma can be decided by aspiration. Drainage of an abscess is often curative and helps to relieve sepsis and symptoms due to mass effect [17].

Contraindications

Contraindications are absence of a safe access such as intervening bowel loops, vascular structures, or certain viscera and uncorrectable coagulopathy. Tumor abscesses may require lifelong drainage, and this must be discussed with the patient and the family. Although not a contraindication, an abscess <4 cm generally should not be considered for percutaneous drainage unless the patient is septic due to the collection. Treatment with antibiotics alone can be alternative for small abscesses. Multiple or multiloculated abscesses also may be better treated by surgery [17].

Alternatives

Surgical drainage can be performed in cases where no safe access route is present and other indications for surgery like obstruction are present.

Preoperative Evaluation

A detailed clinical history should be reviewed, and physical examination should be performed. Current medications such as anticoagulants and antiaggregants patient used should be questioned and stopped, or bridge therapy with low molecular weight heparin is used if required. INR and platelet level should be checked, and any coagulopathy should be corrected if needed.

Review of Previous Imaging Studies

Pre-interventional imaging should be reviewed to identify exact localization of the collection and structures next to it. This review also helps for planning guiding imaging method, access approach, and route. Usually the shortest path to the collection is chosen. Bowel loops, bony structures, and vessels on the way to the collection should be evaluated. It may not be possible to access deeply located abscesses by anterior approach because of intervening bowel loops, bladder, uterus, and adnexa. The content of collection can be decided by imaging, and the size of the catheter can be estimated. Previous surgery may change normal anatomy. Blind ends of end-to-side bowel anastomosis may simulate small fluid collections. A proximal ostomy for diversion of enteral flow may result in many normal or abnormal loops of bowel remaining unopacified on CT. Radiopaque sutures can show the site of anastomosis. Presence of an abscess next to them suggests leakage from anastomosis [18].

Patient Preparation

Intravenous access should be obtained, and patient should fast for 2 h if sedation will be given or 8 h if general anesthesia is planned. Prophylactic antibiotics are recommended for infected collections [19]. If patient is already on antibiotics, routine dose may be adequate. If a transrectal or transvaginal approach is used, prophylactic antibiotics should be given whether or not the collection is infected. Antibiotics are not required in drainage of noninfected collections without transgressing bowel.

Guiding Imaging Method

Ultrasonography (US), computed tomography (CT), and fluoroscopy are the methods used for drainage.

US is the most commonly used guiding method. It is widely available and portable. US is ideal for superficial collections or for angled approach. The patient is not exposed to radiation. Real-time visualization of anatomy and needle advancement into the collection is possible. Transrectal and transvaginal access is performed under US guidance. Obesity, intervening bowel gas, and bony structures limit the use of US [16].

CT guidance is better to assess the bowel loops and to drain deeper and smaller collections and collections which contain gas. If there are intervening bowel loops or vital structures between the needle entry site and the lesion on axial plane, angled gantry approach may be required. The gantry can be tilted either cranially or caudally to find a safe access path and to see the entire needle in an axial plane [20]. Oral contrast material can be given to opacify bowel for interloop abscesses in CT-guided drainages. CT fluoroscopy gives real-time information; however, it has disadvantage of increased radiation exposure [16].

Fluoroscopy is often used in combination with US. Real-time visualization is possible, and contrast may be injected to evaluate presence of fistula. Fluoroscopy is particularly helpful for repositioning catheters [16].

Technique

Catheters

Usually 8–14 Fr locking pigtail catheters are used for drainage of collections and abscesses [21]. 6–8 Fr drainage catheters are enough for clear fluid, 8–10 Fr for thin pus, and 10–12 for thick pus, and 12–22 Fr catheters are required for abscesses with debris. Catheters are connected to standard drainage bags with a three-way stopcock in between.

Approaches

Generally, the safest, straightest, and shortest path to the largest part of the collection is chosen. Patient comfort should also be considered.

Percutaneous drainage of a contained perforation of CRC may result in seeding tumor cells along the drainage tract and may cause metastatic disease [15]. When a malignancy is suspected, catheters should be placed in a manner enabling the skin and drain tract to be later resected en bloc with the cancer. The catheter should be placed in the most dependent part of the abscess. Catheter should be placed in a configuration so that it can be withdrawn to drain more superficial parts of the abscess. If possible, the long axis of the collection is aimed. Angle of approach can be changed accordingly [22].

Compression by US probe during access can displace bowel loops on the route of access. Vessels can be better evaluated with use of color Doppler and unintentional puncture is avoided. Hydrodissection by injection of saline can create a safe

access. Surgical access tracts can be used for access. It is usually safe to pass through liver or stomach for life-threatening subhepatic, paraduodenal, gallbladder bed, or lesser sac abscesses. Large liver vessels, dilated bile ducts, gallbladder, or large perigastric vessels should be avoided. For the completely inaccessible interloop abscess, bowel can be traversed with a 20 G needle and aspiration is done to get sample. Colonic loops and the pancreas should be especially avoided because of the risk of superinfection and pancreatitis, respectively [16].

Most preferred approach is transabdominal followed by transgluteal and lastly transvaginal or transrectal. Transabdominal approach is the most commonly used approach. The shortest route is chosen for access, and this is easily tolerated by most of the patients. Collections superficial to abdominal muscles can often be drained with ultrasound guidance using an anterior or anterolateral approach. Collections deep to the superficial abdominal muscles can often be drained via an anterior approach. This may require CT guidance to identify the abscess as separate from bowel [18, 23, 24].

Deep pelvic abscesses may be difficult or impossible to drain anteriorly. Transgluteal approach is used in collections located in deeper parts of the pelvis and obscured by bowel loops anterior to it. Deep pelvic abscesses can often be drained using a transgluteal approach through the greater sciatic foramen. In transgluteal approach, a route as close as possible to sacrococcygeal margin is chosen to avoid injury to neurovascular structures. Transgluteal approach is often painful. Up to 20% of patients have catheter-related pain lasting more than 24 h. Infrapiriformis approach is less painful and better used if possible [16].

Proximity of a collection to the vaginal fornices or to the low rectum may render a transvaginal or transrectal approach feasible. Transrectal and transvaginal drainage have high technical success rates (95% and 96, respectively) and are successful in managing the majority (94%) of patients with pelvic fluid collections [25].

Transrectal approach is used for collections anterior or posterior to the rectum like prostatic abscess. Transvaginal approach is preferred for pelvic collections anterior to the rectum. Transrectal route is better tolerated than transvaginal route. Placement of a Foley catheter may help to decompress urinary bladder in transrectal and transvaginal approaches. Collection is evaluated by preliminary endorectal or endovaginal US. The risk of catheter fallout is highest in transrectal and transvaginal approaches [26].

Transperineal approach is used for deep pelvic collections after abdominoperineal resection. It may be successfully performed in patients who cannot undergo conventional transabdominal, transvaginal, or transrectal catheter drainage. Transperineal approach can be performed with US or CT guidance. Tissues are typically tight to penetrate. Technical and clinical success rates are high (89% and 88%, respectively) [27].

Techniques

After preliminary CT or US examination, the entry side is considered and marked on skin. The skin is sterilely prepped and draped. Local anesthesia is given, and a dermatotomy is made with a sharp tip scalpel blade. Mainly two techniques of catheter insertion exist, Seldinger technique and trocar technique. A tandem trocar technique has also been described [26].

Seldinger Technique

An 18–21 G access needle is placed into the collection under imaging guidance. After the needle is confirmed inside the collection with imaging, inner stylet is removed. Diagnostic aspiration is done, and drainage catheter size is decided according to nature of aspirate. Aspiration of collection more than a few milliliters may cause collapse of the cavity and complicates catheter insertion. A 0.035-in. guidewire is then introduced through the needle, and the needle is withdrawn. The length of tract from skin to the collection is measured, and serial tract dilatation with dilatators 1 or 2 F above the catheter size is done over the guidewire. The catheter is advanced into the collection at the last step. This method is recommended in deeply located collections with limited access [18].

Direct Trocar Technique

A catheter mounted on a stiffener and a central sharp needle is inserted directly under imaging guidance to penetrate anterior wall of the collection. The central sharp needle is then removed, and a small amount of fluid is aspirated to confirm entry. The outer catheter is then moved further into the collection while the central stylet is held in place. Trocar method is often used for superficial and larger collections. Catheters used with this technique are usually small-sized [18].

Tandem Trocar Technique

An 18–21 G needle is placed into the collection under imaging guidance. A sample obtained through the needle is sent for microbiological and biochemical analysis. Catheter size is chosen according to the consistency of the fluid. Another skin entry 5–15 mm away from the first needle is prepared, and trocar catheter is advanced from this new entry site parallel to the first needle into the collection. Once it is inside the collection, catheter is advanced off the trocar. The final position of the catheter in any technique can be checked by US, CT, or a limited abscessogram. Overdistension with contrast material can result in bacteremia and sepsis. More than one drainage catheter can be placed in large or loculated abscesses [28], or catheter can be withdrawn after deeper locule is drained. Thin loculi can be disrupted mechanically by a pigtail catheter. A three-way connector is attached, and as much as possible material is aspirated. Bloody aspirate may indicate apposition of the catheter to the abscess wall. The drainage catheter is connected to a bag and secured by sutures or adhesive dressings or both. Complete drainage can sometimes be enhanced by irrigation with small quantities of 0.9% saline solution.

Malignant Ascites

Malignant ascites is defined as a collection of proteinaceous fluid containing cancer cells within the peritoneal cavity [29]. About 10% of all patients with ascites have malignant ascites. Of patients with colorectal carcinoma, 4% will develop malignant ascites during the course of their disease. The goal of treating malignant ascites is palliation due to the poor prognosis. Medical treatment is the first option in selected patients. It provides relief in about 40% of patients overall [30, 31].

Interventional procedures for malignant ascites are diagnostic aspiration, large volume therapeutic aspiration, and placement of drainage catheters. First step in all of these procedures is access to ascites. The site with largest fluid volume without intervening viscera is chosen by US. Usually right lower quadrant is preferred. Local anesthetic is administered to the entry site from skin to peritoneum. An 18–22 G spinal needle is inserted with US guidance, and fluid is aspirated to confirm the true place of the needle and sent for gram stain, cytology, cell count, culture, albumin, and protein if required. If the aim is only diagnostic paracentesis, the needle is withdrawn [31].

If therapeutic paracentesis is planned, the needle is connected to a bag via a connector. Therapeutic paracentesis provides temporary relief in 90% of patients; however, repeat procedures are needed on average every 10.4 days [31]. This is associated with several risks, such as visceral injury, bleeding, fluid leak, sepsis, hypotension, and renal damage [32].

Permanent catheters are used in patient requiring frequent paracentesis (more frequently than every 7 days). Drainage catheters are indicated in patients with a life expectancy of longer than 2–3 months and control ascites for an average of 52 days in 83–100% of patients [29, 31]. Permanent catheter drainage allows easy self-drainage and eliminates the need for frequent hospital admissions and the discomfort of repeated paracentesis. Drainage catheters can be tunneled or non-tunneled. Most authors prefer tunneled catheters because of lower infection rates and greater stability than standard non-tunneled pigtail catheters [33, 34]. Complications of placement drainage catheters are similar to therapeutic paracentesis.

Postprocedural Follow-Up

Patient is monitored for pulse, blood pressure, and temperature. Daily drainage should be recorded. Laboratory data (gram stain, culture, leucocyte count) is followed. Analgesics are given if necessary. Antibiotics are continued and adjusted as necessary based on the culture and sensitivity results of the abscess contents. Patient should be in a position in which the distal part of the catheter with holes would be in dependent part of the collection; thus, it can drain all the content. The exit site of the catheter, catheter condition, and integrity of retention are monitored. Catheter is flushed with 10 ml of 0.9% saline solution every 8–12 h to maintain catheter patency [18].

When to Remove the Catheter

Fever and leukocytosis improve in effectively draining catheter. Catheter can be removed in hemodynamically stable patients following clinical improvement and decrease in leucocyte count and daily output falls below 10–20 mL/day. Imaging can confirm resolution of abscess. There should be no fistula or large cavity on catheter injection. In case of no output but persisting signs and symptoms of infection, imaging may be required for current status of collection and presence of new collections. Catheters inside subphrenic abscesses should be removed after tract maturation occurred if pleura is traversed during insertion [18].

Outcomes

Clinical Success

Percutaneous drainage is a safe and effective method of treating collections alternative to surgery. Clinical success of percutaneous abscess drainage is 80–90%. The determinants of high success rate with catheter drainage are occurrence of collection postoperatively, non-pancreatic origin, and being not infected with yeast. Presence of bowel communication or other fistula, multiple abscesses, multiloculated and phlegmonous collections, collections associated with downstream obstruction, infected tumor, and infected clot are determinants of poor success [16, 35].

Problems

Low drainage output may occur due to obstruction of catheter with tenacious fluid, phlegmon, or hematoma or due to catheter malposition and kinking. Catheter may be in a part of collection that has already been drained, and other loculations of collection may persist. Imaging is required in case of low output associated with persistent fever, leukocytosis, or hemodynamic instability. Contrast injection under fluoroscopy can show whether the catheter is malpositioned or not. Malpositioned or kinked catheters should be repositioned over the guidewire under fluoroscopy guidance [36]. Sometimes insertion of a new catheter may be required. In case of viscous fluids, catheter may be exchanged with a larger-sized catheter. Alternatively, 2–10 mg tissue plasminogen activator in 10–40 mL sterile saline can be instilled into the cavity, and catheter is clamped for 60 min [37].

Persistent high drainage output usually suggests a fistulous connection. Fistula associated with pelvic abscess was found to be the only factor decreasing the drainage success [38]. Long-term drainage is usually required. Presence of downstream obstruction should be excluded and if present should be treated.

Complications

Complications are rare (<5% in most series) and include hemorrhage, bacteremia, transient worsening of sepsis, organ injury, bowel injury, and superinfection [16, 17, 22].

Management of Obstructions

Biliary

The underlying cause in majority of malignant biliary obstruction cases is the carcinoma of the pancreas or gallbladder. Metastatic colorectal tumors and lymph nodes at hepatic hilar or peripancreatic location may also cause extrinsic compression of proximal part of common bile duct with resultant biliary obstruction. Although rare, cases with colorectal cancer metastasis to pancreas and intrahepatic bile ducts have been described [39, 40].

Jaundice is a common late feature of advanced colon cancer and usually signifies extensive hepatic metastasis. The onset of jaundice in these patients carries a grave prognosis with a median survival of approximately 1 month. In patients whose jaundice is due to extrahepatic biliary obstruction, obstruction generally occurs due to metastatic lymphadenopathy at the level of the common bile duct or higher in the porta hepatic compressing the common hepatic duct. These periportal nodal metastases can occur frequently without presence of tumor in the liver. Prognosis is better with a median survival of 23 months [41].

Biliary obstruction causes increase in bilirubin levels and disturbance in liver functions. If it occurs during chemotherapy, chemotherapy may be discontinued. In such cases biliary obstruction secondary to colorectal cancer liver metastases is associated with a poor prognosis especially when chemotherapy cannot be restarted [42]. Biliary drainage is performed for decompression of biliary system. Endoscopic retrograde cholangiopancreatography is the first method for relief of biliary obstruction, especially in lower biliary duct obstructions. In cases where endoscopic retrograde cholangiopancreatography fails to reach biliary system such as previous gastric surgery or in high biliary obstructions, percutaneous biliary interventions are preferred [43]. Biliary drainage can also be used in special situations, such as to optimize the drainage of intrahepatic bilomas.

Contraindications to percutaneous biliary drainage (PTBD) are relative and include uncorrectable coagulopathy, ascites, and multiple intrahepatic obstructions.

Preoperative Evaluation

Evaluation of preprocedural imaging studies helps to understand the etiology and level of obstruction and plays role in procedural planning to determine best approach. Presence of variant anatomy that may cause complication during procedure can be recognized. The number of drains that might be necessary to drain the largest amount of liver parenchyma can be determined. Drainage will not provide benefit in atrophied segments or lobes that develop after long-standing obstruction [44].

The Society of Interventional Radiology (SIR) standards of practice guidelines classify new PTBD as a high-risk procedure and recommend correction of international normalized ratio to less than 1.5, cessation or reversal of heparin for activated partial thromboplastin time greater than 1.5 times control, withholding of clopidogrel and aspirin for 5 days, and withholding of fractionated heparin for 24 h or up to two doses prior to the procedure [45].

Transient bacteremia commonly occurs during procedure, even in the absence of clinically overt infection. PTBD is accepted as clean-contaminated or contaminated procedure, and prophylactic antibiotic regimen covering both gram-positive and gram-negative organisms is recommended [46]. Postprocedural antibiotics are considered on case basis.

Technique

Patient is monitored and skin entry site is disinfected and draped sterilely. Intravenous sedation is given. PTBD is performed under guidance of ultrasonography and fluoroscopy (access with US and then fluoroscopy). Following local

anesthesia biliary ducts are accessed using a 22 G needle under US guidance. Anterior subcostal approach for right bile ducts and epigastric subcostal approach for left bile ducts are preferred. Left-sided intervention is used in cases of right lobectomy, right lobe atrophy, and inability to visualize left ducts with a right approach. The risk of catheter withdrawal is less in left-sided approach. In presence of hilar obstruction where there is no connection between right and left lobes, bilobar catheters are inserted. Once the needle tip is seen inside the biliary system, dilute contrast material is injected during fluoroscopic examination, and cholangiograms are obtained. A successful bile duct puncture leads to a slow buildup of the contrast column that does not wash away and forms larger ducts toward the liver hilum. The cholangiogram should confirm that all segments are opacified and, if needed, to place additional drains if there are sequestered segments [44] (Fig. 30.1).

Through the 22 G needle, 18-in. guidewire is inserted centrally and the needle is withdrawn. Over the guidewire, 4–5 Fr coaxial introducer system is advanced. If the biliary tree is not visualized enough during first contrast material injection, repeat cholangiograms are obtained. Care should be taken not to overdistend bile ducts. The stenotic segment, even the obstruction site, can be crossed by using different catheter-hydrophilic guidewire combinations (e.g., angled tip catheter and straight tip stiff hydrophilic guidewire). If the guidewire is advanced into the duodenum, serial facial dilatations are done and 8 Fr internal-external drainage catheter with multiple holes is inserted as the distal holes remain inside the duodenum and the proximal ones in the biliary system (Fig. 30.2). This catheter has an external and an internal part. Internal part is composed of a security locking pigtail tip and distal part of catheter with multiple holes on both sides of obstruction. External component drains bile outside the body. External part is also used for following procedures

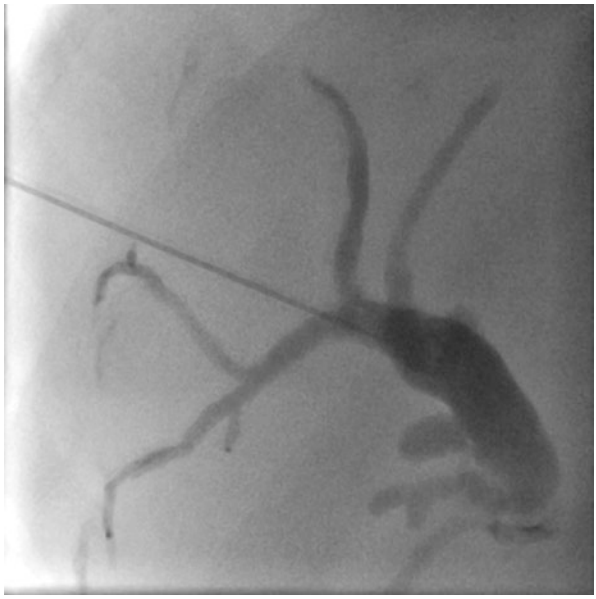

Fig. 30.1 Percutaneous transhepatic cholangiogram obtained after the needle is advanced into the biliary tract

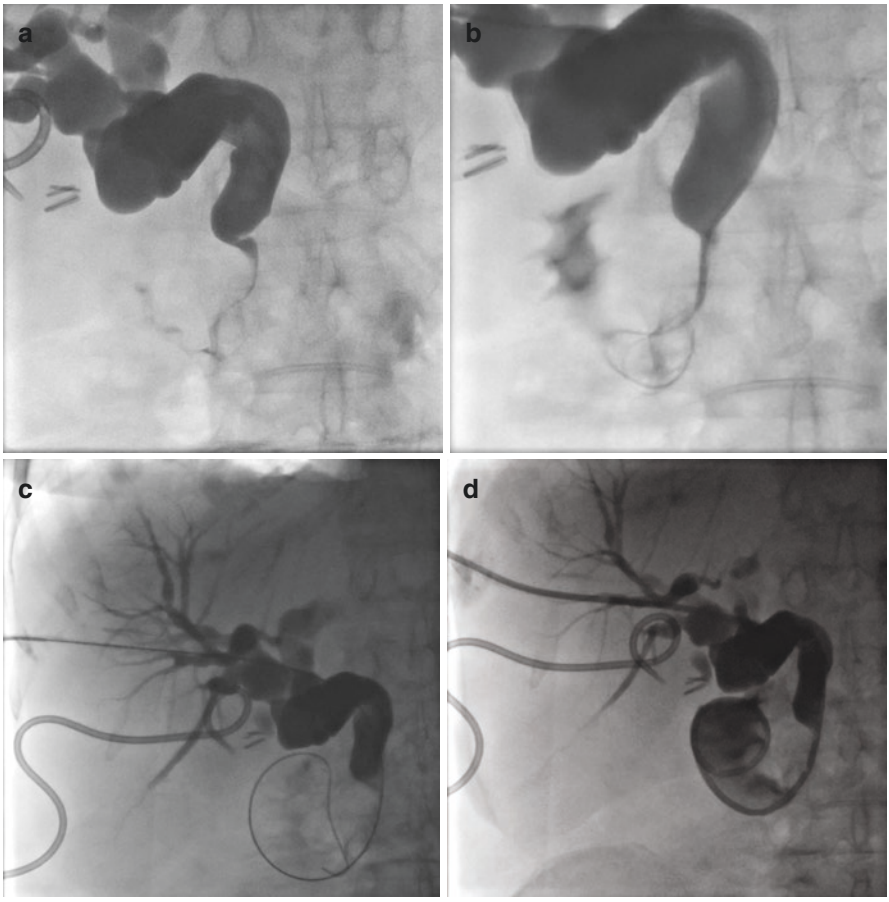

Fig. 30.2 Internal-external biliary drainage catheter insertion. (**a**) Diffused narrowing and displacement of distal common bile duct due to extrinsic compression of a mass lesion. A small amount of contrast material passes through the obstruction. (**b**, **c**) A guidewire is passed across the obstruction. (**d**) An internal-external biliary drainage catheter was placed over the guidewire

such as metallic stent insertion. If it is not possible to traverse the obstruction, an external catheter with holes only at the distal part is inserted just before the obstruction (Fig. 30.3). A drainage bag is connected to the catheter. External biliary drainage catheters have the disadvantages of daily catheter care; loss of fluid, electrolytes, and bile salts due to loss of bile via the catheter to outside the body; malnutrition; and coagulopathy (due to the lack of bile aiding in the digestion of fat and fat-soluble minerals) and discomfort due to drainage bag [47]. Electrolyte loss by drained bile should be maintained orally or intravenously. If the obstruction cannot be passed in the first trail, external drainage catheter is inserted for a couple of days. A few days later, a repeat intervention to cross the obstruction is done, and it can be replaced with an internal-external drainage catheter.

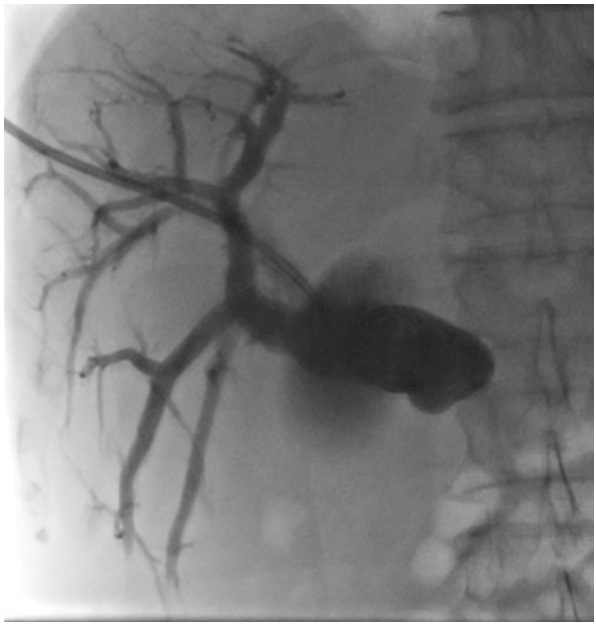

Fig. 30.3 External biliary drainage: obstruction level could not be passed and a drainage catheter was inserted just proximal to level of obstruction

Based on published success rates, the SIR guidelines recommend a success threshold for percutaneous transhepatic cholangiography (PTC) of 90% and a success threshold for accessing the small bowel of 90% [48].

Postoperative Follow-Up

Patient should be on bed rest following procedure. Antibiotics are continued, and if necessary, analgesics are given. The amount of drained bile is followed. Electrolyte levels are checked. External catheters are flushed with 10 mL saline twice a day. Biliary drainage catheters should not be aspirated because of increased risk of infection and sepsis. Hemobilia is frequent and usually transient. In case of hemobilia, frequent irrigation is done. If the underlying cause cannot be treated or a stent cannot be placed, catheter should be changed for every 2–3 months.

Complications

The recommended overall procedure threshold for all major complications of percutaneous transhepatic biliary drainage is 10%. Major, procedure-related complications of PTC and PTBD occur in 4–7% of cases [48] and include sepsis, cholangitis, hemorrhage, hepatic abscess, cholecystitis, pancreatitis, pleural transgression with associated complications, tumor seeding, and death. The likelihood of developing an infection increases with increasing duration of external drain. If long-term drainage is necessary, delayed, catheter-related complications include pericatheter leakage and clogging and dislodgment of catheter.

Prophylactic periprocedural antibiotics can help to lower the rate of infectious complications of biliary drainage. Hepatic abscesses occurring following biliary

interventions typically present several weeks after the drainage catheter insertion. Catheter-directed drainage and a prolonged use of antibiotics may be needed. Transient hemobilia following a percutaneous biliary intervention is relatively common; however, prolonged significant hemorrhage is very rare and usually self-limiting. Significant hemorrhage may occur due to central access to the biliary tract and passage of the catheter through adjacent vessels. In cases of significant or prolonged hemorrhage, hepatic arterial angiography is required to evaluate the cause of bleeding and to embolize the vessel that is source of bleeding if needed. Leakage of bile may occur following percutaneous biliary interventions. Underlying causes are usually catheter occlusion and catheter dislodgement where holes of catheter exit out of the biliary tree. If bile peritonitis develops, any intraperitoneal collection should be drained, and catheter should be repositioned if necessary. Routine catheter exchanges are recommended to reduce the incidence of catheter malfunction [44].

Clinical Outcomes

Biliary drainage can help to improve survival. A study done in patients who had biliary obstruction secondary to liver metastases of CRC, occurring during chemotherapy, and underwent biliary drainage showed that a successful biliary drainage leads to improved survival and allows achievement of chemotherapy in 70% of patients. Overall median survival was 115 days. A previous liver surgery, technical and functional success of drainage, and restarted chemotherapy were significantly associated with an improved survival. Chemotherapy was restarted after a median of 27 days. Survival improved from 33 to 262 days in efficient drainage ($p < 0.001$). Significant protective factors for survival included a previous hepatectomy and functional success of the drainage. Predictive factors for death included increased lines of chemotherapy and fever before drainage [42].

In another study on clinical outcome of biliary drainage for obstructive jaundice caused by colorectal and gastric cancers, percutaneous transhepatic biliary drainage was technically successful in 80% of patients, and 42% of them could receive subsequent chemotherapy. The median survival after PTBD was 273 days in the patients who had undergone successful PTBD and subsequent chemotherapy, 65 days in patients who had undergone successful PTDB but who had not received subsequent chemotherapy, and 34 days in the remaining patients who had undergone unsuccessful PTBD ($p < 0.001$). Multiple liver metastases and hepatic hilar bile duct stricture were independently associated with unsuccessful percutaneous transhepatic biliary drainage. Poor performance status, multiple liver metastases, presence of ascites, multiple prior chemotherapy administrations, undifferentiated type histology, and high serum CA19-9 level were independently associated with a poor prognosis [49].

Biliary Stenting

Internal biliary stent can be placed to the site of obstruction in patients who are not candidates for surgery. Withdrawal of catheter exiting externally to the body following stent insertion improves patient's comfort. Bare or covered metallic stents are used for this purpose. Stent patency should exceed patient lifespan whenever possible to minimize the need for repeat interventions. Metallic stents are associated

with a mean patency of 6–9 months and therefore should be used with patients with limited life expectancy [50]. Because the expected survival rates are low, stents provide lifetime patency for most of these patients, and in most cases, self-expandable metallic stents are favored over plastic stents placed endoscopically to limit the need for future endoscopic interventions [51].

Placement of a single stent is enough to drain in tumors involving the common bile duct or ampulla. If the lesion is at the hilum, bilateral approach is required to drain both right- and left-sided bile ducts. Bilateral drainage is not necessary if one lobe of the liver has a relatively small volume than the other either due to previous surgery or long-standing obstruction. The unilateral approach is effective in palliating obstructive symptoms in most of the patients [52] (Fig. 30.4).

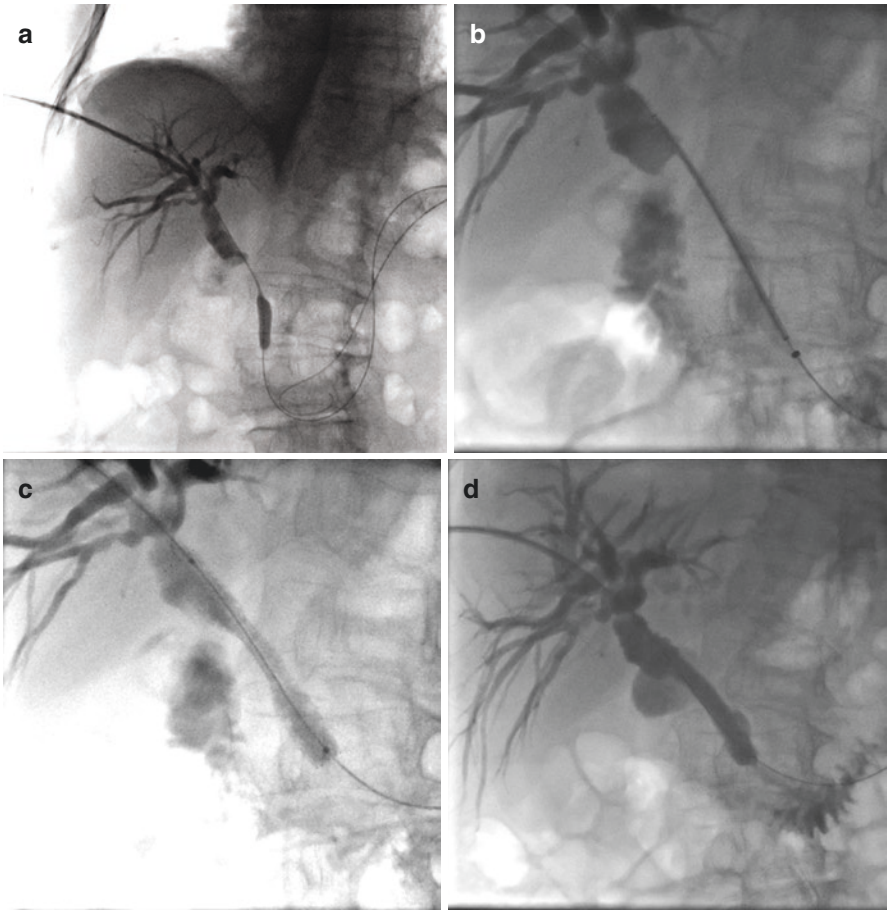

Fig. 30.4 Biliary stenting. (**a**) Obstruction at the proximal part of the common bile duct is crossed by a guidewire. (**b**) A stent is advanced to the site of obstruction. (**c**, **d**) Relief of obstruction by stent placement is seen

During stent placement if possible, papilla should be preserved to avoid ascending cholangitis, orifice of cystic duct should not be covered to avoid cholecystitis, and stent should not cover branching points to avoid associated biliary obstruction. Clearance of biliary tree from sludge with use of balloon may reveal involvement of a shorter segment, and a shorter stent insertion may be possible. Postdilatation is usually not recommended because self-expandable metallic stents continue to expand after insertion in most of the cases. In addition, postdilatation can cause bleeding because of tumor vascularization and cause obstruction of the stent due to tumor incursion through the cells and edges of stent [50].

One major drawback of self-expandable metallic stents is tumor overgrowth at the ends of stent and tumor ingrowth through the interslices of stent. Covered stents have been introduced to overcome this disadvantage. Although the long-term patency of covered stents was found better than the bare stents [53, 54], there are reports that show no significant difference in terms of patency or survival rates between covered and bare stents [55].

Complications of Stents

Complications of biliary stents include cholangitis, cholecystitis, pancreatitis, migration, and obstruction [56]. Cholangitis is treated with antibiotics, and reintervention is done to clear stent if an obstruction is found. The risk of cholangitis may be decreased by avoiding overdistention of the biliary system with contrast material, placement of stents suprapapillary rather than transpapillary, avoidance of stent placement at branch points, and treatment of an already present cholangitis by temporary drainage and antibiotics before stent placement. Cholecystitis occurs in approximately 5% of cases where stent is placed across the cystic duct ostium and can be treated by percutaneous cholecystostomy. Migration of stent is found more in covered stents than bare stents; however, the rates of other complications are similar [55]. In case of obstruction, additional stent placement may be required.

Colonic Obstruction

Colonic Stenting

Malignant colonic obstruction (MCO) occurs in 4.4–24% of CRC [57]. It presents most frequently in advanced stage cancer patients. MCO due to CRC requires urgent decompression as a malignant gastrointestinal emergency. If not adequately treated, MCO can lead to electrolytic fluid imbalance, colonic necrosis, bacterial translocation, and death.

Conventional treatment for MCO is surgery either in the form of defunctioning stoma or primary resection; however, these patients with advanced malignancies often have a poor nutritional status and usually have significantly deranged physiology at presentation. Emergency surgery for large bowel obstruction is associated with a morbidity rate of 32–64% and mortality rate of 15–34% [58]. Adequate staging of cancer is not possible in this emergency situation. Colonic stent placement may be alternative to surgery in patients with MCO.

Indications

Main indications for stent placement in MCO are palliation of surgically incurable colorectal cancer and as a bridge to surgery (BTS) to avoid an emergent, two-step procedure to allow for optimization of medical status and for preoperative staging including colonoscopy [59].

Contraindications

Colonic stenting is contraindicated if there are signs of systemic toxicity. Emergency surgery is recommended in patients with complete colonic obstruction with evidence of systemic toxicity, as these patients may have already developed colonic ischemia and/or perforation. Stent placement to treat distal rectal lesions (i.e., within 5 cm of the anal verge) is usually avoided because a stent in this location can induce severe pain, tenesmus, and rectal bleeding. However, some patients who wish to avoid an ostomy can undergo stent placement very low in the rectum with good tolerance. High perforation rates have been reported in patients receiving the anti-angiogenic agent bevacizumab [60, 61]. It is recommended that colonic stenting should be avoided, if possible, in patients who are or who will be receiving antiangiogenic agents (e.g., bevacizumab), especially if the obstruction is subtotal. Other contraindications are presence of intra-abdominal abscess, complex or elongated stenosis, excessive dilatation of the cecum (>9 cm) because of high risk of colonic perforation, hemorrhage, and presence of perforation [59].

Methods of Stenting

There are two methods of colonic stent insertion: endoscopic (through the scope) and radiological. In radiological delivery system, also referred to as over-the-wire delivery, the stent is inserted over the guidewire and implanted under fluoroscopic guidance. This technique may be helpful when there is an acute angulation or other factors limiting endoscopic visualization. Endoscopic method of stent placement is preferred mostly. In a study comparing radiological and endoscopic colonic stent insertion techniques, although the technical success rates were similar (95%) in both groups, clinical success rate was higher in endoscopic group (%81 vs. %77, $p > 0.05$) and complication rate was higher in radiological group (38% vs. 20%, $p = 0.006$) [62].

Radiological method is an alternative for failed endoscopic stent placement. In a recent study, the evaluated fluoroscopic stent placement for obstructing colorectal malignancy as a rescue procedure for failed endoscopic method was found to have a technical and a clinical success rate of 92.7% and 97.4%, respectively. Major complication rate was 7.9%. All of the patients with stent placement as a bridge to surgery underwent elective colectomy. In 32 patients with technically successful stenting for palliative purpose, the median primary stent patency duration was 353 days and patient survival was 335 days [63].

Preprocedural Preparation

Radiographic imaging may be helpful prior to colonic stent placement. CT can help to evaluate the extent of the tumor and to assess the site, degree, and length of the obstruction. Antibiotic prophylaxis is unnecessary for most patients undergoing

stent placement. However, prophylactic antibiotics are suggested in completely obstructed patients who have a markedly dilated colon because insufflation during the procedure may lead to microperforation and bacteremia. In contrary to endoscopic stenting, bowel preparation is not necessary [64].

Technique for Radiological Colonic Stenting

The patient is placed in the left lateral decubitus position. Intravenous access is obtained and oxygen administered via nasal prongs. Sedation and analgesia were given, and patient is monitored for heart rate, blood pressure, and oxygen saturation. After lubricating anal canal, a 5-Fr angiographic catheter and a 0.035-in.-diameter hydrophilic guidewire are introduced through the anus and manipulated to approach the obstruction. A mixture of iodinated contrast medium and room air were injected through the catheter during the procedure to distend and outline the colon. If difficulty in advancement of catheters due to tortuous or redundant colon occurs, various support devices (e.g., 8-Fr guiding catheters) and 6- or 8-mm guiding sheath are used as needed to straighten the tortuous colon or prevent prolapse of the catheter into the redundant colon [63].

The obstruction is negotiated and passed using 5-Fr angiographic catheters with variable tip shapes and 260-cm-long, 0.035-in.-diameter hydrophilic guidewires. Once the catheter and guidewire combination passed through the obstruction, a small amount of contrast medium was injected to determine the length and geometry of the obstruction. Then, the guidewire was replaced with an exchange stiff wire. A self-expandable metallic stent of 22- to 24-mm diameter and 6- to 12-cm length is used. Stent length is chosen to cover at least an extra 2 cm on each side of the obstruction. For long segmental obstruction of more than 8 cm, two or more overlapping stents are placed. Ideal stent placement reveals a "waist" in the stent region traversing the tumor with a flare of the proximal and distal ends of the stent. If either end of the stent is not flared or expanded to produce a waist, the stent may be too short to traverse the stricture. In such cases, a second or third stent can be used end to end with the first to completely traverse the stricture. In patients with multiple obstructions, stents are placed for all obstructions in a single session. If the obstruction does not allow advancement of the stent delivery system, balloon dilation (10 mm) can be performed before stent placement. Balloon dilation (14 or 16 mm) is performed after stent placement if the stent expanded less than 25% of its nominal diameter with disturbance of contrast-medium passage. During dilatation before and after colonic stent placement, care should be taken because dilatation is thought to predispose to higher rates of perforation. A final contrast study is performed to exclude perforation or misplacement [65].

The use of angiographic catheters with variable tip shapes and easily shapeable guidewires can facilitate passing the complete or acutely angulated obstruction, which was the most common cause of endoscopic failure [63, 66, 67]. On the other hand, tortuous or redundant sigmoid colon may be more problematic in the fluoroscopic procedure, because 5- or 6-Fr angiographic catheters are easily prolapsed into the redundant colon. Right-sided colon obstructions can be successfully

recanalized using those devices in 94.4% of cases [68–70]. In addition, the fluoroscopic procedure does not need air inflation or sedation and, more importantly, is not affected by bowel preparation status.

Follow-Up

Patients are observed for defecation and relief of obstructive symptoms following stent placement. Abdominal radiograms are obtained each day to evaluate bowel decompression and to exclude stent migration and bowel perforation. Catheter-directed colon imaging for possible reintervention is done in patients who fail to defecate in 3 days. Contrast-enhanced CT may be required in patients with non-improved obstructive symptoms for 7 days to reveal the underlying cause of persistent symptoms. Patients are instructed to take stool softeners to reduce the complication of fecal impaction after discharge. Patients are followed in outpatient clinics for every 3 months. If there is suspicion of recurrent obstruction, contrast-enhanced CT is performed and additional stent placement or bypass surgery is done if necessary [63].

Outcomes of Stenting

Technical success is defined by the ability to cross the lesion and deploy a stent successfully. Clinical success is defined as the ability of the stent to maintain luminal patency. The technical and clinical success rates of colonic stenting vary between 80% and 100% [65, 69, 71, 72]. The site of lesion influences the technical success rate, with rectosigmoid lesions being easier to treat than transverse colon lesions.

In a study comparing short- and long-term clinical outcomes of self-expandable metallic stents inserted for colorectal obstruction and efficacy of radiological and endoscopic insertion techniques, technical success (95% in both) and clinical success rates (77% in the radiological group and 81% in the endoscopic group) were similar in both methods [62].

The use of stent for palliative purposes in advanced CRC is found to be effective in literature [73–75] with high rates of technical and clinical success. In particular placement of colonic stent in patients with poor general condition and limited life expectancy may contribute to improve quality of life with longer survival compared to surgery [59].

Debate persists over the role of self-expandable metallic stent placement as a bridge to elective surgery for symptomatic malignant colonic obstruction. A meta-analysis revealed that the patients in the elective surgery group following stent insertion had a higher one-stage anastomosis rate compared to patients in emergency surgery group. Patients in the elective surgery group also had lower mortality rates and minor complications. There was no significant difference in anastomotic leakage between the two groups [76]. Another meta-analysis compared colonic stenting with the emergency surgery group, and the colonic stent group achieved significantly more favorable rates of permanent stoma, primary anastomosis, wound infection, and overall complications. There was no significant difference between the two groups in anastomotic leakage, mortality, or intra-abdominal infection [77]. Thus, stent placement is motivated by the ability to convert an emergency surgery

into an elective one, reducing preoperative morbidity and allowing adequate oncological staging, good colonic preparation, the possibility of a laparoscopic approach, and a quicker initiation of chemotherapy [59].

The interval between stent insertion and elective surgery is also under debate. Although a longer time between stent placement and surgery would improve general condition of patient and reduce consequent postoperative complications; this may be associated with stent-related complications and worse oncological outcomes. A short interval from stent placement to surgery is an independent predictor of postoperative complications in patients undergoing elective surgery as a bridge to surgery setting [72, 78]. An interval of over 15 days is recommended to minimize postoperative complications [59].

Types of Stents

Colorectal self-expanding metal stents may be uncovered (meshwork is bare wire) or covered (meshwork is covered to decrease tissue growth into the stent). All colorectal self-expanding metal stents function very similarly. Covered stents have been used mainly in the setting of malignant colo-vesical, colo-enteric, and colo-vaginal fistulas. While a theoretical advantage of covered self-expanding metal stents is the decreased risk of tumor ingrowth, they also have a greater tendency to migrate compared with uncovered self-expanding metal stents. Studies have not shown a significant advantage for covered stents. In a randomized trial including 151 patients with acute obstruction due to CRC, there was no difference in the clinical success rate for the placement of covered stents compared with uncovered stents (96% vs. 92%). There was a higher rate of migration (21% vs. 2%) and a trend toward less tumor ingrowth in covered stents (4% vs. 15%). There were no differences in relation to adverse events or obstruction by debris [79]. In a systematic review and meta-analysis (one randomized clinical trial and nine observational studies including 753 patients) comparing covered and uncovered stents in management of malignant bowel obstruction, uncovered stent was found to be associated with lower risks of complications, tumor overgrowth, and stent migration, longer duration of patency, lower need for stent reinsertion, and higher risk of tumor ingrowth. Rates of technical success, clinical success, perforation, bleeding, stool impaction, and stent obstruction were similar [80].

Complications

Perforation is the most frequent adverse event of colonic stenting, accounting for 42.8% of all adverse events reported in the meta-analysis [75]. The risk of perforation is strictly dependent on operator experience. The causes of perforation include guidewire or catheter malposition, dilation of stricture pre- and poststent insertion, stent-induced perforation, and distension of colon proximal to the obstruction due to inadequate colonic decompression or excessive air insufflation.

Other complications include transient anorectal pain, tenesmus, rectal bleeding, perforation, and stent migration [52]. The use of larger diameter stents, however, has decreased the incidence.

In a recent study, immediate and post-procedural stent-related complication occurred in 6% and 13% of cases, whereas surgery-related complications occurred in 28% (bridge-to-surgery: 15% vs. emergency surgery: 41%, $p = 0.004$) [81]. In another prospective multicenter study, major complications, including perforation, occurred in 1.6%, persistent colonic obstruction occurred in 1.0%, and stent migration occurred in 1.3% patients [72].

In a study comparing radiological and endoscopic stenting methods, the rate of complication was higher in the radiological group compared with the endoscopic group (38% vs. 20%, respectively; $p = 0.006$) [62].

Urinary Obstruction

Locally advanced colorectal tumors are known to constitute about 5–22% of all colorectal cancers at the time of presentation [82]. These colorectal tumors show aggressive local behavior and invade adjacent organs or structures without distant metastasis at time of presentation. The kidney and/or the ureter may be invaded both in right and left T4 colon cancer, and the tumor may adhere to the bladder in a cecal or sigmoid cancer [83, 84]. These involvements may cause obstruction in the urinary tract. Urinary obstruction can also occur secondary to colorectal cancer surgery. After cystectomy and ureteric resection for invasive colorectal carcinomas, urinary leakage and ureteric stricture are common complications [85] (Fig. 30.5).

Progressive obstructive uropathy may likely lead to clinical manifestations, uremia, electrolyte imbalances such as hyperkalemia and metabolic acidosis, and persistent urinary tract infections, if obstruction is not bypassed. Palliative decompression of the obstructed urinary system, either by percutaneous nephrostomy

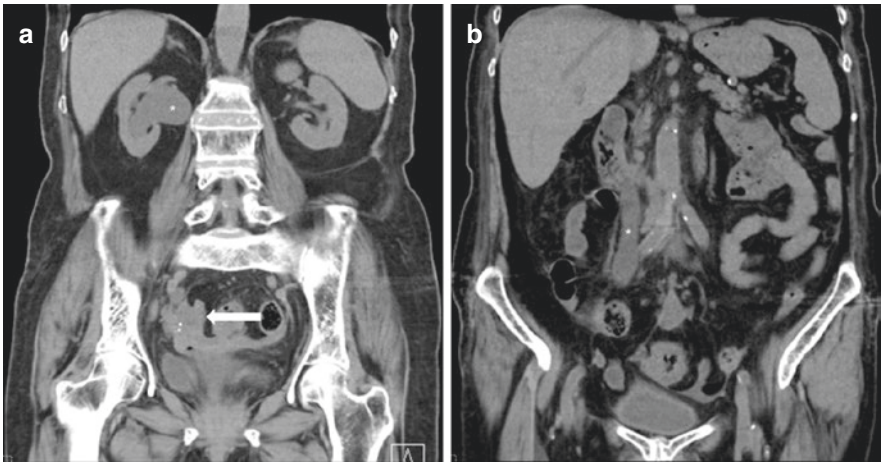

Fig. 30.5 Urinary obstruction as seen dilatation in renal pelvis and ureter (*) due to extrinsic compression of lymph nodes (arrows).

(PCN), ureteric stent, or a combination of both, is a well-known and effective method of improving renal function, with presumed low morbidity, and improving quality of life. The goal of treatment in the palliative setting may be to offer symptom relief, avoid complications from renal insufficiency, or allow further oncological systemic therapy. PCN is also indicated for urinary diversion to treat urinary leaks and urinary fistula [86–88].

Ureteric stent placement by cystoscopy is usually the first option for urinary diversion. If it is not possible to place a ureteric stent with this technique, PCN catheter placement is applied for relief of malignant urinary obstruction. Percutaneous antegrade ureteric stent placement can be an alternative option in cases where retrograde insertion failed [89].

In presence of associated sepsis, PCN is an urgent intervention; otherwise, it should be done as early as possible. Patient preparation is same as all biopsy and drainage procedures. Coagulation parameters and hemogram are checked before the procedure. Antibiotic prophylaxis is recommended by the Society of Interventional Radiology guidelines [90] and should be started 1 h before the procedure and continued for at least 24 h.

Most commonly used and reliable guiding method is combination of ultrasonography and fluoroscopy. In case of PCN insertion alone, the lower pole posterior calyces are aimed to access. If antegrade ureteric stent placement is planned simultaneously with PCN placement or later, an interpolar or upper calyx is targeted. Access via a lower pole calyx does not preclude antegrade ureteral interventions; however, a more pushing force may be required with such an approach [89].

Technique

A 21 or 22 G needle is advanced under US guidance to the aimed calyx with percutaneous entry site below the 12th rib to minimize transpleural complication [91]. An 18 G needle can be used; however, this may increase bleeding risk. When the tip of needle is seen inside the calyceal system, urine is aspirated and if infection is suspected or purulent urine is aspirated, sample for culture is obtained. Too much aspiration may cause collapse of the collecting system and failure of the procedure. Contrast material, not more than aspirated, is instilled to visualize the collecting system. Overdistension of renal collecting system may increase infection and sepsis risk. A 0.018-in. guidewire is advanced into the collecting system, and the tract is dilated to allow introduction of 0.035-in. guidewire. If antegrade ureteric stent placement is not planned at the same session, an 8 Fr locked nephrostomy catheter is advanced over the guidewire as its distal part with holes forms a pigtail form in the renal pelvis. Catheter position and level of obstruction can be evaluated by contrast material injection (Fig. 30.6). Catheter is fixed to skin and connected to a drainage bag [91, 92].

PCN is an effective method of diversion in patients with ureteral obstruction secondary to advanced malignancies. This should be the primary method of decompression in patients whose tumors are visualized to involve the urinary bladder.

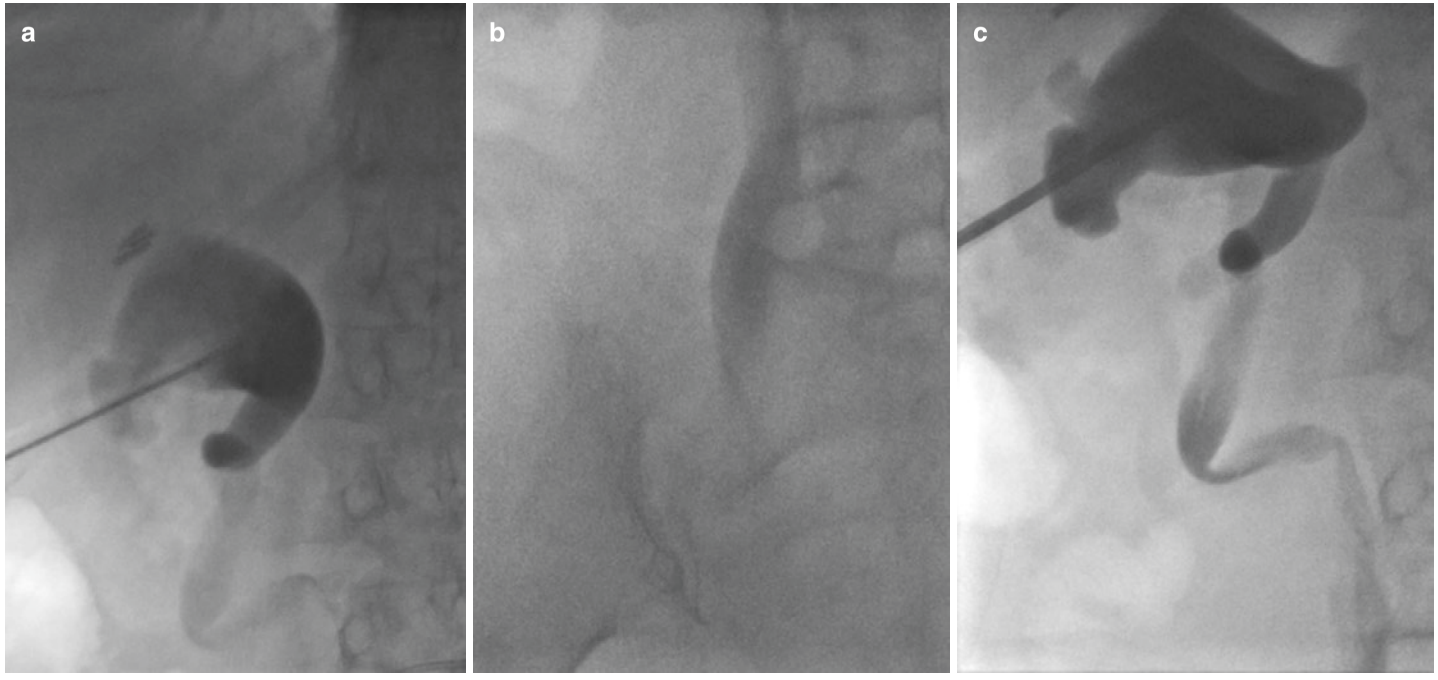

Fig. 30.6 Percutaneous nephrostomy insertion at the same patient in Fig. 30.5. (**a**) Contrast material was given through the access needle. (**b**) Obstruction at distal ureter. (**c**) Distal end of percutaneous nephrostomy catheter is placed inside the renal pelvis

When adequate urinary decompression has been achieved, conversion of a PCN to an antegrade stent is possible. This may be done simultaneously with PCN insertion or later as a two-stage procedure (PCN followed by antegrade stenting a few days later). It should be remembered that only 34.4% of patients were able to have their PCNs completely converted to internal ureteric stents following PCN placement. The remaining patients were left with at least one PCN in situ [89].

For antegrade stent insertion, an introducer sheath is placed into the collecting system either by replacing the existing PCN catheter or as the initial step after access to the calyceal system. Using combinations of catheter and guidewire, the stenosis or obstruction level is tried to pass. Dilatation with 4- to 5-mm diameter balloon is done if stenosis is too tight. Ureteric stent, with the distal part inside the bladder and proximal part in renal pelvis, is placed over the guidewire under fluoroscopic guidance. A nephrostomy catheter is placed to relieve pressure due to obstruction and control the patency of ureteric stent. PCN catheter is allowed to drain urinary system for a few days and then closed for 2–3 days. A control antegrade pyelogram is performed through the PCN catheter to decide whether the passage through the ureteric stent is sufficient or not. If contrast passage through the ureteric stent is enough, the nephrostomy catheter can be withdrawn [93, 94]. Although PCN offers excellent drainage, it requires a drainage bag that can reduce a patient's quality of life. Bleeding, sepsis, bowel transgression, and pleural complications can all be encountered when inserting a PCN catheter. Ureteric stents improve patient independence, and significant bleeding and other complications are less; however, quality of life is still affected by lower urinary tract symptoms caused by irritation they cause.

Technical Success and Long-Term Results

Image-guided relief of obstruction in malignancy cases has high technical success and clinical success. Initial management with PCN achieved 94% success in decompression of dilated urinary system in patients with malignant ureteral obstruction [87]. Technical success depends on degree of dilatation in the calyceal system and the body habitus of patient [88].

Antegrade ureteric stent placement has a technical success rate over %95 [93, 94]. In a recent study on experience of a single center on percutaneous antegrade ureteral stenting among neoplastic (654 procedures in 407 patients) and non-neoplastic group, technical success rate was found as 97.7% in neoplastic group. Complication rate in neoplastic group was 3.1% [94]. Although limited number of patients had colorectal cancer as the primary malignancy, a study about the role of nephrostomy in malignant ureteric obstruction reported a median survival of 128.1 days [86].

Long-term survival is possible in selected patients with recurrent or irresectable colorectal cancer and malignant ureteric obstruction and treated by stenting. This appears to be more likely in those patients in whom other treatments, particularly chemotherapy, are available [95].

Postoperative Follow-Up

Patient should be on bed rest for at least 4 h following nephrostomy catheter insertion. Vital signs should be monitored during this time. If infected urine is aspirated during procedure, antibiotic therapy should continue. Catheter should be irrigated with saline every 6–12 h, and the amount of drainage should be recorded. The first drained urine may be hematuric; however, it becomes normal within 1 day. The catheters that remain in place for long periods should be replaced in 3-month periods [92].

Complications

PCN and antegrade ureteric stent placement are relatively safe procedures in appropriately selected patients. The major and minor complication rates reported are around 10% [92]. Major complications of PCN include bleeding, sepsis, and injury to adjacent organs. The most frequent minor complications are pain and microscopic hematuria and are mostly transient. Complications with double-J ureter stents are hematuria, ascending urinary tract infection and pyuria, malpositioning of the stent, encrustation, and perforation of ureter. The overall complication rate for antegrade ureter stent insertion is 2–4% [96].

Transarterial Embolization for Bleeding

Lower gastrointestinal tract bleeding (LGTB) is described as the hemorrhage beyond the ligament of Treitz [97]. About 20% of gastrointestinal tract hemorrhage is caused by the lower gastrointestinal system [98]. The clinical presentation of bleeding can be divided into two groups: acute hemorrhage with life-threatening condition or chronic. The etiological spectrum of acute LGTB consists of various conditions including diverticulum (17–40%), angiodysplasia (9–21%), colitis (2–30%), neoplasia (11–14%), anorectal varices (4–10%), and upper gastrointestinal bleeding (0–11%) [99]. Colorectal carcinoma, which causes approximately 10% of LGTB, is the most frequent pathology of the chronic LGTB [97]. Descending and sigmoid colon tumors generally provoke visible bleeding in the beginning, whereas ascending colon tumors mostly cause iron-deficiency anemia [97].

In advanced staged malignancy, hemorrhage is reported to be a frequent and challenging complication [100]. Regional vascular injury, vascular invasion, systemic responses like disseminated intravascular coagulopathy, or thrombocytopenia may be assumed as reasons for bleeding in patients with malignancy [101]. Severe LGTB is an emergency, and treatment should be performed to stabilize the patient and keep down the hemorrhage. The criteria for severe bleeding are described as (1) continuous hemorrhage within 24 h, (2) decrease in the hemoglobin of >2 g/dL, or need of blood transfusion >2 U [102].

Colonoscopy has been demonstrated as the main diagnosis and treatment method in acute severe colorectal bleeding [103]. However, colonoscopy may fail to reveal

the source of hemorrhage due to substantial bleeding. Considering the high rates of morbidity after surgery and the urgency, transcatheter embolization can be used as an alternative and feasible treatment [104]. Angiography has an effective role in detecting the bleeding location and also cessation of the flow in the pathologic vessel [105]. In patients with malignancy, LGTB often cannot completely cease. However, palliative management mostly succeeds in decreasing blood transfusion need, allowing for new cycle of chemotherapy, and sometimes bridging to surgery [106].

Selective catheter angiography can display bleedings greater than 0.5 mL/min with a sensitivity of 40–86% and a specificity of up to 100% for LGTB [107, 108]. After obtaining access via the common femoral artery, the main purpose of transcatheter embolization is to detect and selectively catheterize the bleeding vessel(s) [109]. Superior mesenteric artery and inferior mesenteric artery should be initially catheterized in LGTB. In case of negative findings, the internal iliac arteries should be evaluated because their branches such as middle and inferior rectal arteries may be the cause of bleeding [110]. After positioning a 5 Fr catheter in the suspected arteries and detecting the bleeding vessel, a microcatheter should be advanced as near as possible to the hemorrhage region via a 0.018-in. or smaller guidewire. Due to the fact that bowel segments distal to the ligament of Treitz do not have multiple blood supply, the possibility of bowel ischemia is raised in these bowel segments [111]. There are several embolic agents that can be used including coils, glue, onyx, gelfoam, polyvinyl alcohol particles (PVA), and Amplatzer vascular plugs. Although the preference is mostly based on the operator's choice and experience, PVA and coils are the most commonly used agents [112]. PVA particles smaller than 250-μm and gelfoam are reported to move distally and block intramural or submucosal circulation, which ends up with increased risk of ischemia [113]. In a retrospective study consisting of 22 patients with acute LGTB, two early rebleeding (7.7%) and two bowel ischemia (7.7%) were observed in the follow-up [105]. Another retrospective study evaluated the efficacy of rectal artery embolization for the treatment of rectal bleeding in 34 patients. No bowel infarction was experienced during follow-up in their study [104].

Acute LGTB due to colorectal malignancy should be examined carefully, and early management is essential in patients with severe bleeding. Interventional radiological techniques provide fast and effective stabilization in unstable patients.

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Interventional Radiology in Management of Colorectal Carcinoma Metastasis

31

Orkun Sarioglu, Ahmet Ergin Capar, and Umit Belet

Liver Metastasis

Ablative Therapies

Ablative treatments are rising and promising techniques for colorectal cancer metastases (CML) in proper indication spectrums. However, these treatment options remain unclear at some circumstances; they are giving hope about survival rates on well-chosen patients. Ablative treatment of CLM can be divided into cold ablations (cryotherapy) and hot ablations. Hot ablations are microwave ablation (MW), radiofrequency ablation (RF), and laser-induced thermotherapy (LITT) [1].

Ablation Management of Colorectal Cancer Liver Metastases

Percutaneous ablation in patients with no chance of surgery in oligometastatic disease has been accepted by the authorities and is a recommended option in well-selected patients.

As an alternative to systemic chemotherapy, tumor ablative therapies must be considered as an option for isolated CRC metastases which are not amenable to curative resection options because of multifocality, insufficient hepatic reserve, and comorbidities. Also, ablation therapies can be used with surgical resection and chemotherapy (each separately) as a combination. When applied to target all disease foci, ablation combined with resection and ablation alone is presented as category 2A recommendation according to NCCN guidelines [2]. The lesions which are solitary and also under 3 cm are preferable for ablation

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therapies. However, it is controversial that lesions do not exceed 5 cm and may remain within the limits of ablation indications in patients who is not appropriate for the surgery [3].

Radiofrequency Ablation (RFA)

RFA is the most used and published technique that uses thermal energy for cell necrosis by increasing the local temperature up to 58 °C. In radiofrequency ablation, heat energy arising from the friction energies of molecules in tissues that are resistant to electric current between the two electrodes called Joule effect is the basic mechanism of ablation. The temperature closest to the electrode is higher, and heat dissipates to the surrounding tissues by thermal conduction. Therefore, the heat sink effect is higher than MW at the levels adjacent to large vascular structures and bile ducts. RFA can be performed by laparoscopic, percutaneous routes and during open surgery. Some studies indicate that the application way of the RFA has an effect on tumor recurrence and that recurrence occurs at least in open surgery compared to laparoscopic and percutaneous approaches [4–6]. In a study in which ASCO (American Society of Clinical Oncology) tried to determine the efficacy of RFA on colorectal cancers, there was insufficient evidence to suggest which of the RFA methods is better [7]. The best results in RFA are obtained in solitary or small number of metastases less than 3 cm [8–11]. The area where coagulation necrosis occurs in RFA is important, and the chance of success is significantly increased when the tumor is smaller than this area and ablation is created with at least 5–10 mm safety margin outside of the tumor. The incidence of local recurrence increases dramatically when the tumor size exceeds 3.5–4 cm [12–14].

Metastatic lesion localization is also an important factor in RFA success.

In other words, failure rates of ablation procedure increase due to heat sink effect in lesions adjacent to the vascular structure with a diameter of 1 cm or more [12, 15, 16].

Lesion size, distance to major vascular structures, and ablation margin are well-known factors that affect local tumor control. Tumors up to 3 cm are the best candidates for RFA, with similar oncologic outcomes to surgical resection [17–19].

RFA Outcomes

According to a recent meta-analysis, radiofrequency ablation (RFA) + systemic chemotherapy (SC) is more effective than systemic chemotherapy alone. The results obtained by partial hepatectomy are superior to RFA alone and not superior to microwave ablation (MWA) or partial hepatectomy (PH) + RFA alone [20]. According to EORT-CLOCC trial (a randomized phase 2 trial), combination of resection with RFA and SC may be associated with a significant improvement in overall survival (OS). When the OS was compared, the rate was 61.7% in the chemotherapy + RFA group and 57.6% in the only chemotherapy group over a 30-month period. In a median follow-up period of 9.7 years, OS was significantly higher in the RFA + SC group with a ratio of 35.6–8.9% in SC only group [21].

In a recent meta-analysis, which the results of many studies that compare RFA and PH were compiled together, it is reported that PH is superior to RFA alone. In the same study, when RFA + PH was compared with PH, it was reported that there was no significant difference in terms of OS in both groups [20]. Local recurrence rates after RFA vary between 2% and 60% in the reported publications. Today, local recurrence is an obstacle to widespread use of RFA [5, 22, 23].

In a prospective study, 12 months LTP (local tumor progression rate) of 3% and 30 months PFS (progression-free survival) were found to be above 95% in ablation patients with ablation margin above 5 mm and demonstrated complete tumor necrosis by biopsy [24]. Ablation margin above 5 mm after RFA is directly associated with increased local tumor control and increased LPFS (local progression-free survival) on computed tomography (CT) taken at postoperative 4–8 weeks. If it can be achieved safely, it is recommended that the ablation margin be kept at least 10 mm around the entire target tumor tissue [17, 25].

RFA Complications

RFA is a comfortable treatment technique that is tolerable for the patient when performed under safe and appropriate conditions. Mortality varies between 0% and 2%, and major complication rate varies between 6% and 9% according to ASCO data [7].

Microwave Ablation

Electromagnetic energy is the basis of microwave ablation. The phenomenon called "dielectric hysteresis" causes kinetic energy resulting from resonance movements in water molecules, and as a result, increased heat and ablation occurs [26, 27].

MW offers several advantages compared to RF. Heat can be penetrated more easily into tissues with low conductivity. Less heat sink effect occurs, and carbonization at the probe tip does not occur in the MW probe. Grounding pads do not have to be used for MW [28, 29]. In MW ablation, it is possible to reach more heat faster than RF ablation, and its destruction capacity is higher than RF. Heat peaks are significantly faster in MW ablation than RF [30]. Although MW seems to be superior in terms of technical characteristics and theoretically, MW ablation has not demonstrated a significant advantage over RF ablation. The proximity to large vascular structures and diameter of the tumor (3 cm and above) is more important for the success of complete tumor ablation [31].

Microwave Ablation (MWA) Outcomes

In a study by Shibata et al., the 3-year survival rate after hepatectomy was reported to be 23% and 14% after MWA, with median survival rates of 25 months versus 27 months, and median disease-free survival (DFS) rates were 13.3 months versus

11.3 months, respectively [32]. In one study, there was no significant difference between MWA + PH and PH in terms of survival. The 3-year survival rate is 50.9% for MWA + PH and 48.8% for PH. Median survival is 28 months for MWA + PH and 39 months for PH. The 4-year DFS was 39% versus 35%, respectively [33]. Although there is no suggestion specifically pointed out by the ACR (American College of Radiology) guideline, RFA is considered inappropriate for colorectal liver metastases without solid scientific support [34]. According to ESMO (European Society for Medical Oncology) guidelines, RFA is suitable for use in patients with surgical contraindications for colorectal liver metastases less than 4 cm [35].

According to the IKNL (Dutch Comprehensive Cancer Center) guidelines, thermal ablation therapy is not a substitute for surgical resection but is considered a viable treatment option for unresectable colorectal liver metastases in order to completely eliminate CRLM lesions [36]. Percutaneous thermal ablation should be considered in patients who have previously undergone extensive abdominal surgery, advanced age, comorbidities, and unsuitable metastatic locations. Although RFA is the first choice, MWA may be the first choice for lesions close to large vascular structures and thought to be affected by the heat sink effect [20].

MWA Versus RFA

MWA has started to gain popularity in front of RFA with several advantages in recent years. In a recent meta-analysis comparing MWA and RFA, it is reported that the local tumor progress (LTP) rates are similar and there is no significant difference between LTP rates, respectively [37]. In comparisons made with liver metastases, significantly lower rates of LTP have been reported with MWA [38, 39]. Also in studies comparing MWA and RFA, MWA is reported to be more effective in perivascular lesions [40–42]. When comparing MWA to RFA in peribiliary lesions, it is reported that more complications occur in MWA with the rates 57% and 3%, respectively [40]. In a 9-year series in which percutaneous MWA was evaluated in colorectal liver metastases, 36.6 months of median cancer-free survival and 45.7% local recurrence frequency were reported [43]. In a study with an average lesion diameter of 3.7 cm, it is reported that MWA can be applied in large lesions with 20.5 months of disease-free survival and 12.9% local recurrence rates [41]. In a recent study, it is reported that there is no significant difference between RFA and MWA in terms of local recurrence, with the similar rates of 40% and 38%. In the same study, it was stated that the MWA ablation group was not affected by the perivascular heat sink effect in the perivascular lesions compared to the RFA group where LTP was higher.

The most important message from this study is that when the ablation margin is more than 10 mm, both MWA and RFA groups provide long-term disease-free survival without LTP [17]. As a similar conclusion, Wang et al. reported that there was no significant difference between RFA and MWA success rates when sufficient ablation margin was reached [25].

Laser Ablation

Laser ablation emits 600–1000 nm wavelength by emitting light energy and realizes heat generation with electromagnetic heating [44]. It is compatible with MR because there is no metal antenna and CT does not produce metal artifact [45]. The penetration of the light waves in the tissue is restricted due to charred tissues and carbonization. Because of these reasons, the ablation occurs in small sizes between 1 and 2 cm [46]. For the reasons mentioned above, the frequency of use has not increased.

Cryoablation

The main mechanism in the cryoablation is the temperature change that develops as a result of sudden compression and expansion of the gas in the gas chamber at the end of the cryoablation probe, argon gas is used in these probes, and cooling effect occurs as a result of the compression and sudden expansion of this gas. As a result of this cooling effect, crystal formation at intracellular level leads to destruction in cell membranes and organelles [47]. Tumor ablation is correlated with cooling effect, hypothermia depth, freeze-thaw cycle number, and the amount of ischemia after thawing [48]. Due to large probe diameters, multiple probe requirements, and cryoshock syndrome characterized by DIC, kidney failure, and ARDS, its application in the liver has been very limited [49].

Intra-arterial Therapies

Surgery is proven to be the first-line management of colorectal liver metastases (CLM) [50]. Nevertheless, among patients with CLM, only 10–25% are eligible for surgical excision [51]. In inoperable CLM, National Comprehensive Cancer Network (NCCN) guidelines suggest systemic chemotherapy with 5-fluorouracil (FU) and oxaliplatin (FOLFOX), 5-FU and irinotecan (FOLFIRI), or capecitabine and oxaliplatin (CapOX) [52]. In the management of unresectable CLM, current studies showed that these cytotoxic drugs with or without additional biologic agents like anti-epidermal growth factor receptor (EGFR) and anti-vascular endothelial growth factor (VEGF) antibodies followed by surgical excision are a convenient approach [53, 54]. However, these medical treatments lead to a rate of overall survival as 40% at 15 months [55]. Moreover, systemic chemotherapy in unresectable disease provides downsizing for excision in only 10–30% of cases [56]. Along with intolerance for the patients, there are also some critical problems that can be caused by systemic chemotherapy such as sinusoidal obstruction syndrome, steatohepatitis, and chemotherapy-associated liver injury [57].

In the lack of response to systemic chemotherapy, intra-arterial locoregional therapies are considered as useful and effective treatment procedures in the interdisciplinary management of unresectable CLM. The main rationale of the intra-arterial therapies is based on the difference between the blood supply of the normal liver

tissue and the CLM. 75% of the blood supply of the normal liver tissue is provided from portal veins. However, CLM obtain 95% of their blood supply from hepatic arteries [58]. Intra-arterial therapies have the potential to relieve some of the undesired symptoms and improve the response rates of systemic chemotherapy by supplying a higher amount of drugs or radiation inside a selected liver area. Moreover, these treatment modalities can embolize the feeding arteries, cause tumor ischemia and necrosis, and make the lesions more sensitive to chemotherapeutic agents [59]. Hepatic arterial infusion (HAI), conventional transarterial chemoembolization (cTACE), transarterial chemoembolization with drug-eluting beads (DEB-TACE), and transarterial radioembolization (TARE) are the current intra-arterial therapies.

HAI

In HAI, chemotherapeutic drugs are injected into the hepatic artery from a port device or a catheter. The circulation of chemotherapeutic agent is mostly localized, and the total concentration of drug in the peripheral blood is significantly decreased. Thus, the impact of the drug is increased, whereas adverse effects are lessened [60]. Optimal agent should have a short half-life and great first-pass metabolism to expose high doses to the tumor while decreasing the peripheral concentration [61]. Floxuridine (FUDR) is reported to be the most commonly used chemotherapeutic drug in HAI. The liver extracts almost all of FUDR at the time of first pass, and this metabolism provides a local/peripheral drug ratio of 1/4 [62]. 5-FU, irinotecan, and oxaliplatin are the newly used chemotherapeutic drugs for HAI.

HAI can be performed in unresectable CLM either alone or in combination with systemic chemotherapy [63]. Moreover, HAI is preferred as a neoadjuvant [64] or adjuvant management [65]. Liver and kidney dysfunction, severe bone marrow suppression, uncontrolled severe infection, intracranial metastasis, terminal stage, and tumor/liver ratio >75% are the contraindications.

A large meta-analysis including ten randomized trials with 1277 patients showed that fluoropyrimidine-based HAI demonstrated greater tumor response when compared with fluoropyrimidine-based systemic chemotherapy (42.9% vs. 18.4%, respectively) [66]. However, they concluded that their results did not support the use of HAI alone as a first-line therapy because current systemic combination chemotherapy regimens provided comparable results. In a phase I trial, combination therapy with HAI FUDR and dexamethasone plus systemic irinotecan in patients with unresectable CLM provided a response rate of 74% [63]. In addition, a recent study demonstrated the effectiveness of combination HAI and systemic chemotherapy for high-volume unresectable CLM with a high rate of conversion to surgery (52%) and long-term survival (38 months) [64]. For adjuvant use of HAI, a phase II intergroup trial was conducted to evaluate adjuvant HAI FUDR alternating with systemic capecitabine and oxaliplatin after surgery. They showed quite hopeful results with higher than 85% survival at 2 years [65].

Catheter occlusion, arterial thrombosis, and dislocation of the port are complications due to technical procedures. Biliary sclerosis and gastric ulceration are the

toxicities of HAI FUDR that should be closely monitored and managed [61]. Further trials are needed to determine the optimal use of HAI with systemic chemotherapeutic agents.

cTACE

cTACE is the first used intra-arterial locoregional therapy, and basic principles of TACE were first described by Yamada et al. [67]. cTACE is a combined locoregional therapy that comprises of administration of chemotherapeutic agents into the tumor-feeding hepatic artery and embolization of the vessel subsequently. Treatment failure after systemic chemotherapy is the main reported indication for TACE in CLM [68]. The other indications are the following: neoadjuvant chemotherapy before surgery, prevention of recurrence after liver metastasis surgery, and rupture of CLM [60]. Decompensated cirrhosis (Child-Pugh B, score > 8), decreased portal-vein flow (portal-vein thrombus or hepatofugal blood flow), tumor/liver ratio >75%, technical impossibility for hepatic intra-arterial treatment (e.g., untreatable arteriovenous fistula), and renal dysfunction (creatinine ≥2 mg/dl or creatinine clearance <30 ml/min) are the absolute contraindications for TACE. Large tumor size (>10 cm), severe comorbidities, and biliary dilatation are described as relative contraindications for TACE [69].

Contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI), tumor markers, and biochemical parameters should be assessed before all types of intra-arterial therapies. After placement of an introducer into the common femoral artery, cTACE procedure is performed by advancing a catheter through the coeliac trunk into the main hepatic artery [70]. Superior mesenteric angiogram can be performed prior to the catheterization of coeliac trunk in order to notice any anatomical variations. Selective hepatic angiograms should be obtained after positioning a microcatheter into the feeding hepatic artery to realize any arteriovenous fistulas or reflux into gastric or duodenal arteries. In concerns for severe reflux into these vessels, embolization of them can be performed prior to drug infusion [71]. Then, chemotherapeutic agents (e.g., mitomycin C, gemcitabine, and/or irinotecan) are injected into the hepatic artery with lipiodol. Lipiodol facilitates carrying the chemotherapeutic agents straight to the intended liver cells with its lipophilic nature [72]. After the injection, embolization of the relevant vessel is performed with polyvinyl alcohol (PVA) or Gelfoam. The embolization provides reduction of blood flow through the selective hepatic artery. Thus, local amount and effect of chemotherapeutic drugs are increased [73].

Various studies were conducted to assess the efficacy of cTACE in patients with CLM. Lang et al. [74] described the value and efficiency of cTACE by using doxorubicin and lipiodol in a study consisted of 46 patients with CLM. In their study, 6 of 46 patients (13%) showed no response to the treatment, and the complication rate was observed as 15/46 (32.6%). Albert et al. [68] reported the results of cTACE with cisplatin, doxorubicin, mitomycin C, lipiodol, and PVA particles in 121 subjects with a failure of systemic chemotherapy to control unresectable CLM. Median

survival time was declared as 33 months from the detection of primary colon cancer and 27 months from the diagnosis of hepatic disease. Postembolization syndrome (PES) symptoms that were controlled with medication occurred in most of the patients. However, they reported complications that prolonged hospital stay as 11% (20 in 174 treatments). In another study conducted by Gruber-Rouh et al. [75], cTACE with lipiodol and mitomycin C or mitomycin C + irinotecan or mitomycin C + irinotecan + cisplatin was performed in 564 subjects. Assessment of local tumor control displayed partial response in 16.7%, stable disease in 48.2%, and progressive disease in 16.7%. Median survival from the start of chemoembolization treatment was reported as 14.3 months.

Complications of TACE can be divided into two groups: puncture or catheterization-related and drug or embolization-related. Puncture site hematoma, pseudoaneurysm, arterial dissection, arterial spasm, and vagal reflex are the puncture or catheterization-related complications. Infusion of chemotherapeutic agents from hepatic arteries causes a higher concentration of the drug in the liver compared to peripheral blood. Thus, the incidence of bone marrow suppression, alopecia, diarrhea, and other systemic reactions are lower than those in the intravenous chemotherapy [60]. PES, liver failure, renal failure, ectopic embolization, bile duct sclerosis, and liver abscess are the drug or embolization-related complications. PES is the most commonly experienced complication of TACE, and it usually occurs in ~90% of patients [76]. Patients should be informed, and clinicians should be prepared for the management of following PES symptoms: fever, malaise, right upper quadrant pain, nausea, and vomiting. TACE procedure can be performed as an outpatient procedure, or patients can be monitorized in the hospital approximately one night for the mentioned complications [68].

Over the past few years, the effect of combined therapy with TACE and percutaneous ablation techniques has been investigated widely in hepatocellular carcinoma [77–80]. However, the informative data regarding combined treatment in CLM is limited. 1-, 3-, and 5-year estimated survival rates were reported as 93.8%, 50.0%, and 10.1% after combined intra-arterial therapy (TACE or TARE) and percutaneous ablation in CLM in a retrospective study [81]. In 2016, another retrospective analysis was conducted in patients with CLM to evaluate the therapeutic efficacy and safety of percutaneous microwave ablation (MWA) combined with cTACE (consisted of 50–150 mg oxaliplatin, 10–50 mg epirubicin, and 1.5–10 ml ethiodized oil) [82]. cTACE was performed on the same day after the MWA in this study. Progression-free survival and overall survival rates were declared as 5.0 months and 11.0 months, respectively. No major complications or perioperative mortalities were observed, and they concluded that percutaneous MWA combined with synchronous cTACE is a safe and effective management for patients with CLM. The most recent retrospective study assessed the efficacy of TACE followed by percutaneous ablation in liver metastases [83]. Thermal ablations (RFA, MWA, or CA) were performed 1 day after cTACE (100 mg cisplatin, 50 mg doxorubicin, and 10 mg mitomycin C) except two patients who were treated 14 days after the initial cTACE procedure. Major complications including prolonged fever, hepatic abscess,

portal vein thrombus, biliary fistula, and retroperitoneal hematoma were experienced in 19% of the patient cohort. It was decided in this study that TACE and subsequent ablation could be an effective combination for the local control of liver metastases up to 8 cm [83].

DEB-TACE

New chemotherapeutic drugs and embolization techniques have been announced for various hepatic diseases recently. DEB-TACE is defined as a locoregional therapy that involves administration of irinotecan-loaded drug-eluting beads (DEBIRI) from the hepatic artery (Fig. 31.1). Irinotecan-binded microspheres used in DEBIRI procedure transport high doses of drugs to the tumor and elute the drug in a period of time [84]. When compared to cTACE, this mechanism provides a lower concentration of the drugs in the blood and leads to prolonged interaction of the chemotherapeutic agents with the tumor [85].

Irinotecan makes DNA replication and transcription inhibition by inhibiting topoisomerase I enzyme. Irinotecan needs to be activated by the normal liver cells to have an effect on topoisomerase I [86]. There is a critical difference in DEBIRI practice compared to cTACE for other malignancies: superselective embolization is not advised. Two main reasons were described for this treatment. One of them is irinotecan which needs activation by normal liver tissue as mentioned above. The other reason for non-superselective injection is to ensure that all metastatic lesions are exposed to the drug [50]. The optimal dose of irinotecan that should be administered is not obvious and needs strong evidence. A recent trial suggested two-session treatment with 1 month apart, with an injection of 100 mg irinotecan at each

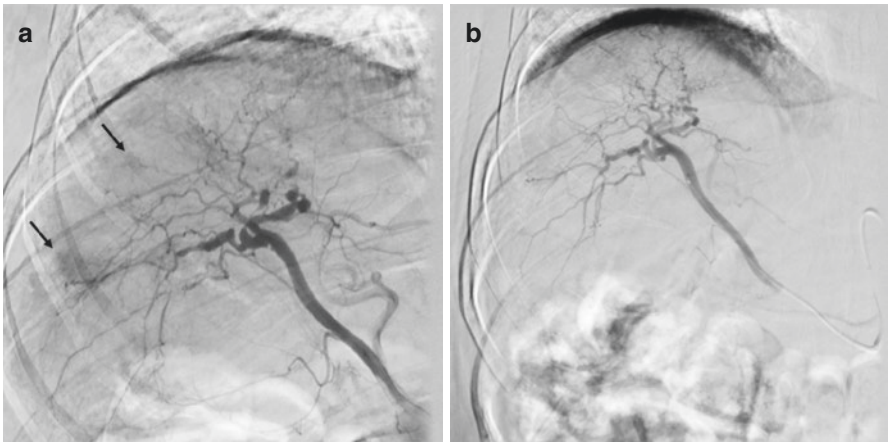

Fig. 31.1 Two CLM supplied by the right hepatic artery in a 56-year-old man. (**a**) Angiogram of the common hepatic artery shows the hypervascular tumors (black arrows). (**b**) Angiogram after TACE shows no residual tumor hypervascularity

procedure [87]. In the same study, it is mentioned that in bilobar involvement, each lobe should be treated twice by making a four-session treatment. There is also no consensus for the selection of particle size in the literature. It is clearly understood that small-sized particles can pass inside the lesion more powerfully, but they may cause rapid elution of the drug [88]. In a prospective, multi-institutional, noncontrolled study, it was demonstrated that small-sized particles (70–150 to 100–300 μm) provide higher-dose transport and have fewer side effects compared to large-sized particles (100–300 to 500–700 μm) [89].

Patients with CLM who are not eligible for surgery or percutaneous ablation are seemed to be available for DEBIRI. Not only cases with liver-limited metastases but also patients with liver-dominant metastatic disease are reported to be suitable for DEBIRI [90]. According to various published studies, DEBIRI can be performed as a first-line, second-line, or salvage therapy [91–95]. Additionally, concomitant use of DEBIRI with different chemotherapeutic agents like FOLFOX [96], cetuximab [97], and capecitabine [98] were reported as safe and effective managements. Various trials have assessed the safety and efficacy of DEBIRI on different study cohorts.

Two randomized controlled trials on the effect of DEBIRI have been conducted in the literature. Martin et al. [96] aimed to compare FOLFOX and DEBIRI to FOLFOX alone in patients with CLM. They demonstrated better results in overall response rates at 6 months and liver progression-free survival time in DEBIRI group, despite increased serious adverse effects rate. In the other prospective randomized trial, DEBIRI was compared with FOLFIRI regimen [99]. It was illustrated that overall survival and progression-free survival rates were superior in a two-session (4 weeks interval) DEBIRI treatment with 100–300 μm beads (a total of 200 mg irinotecan). Apart from these trials, numerous single-center prospective studies have declared the safety and efficacy of DEBIRI [91–93, 97–100]. Different treatment methods, lobar injection of 100–200 mg of irinotecan loaded onto 100–300 or 300–500 μm beads [91], <150 μm beads loaded with 100 mg of irinotecan [100], and up to 400 mg of irinotecan loaded onto 100–300 or 300–500 μm beads [92], were performed in different studies. They all concluded that DEBIRI seemed to be a reliable, technically feasible, and well-tolerated treatment in chemotherapy-refractory liver-dominant colorectal metastases. The most commonly experienced side effects were mild disorders compatible with PES. In a retrospective study, Narayanan et al. [101] administered 100 mg of irinotecan loaded into 100–300 μm particles for unilobar disease. In bilobar involvement, one vial of 100–300 μm and a second vial of 300–500 μm particles each loaded with 50 mg of irinotecan were injected. They stated that DEBIRI could be used in the palliative management of CLM.

It is now well-established that chemoembolization procedures achieve local control of liver metastases and extend progression-free survival time. DEBIRI can be used safely and effectively in CLM after failure of systemic chemotherapy. Further randomized controlled trials are needed to decide the ideal patient selection, optimal procedure technique, and combined therapies for the management of CLM.

TARE

TARE is defined as the administration of resin or glass particles loaded with yttrium-90 (90Y) into the hepatic artery. The particles stay for a long time in the tumor vasculature and allow regional distribution of a high amount of β radiation [102]. 90Y particles have a short half-life (64 h), high mean energy (0.936 MeV), and slight penetration ability (2.4 mm) [103]. These features make 90Y be a feasible locoregional therapy agent. Potential damage risk to adjacent viscera, respiratory and cardiac movement, and radiation-induced liver disease (a clinical entity consisting of ascites, anicteric hepatomegaly, and elevated liver enzymes) are the main factors that make an effective external radiotherapy difficult [104]. The locoregional mechanism of TARE results in the delivery of effective and high-dose radiation to the lesions while relatively preserving normal liver tissue. In addition, adjacent internal organs are not affected by the radiation toxicity. Although mechanisms of both TACE and TARE procedures seem to be similar, their working processes are different. Ischemia and chemotherapy are the main effects in TACE. However, the primary function of TARE is irradiation [105].

Patients with liver-dominant metastatic disease and >3 months of expected survival time with an Eastern Cooperative Oncology Group (ECOG) status ≤2 are eligible for TARE procedure. Increased total bilirubin >2.0 mg/dL, reduced albumin <3 g/dL, the potential lung dose of >30 Gy or hepatopulmonary shunting >20%, and nontarget embolization of gastrointestinal system that cannot be prevented are the absolute contraindications of TARE [106]. Unlike TACE, portal vein thrombosis is not an absolute contraindication for TARE. The safety of TARE in patients with portal vein thrombosis without cavernous transformation is demonstrated [107].

The most essential part in order to achieve a safe and successful TARE procedure is the pre-treatment planning hepatic angiogram. In this hepatic angiogram, hepatic arterial flow dynamics and vascular suppliers of the tumors should be evaluated carefully. Undesired transition of radioactive particles to the pulmonary or gastrointestinal system may result in severe complications including radiation gastritis or enteritis [90]. Preventive embolization of any vessels supplying the blood to the gastrointestinal system is recommended in case of reflux flow [108]. After deciding the injection spots, technetium-99 macroaggregated albumin (^{99}Tc-MAA) is administered to outline the circulation of 90Y in the hepatic vascular territory. Afterward, MAA scintigraphy displays the liver uptake, demonstrates any reflux to the gastrointestinal tract, and measures the hepatopulmonary shunting. In cases of hepatopulmonary shunting between 10% and 20%, the dose should be decreased to reduce the risk of radiation pneumonitis [105].

Whole liver, consecutive (one hepatic lobe followed by the other), or lobar therapies can be performed in TARE depending on disease burden, liver function, and patients' performance [71]. Personalized dose calculations are essential when considering the main purpose of TARE, which is to distribute optimal dose to the tumor while conserving normal liver tissue. Complications and post-procedural toxicity usually occur because of abnormal distribution of 90Y particles and damage of normal liver parenchyma. Post-radioembolization syndrome (PRS) contains similar

symptoms with PES including fatigue, nausea/vomiting, cachexia, and/or abdominal pain. Although the incidence of PRS varies from 20% to 70%, the need for hospitalization is quite rare [109]. Extrahepatic distribution of the 90Y particles induce other complications such as radiation gastritis or ulcer (5–10%), radiation pancreatitis (<1%), and radiation cholecystitis (<1%). However, appropriate planning prior to the procedure avoids these serious problems [110]. Radiation-induced liver damage is one of the most difficult complications for management. Direct radiation damage to the healthy liver is the main reason in this clinical entity, and it occurs about 4% [102]. Clinical findings indicating hepatic insufficiency (jaundice, ascites) arise 4–8 weeks after the treatment. Bilobar treatment, broad tumor burden, high doses of radiation, history of chemotherapy, and liver test abnormalities prior to procedure are associated with radiation-induced liver damage [102, 111].

In patients with CLM, TARE is most commonly recommended as a salvage therapy after failure of first-line systemic chemotherapy. It can be used either alone or along with 5-FU, leucovorin, oxaliplatin, or irinotecan [112]. In a retrospective study, outcomes of TARE as a salvage therapy for chemotherapy-resistant liver metastases from colorectal cancer were evaluated [113]. They performed TARE alone after failure of chemotherapy and displayed partial response and stable disease rates as 2% and 71%, respectively. A prospective study including 72 consecutive patients assessed the safety and efficacy of TARE for salvage in CLM [114]. The target tissue dose was determined as 120 Gy, and positron emission tomography (PET) response rate was 77%. Grade 3 and 4 toxicities were in 9 of 72 cases, while median survival time from the time of TARE was 23.5 months. Moreover, one of the largest series consisted of 302 patients with chemorefractory CLM demonstrated the value of TARE [115]. Median survival after TARE was 10.5 months; complete response, partial response, and stable disease rates were 1%, 38%, and 33%, respectively. Minor toxicities that did not require any critical monitorization were observed in 115 patients (38%) in this study. A prospective, multicenter, randomized phase III trial in patients with unresectable, chemotherapy-refractory CLM was conducted to compare 5-FU and 5-FU plus TARE [116]. Median time to liver progression and median time to tumor progression were significantly longer in TARE plus 5-FU group.

It is reported that TARE may be preferred as an adjuvant procedure to first- or second-line chemotherapy [116–119] despite conflicting results. As a first-line therapy in patients with unresectable CLM, a phase I study was performed to demonstrate the efficacy of TARE with modified FOLFOX4 systemic chemotherapy [119]. They reported median progression-free survival time as 9.3 months and median time to progression in the liver as 12.3 months. A large randomized phase III SIRFLOX trial displayed that the addition of TARE to FOLFOX-based first-line chemotherapy did not improve progression-free survival but significantly postponed disease progression in the liver [120]. Furthermore, FOXFIRE and FOXFIRE-global randomized phase III trials reported that FOLFOX plus TARE combination did not improve overall survival when compared to FOLFOX alone [121]. They concluded that TARE as a first-line therapy with systemic chemotherapy was not recommendable for all patients with CLM.

Conclusion

In recent decades, interventional radiological treatment methods have evolved and taken part in the management of CLM. Intra-arterial treatments with 90Y, cTACE, and DEB-TACE have been examined comprehensively in patients who are unsuitable for resection, and strong evidence was gained regarding their capacity to obtain local control. Multidisciplinary approach and future randomized trials are essential to optimize the treatment algorithm for this challenging patient group.

Portal Vein Embolization

Surgical resection of liver CLRC metastases is the first choice in patients with good liver function, favorable tumor location, and who are not candidates for liver transplantation; however, only 10–20% of metastatic lesions are amenable to surgery. Hepatic insufficiency occurring after surgery is the main limiting factor. The capacity of anticipated volume of the liver remaining after partial hepatectomy called future liver remnant (FLR) is important to sustain liver functions without liver failure. Given the risk of liver failure and related complications as sepsis, multiorgan failure and mortality following resection interventions to increase the volume and function of FLR are required [122].

Portal vein embolization (PVE) is preoperative embolization of a selected portion of portal vein branches to divert blood flow away from the tumor-bearing liver and to induce hypertrophy of unembolized portion of the liver. The increase in FLR occurs as a result of hyperplasia of liver cells (clonal expansion of the number of hepatocytes), not hypertrophy (increase in size of existing hepatocytes). Following PVE portal flow is redistributed to the FLR, and this increase stimulates regenerative response [123]. PVE is usually used in cases of diseased (metastasized) right lobe requiring embolization to induce hypertrophy of left lobe. As right lobe is normally larger than left, it is usually of sufficient size for resection of left lobe without PVE.

Pre-op Evaluation

The indication of PVE should be given with a multidisciplinary approach. The surgical plan and necessity of segment IV portal branch embolization should be discussed with the surgeon. A detailed history should be reviewed, and physical examination should be done. Underlying conditions including diabetes mellitus, portal hypertension, biliary obstruction, age, nutritional status, baseline liver function, history of ongoing alcoholism, and hepatitis may disturb liver regeneration and should be undertaken into consideration before performing PVE [124, 125].

Complete blood count, prothrombin time, liver function tests, blood urea nitrogen and creatinine levels, and viral screening should be ordered. A total bilirubin >3 mg/dl and a platelet count <100,000/dl are predictors of poor response to PVE and should be corrected before the procedure [126, 127].

Dynamic contrast-enhanced liver CT examination can show extrahepatic and intrahepatic disease and anatomical variation in portal venous tree and can be used for FLR volume calculation [128, 129].

Prophylactic antibiotics covering gram-negative and anaerobic bacteria should be given before the procedure for prevention of biliary sepsis [126].

Preoperative measurement of FLR is important to ensure adequate functional liver postoperatively. Live volume can be measured using manual or software-associated methods using a number of imaging techniques such as CT, MR, or scintigraphy. 3D CT volumetry has become standard for measuring liver volume. CT volumetry can be used to measure total liver volume as well as lobar or segmental volumes as needed. It should be remembered to exclude tumor volume when measuring FLR [130].

The recommended minimum FLR should be at least 20% for normal livers, 30% for patients subjected heavy and prolonged (>12 weeks) chemotherapy, 30% for patients with nonalcoholic steatohepatitis, and 40% for patients with cirrhosis [131–133]. The FLRs less than these limits are associated with increased rate of liver failure [134]. Systemic disease such as diabetes may additionally limit liver hypertrophy and the success of the procedure.

Contraindications

PVE may be contraindicated in patients unfit for major resection and unfit for intervention, and in too extensive diseases; in conditions where PVE is not feasible, technically predicted FLR is inadequate. Patients with significant cardiopulmonary diseases, poor performance status, high score Child B or Child C status, and portal hypertension are not convenient for major hepatic resection. PVE is also contraindicated in patients with metastases outside the liver and metastatic involvement of FLR where R0 resection is not possible and predicted FLR less than the expected (usually in cirrhosis). Uncorrectable coagulopathy, overt sepsis, renal insufficiency requiring dialysis, biliary obstruction, and ascites are relative contraindications. Correction of some of these factors may enable the procedure. Biliary obstruction due to metastatic tumor or lymphadenopathy compression should be treated by biliary drainage. PVE can be done after serum bilirubin level decreases to a level <3 mg/dl [135].

Lack of portal vein bifurcation, complete thrombosis of the right portal vein, tumor thrombus extending into the FLR, and presence of tumor in the way to access portal vein branch are the technical issues that impede PVE.

Technique

Guiding Method

Procedure is performed under ultrasound and fluoroscopy guidance. Access to portal vein branches is accomplished under ultrasound guidance, and then the following steps are done under fluoroscopy.

Approaches

PVE is performed under moderate sedation and local anesthesia. A peripheral or mid-portion of portal vein is targeted to prevent inadvertent injury to central hepatic artery. After accessing portal vein, an introducer sheath is placed. A flush catheter is advanced over a guidewire into the main portal vein, and baseline portal vein pressure is measured, and a venogram is obtained. The portal tree is imaged; anatomic variations are reviewed. Sluggish or reverse flow inside the portal vein suggests portal hypertension. A decision has to be made whether to proceed the procedure or not [136].

Three access techniques are described for percutaneous PVE: contralateral approach, ipsilateral access, and transsplenic approach.

Contralateral Access

In this approach percutaneous access is on the opposite side of embolization target (left access for right portal vein embolization). Anterior subxiphoid area is the preferred side of entry. This approach is easier for antegrade catheterization of right portal vein branches due to a more linear approach to embolization. Extended embolization of segment 4 portal vein branches is also generally technically easier from the contralateral approach relative to ipsilateral. Since FLR must be traversed, there is risk of injury to FLR which jeopardizes surgical candidacy [137].

Ipsilateral Access

Access is on same side of the intended resection (usually right access). The skin entry side is on right midaxillary line. Ipsilateral approach has the advantage of not going through the FLR. However, in this approach there is theoretical risk of seeding if tumor is traversed. Care should be given not to traverse the tumor while accessing the portal vein. It may be difficult to catheterize right portal vein branches due to sharp angulations in this approach. Utilization of reverse curve catheters to access the portal vein branches are helpful; however, use of these catheters may be more technically challenging and increase procedure time and radiation exposure [132].

Transsplenic Approach

In case of multiple metastases that preclude a safe transhepatic puncture, percutaneous access of portal system through spleen can be used. The access is through the left upper quadrant inside a splenic vein branch. Transsplenic access may prevent the risks of transhepatic access. It provides a contralateral access traversing FLR. This is useful in patients in whom tumors precluded a safe trajectory puncture. This access is equally as successful as transhepatic approach for PVE in those experienced with transsplenic access [138].

Procedure

The skin at entry site is prepared sterilely and draped. Local anesthetic agent, 1% lidocaine, is administered at access site and along tract. Portal vein has hyperechoic

halo peripherally. Medium caliber, somewhat peripheral portal vein branch, is identified. In cirrhotic patient main portal vein can be used as the target. In contralateral approach segment III left portal vein is targeted on ultrasonography. A 22G Chiba needle is introduced in anterior subxiphoid area, directed slightly right. In ipsilateral approach, needle targets peripheral right portal branch. Chiba needle is introduced at mid-axillary line below last rib, or in most intercostal space, perpendicular to lateral abdominal wall, angling needle toward T12-L1 vertebra [139].

Once the needle is inside the targeted portal vein branch, the blood is aspirated. Upon blood return, contrast material is injected to opacify the vein (Fig. 31.2). Contrast in portal vein flows peripherally, whereas contrast in hepatic vein flows centrally to inferior vena cava.

Once needle is in portal branch, a 0.018 "guidewire is advanced into main portal vein and needle is exchanged for coaxial introducer and 0.035" guidewire. A 5- to 6-Fr vascular sheath is placed, and through the sheath, a pigtail catheter is advanced into main portal vein. DSA portogram is obtained in multiple projections (Fig. 31.3). The portal branches which will be embolized are decided. Four- to five-Fr catheter is advanced into target branch. Reverse-curve catheter is used for ipsilateral approach, whereas forward-facing catheter is used for contralateral access. Portogram is performed to ensure catheter is sufficiently selective to prevent nontarget embolization. A microcatheter can be used to achieve distal access.

Embolization of right portal vein branches will result in segment IV hypertrophy together with hypertrophy of left lateral segments. Since segment IV is resected in right trisectionectomy and will not contribute to FRL, embolization can be extended to segment IV branches [140]. Segment IV branch embolization is also required if

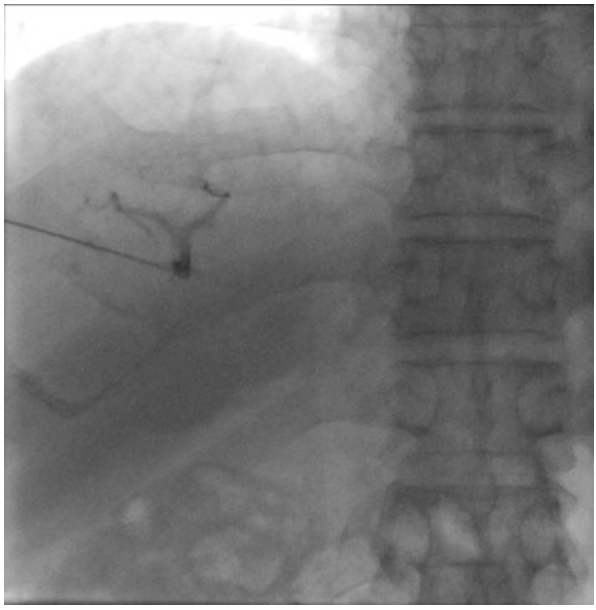

Fig. 31.2 After US-guided access into the right portal vein branch, contrast material is given through the needle to opacify the vein

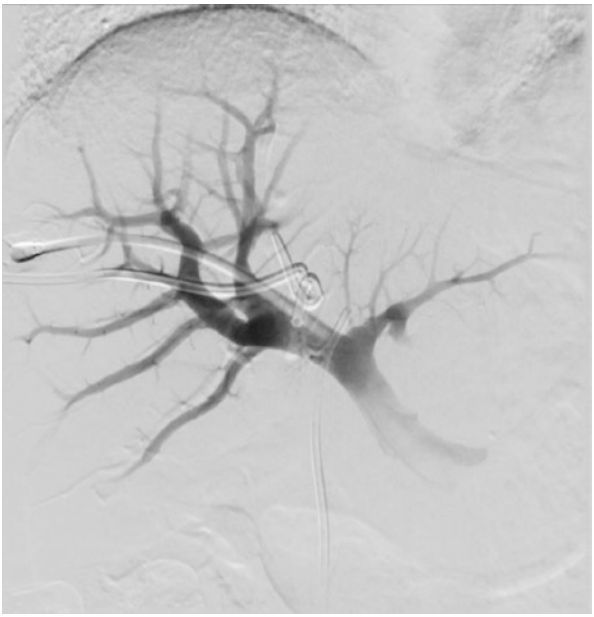

Fig. 31.3 Preembolization portogram is obtained to evaluate the portal venous anatomy

metastases exist in segment IV. In case of planned segment IV embolization, segment IV is embolized first at ipsilateral approach and last at contralateral approach. It should be kept in mind that extending PVE to include segment 4 is more technically demanding [132].

Embolic Agents

Most commonly used embolic agents for PVE are *N*-butyl cyanoacrylate (NBCA) glue, PVA and microspheric particles, coils, and plugs. It is reported that inadequate distal embolization may result in suboptimal FLR hypertrophy [141]. It is not possible to embolize distal segmental branches of portal veins with plugs, and embolization with coils are expensive and time-consuming; thus usually particles and glue are used for distal embolization, and proximal branches are occluded with coils and plugs (Figs. 31.4 and 31.5).

In particle embolization 300- to 500-μm-sized microspheres are usually used for distal embolization. In the presence of portal-to-hepatic venous shunt, size is chosen accordingly to close shunts initially, and then smaller-sized particles are used. Particle size can be increased to 700–900 μm as occlusion level approaches to proximal branches. Following stasis, proximal branches can be occluded with coils and plugs. The most proximal 1 cm parts of the right or left portal vein should be preserved for surgical clamping. NBCA has become a popular embolic agent in recent years for PVE. It is mixed with ethiodized oil, lipiodol. The concentration of NBCA should be such that it can reach distal portal vein branches. A ratio of 1:1 or 1:2

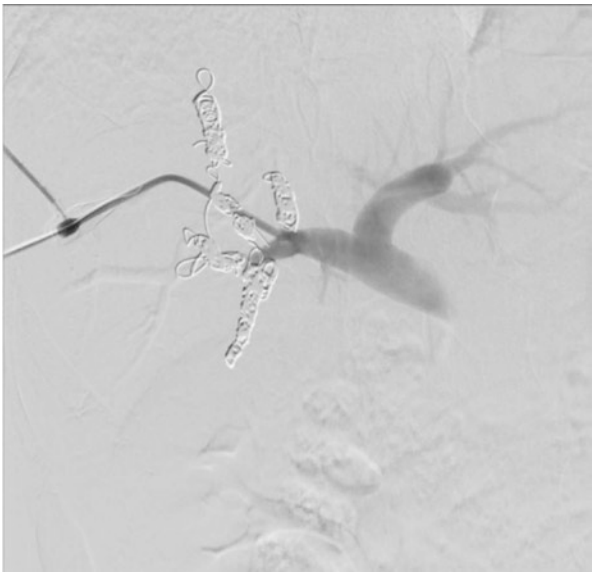

Fig. 31.4 Coils are seen at the proximal parts of right portal vein branches

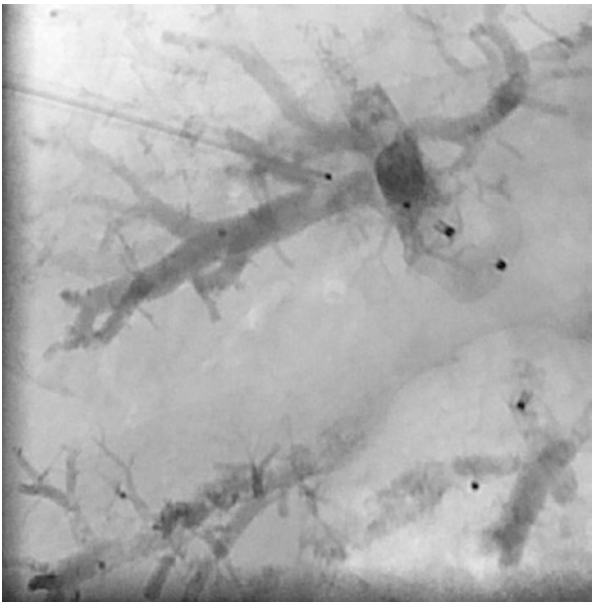

Fig. 31.5 Two Amplatzer plugs are placed at the proximal parts of right portal vein branches

(NBCA/lipiodol) is used in most cases [142]. NBCA is preferred in contralateral approach than ipsilateral approach. Embolization with glue has the advantage of short procedural time. Although improved hypertrophy is reported in literature [143], outcomes are similar. The disadvantages of glue are requirement for experience and pain due to the exothermic nature of the polymerization of NBCA.

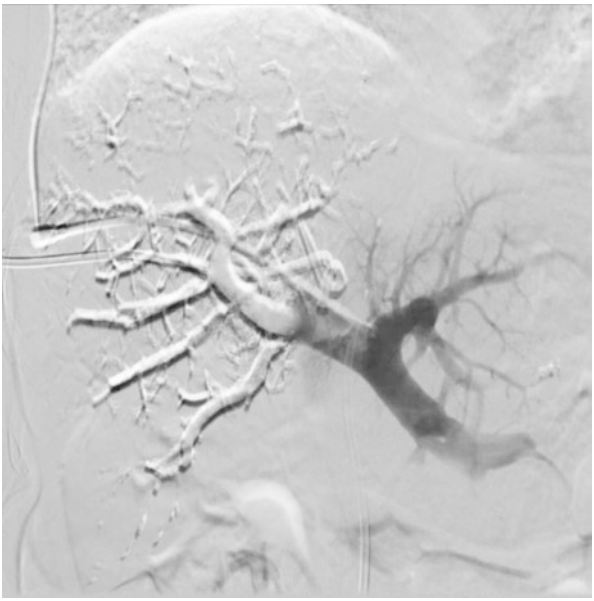

Fig. 31.6 Final portogram shows the complete occlusion of right portal vein branches after N-butyl cyanoacrylate, same patient in Fig. 31.3

The embolization endpoint for PVE should be complete stasis. A final portogram is obtained with the flush catheter positioned within the main portal vein to assess the completeness of the embolization (Fig. 31.6). At the end of the procedure, the access tract is embolized with coils and/or absorbable gelatin compressed sponge to minimize the risk of bleeding at the liver puncture site (Fig. 31.7).

Additional Strategies to Improve FLR Hypertrophy

Intraportal Administration of Stem Cells

Simultaneous administration of stem cells with PVE was found to induce more gain in FLR compared to PVE alone [144, 145].

Dietary Supplementation

In a small randomized study, dietary supplementation of branched-chain amino acid before PVE and continued for 6 months after liver resection showed an increased functional liver capacity compared to PVE without dietary supplementation [146].

PVE and Transarterial Embolization

Transarterial embolization, either following PVE or simultaneously with PVE, may offer a better FLR hypertrophy. A study evaluating the role of additional transcatheter arterial embolization done after insufficient FLR hypertrophy and after preoperative transhepatic portal vein embolization showed that the changes in left liver

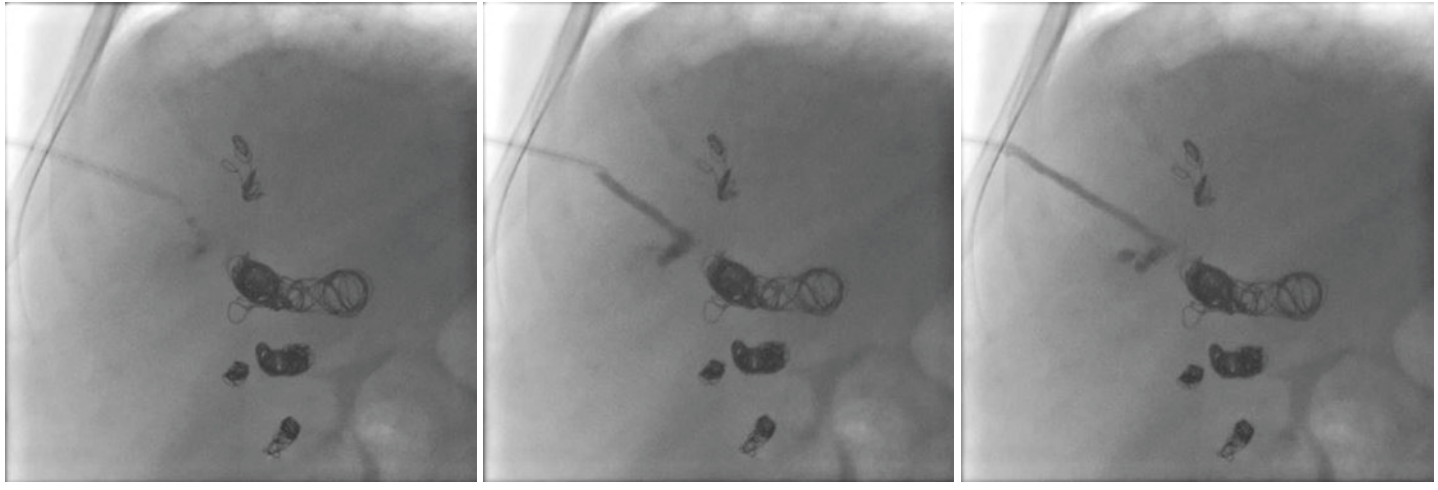

Fig. 31.7 N-Butyl cyanoacrylate is injected through introducer sheath while withdrawing the sheath to embolize the access tract. The path of embolization is seen up to the liver capsule on serial images

volume after preoperative transhepatic right portal vein embolization/transcatheter hepatic arterial embolization was more favorable than those after preoperative transhepatic PVE alone [147]. In another article where simultaneous right PVE with partial right hepatic artery ligation and ligation of the glissonian branches of segment IVb along the round ligament without parenchymal transection was done, a rapid and extensive hypertrophy of the FLR (over 100 percent at 1 week) was found [148]. Hepatic infarction and abscess formation are the main concerns of this technique, and to avoid these complications, the type of embolic material, territory of embolization, and embolization endpoint should be considered carefully.

Sequential and Simultaneous PVE and Hepatic Vein Embolization

Hepatic vein embolization either following PVE or simultaneously with PVE was found to increase FLR volume [149–152]. Embolization of hepatic vein increases outflow obstruction; this in turn obstructs hepatic arterial blood supply and further decreases any residual portal blood flow. Hepatic vein embolization was first tried as an adjunctive technique in patients with insufficient FLR volume increase following PVE [149]. In a series where 42 patients treated with adjunctive HVE following PVE, the degree of hypertrophy following PVE was 13.35% and 28.95% following PVE-HVE [150], and no procedure-related complication was found. Although the current clinical experience is limited, HVE following PVE appears to be effective and well-tolerated by patients with insufficient FLR hypertrophy following PVE.

Simultaneous PVE and HVE (liver venous deprivation (LVD)), embolization of right portal vein and hepatic vein during the same procedure, was also found to induce more FLR volume increase with no postprocedural complications [151, 152]. In 17 published literature on patients who have undergone LVD, surgical resection was not possible in only 17.6% of patients. Two patients experienced interval disease progression, and one patient had insufficient FLR hypertrophy. No patients who underwent surgery developed postoperative liver failure [136].

Alternative Procedures/Therapies

Associating liver partition and portal vein ligation in staged hepatectomy strategy (ALPPS), portal vein ligation without liver partition, and radiation lobectomy are alternatives of PVE.

ALPPS is a two-staged procedure. In stage I in situ splitting of liver and PV ligation is done. Splitting prevents tumor spread and collateral portal vein formation. Ligation of portal vein induces FLR hypertrophy. Hepatectomy, same procedure as performed following PVE, is done in stage II [153].

The main advantage of ALPPS over PVE is the greater increase in FLR size in less time. ALPPS induces rapid hypertrophy of FLR with an estimated growth rate of 22–35 ml/day (compared with 3–5 ml/day after PVE) [154]. A greater FLR

hypertrophy (76% vs. 37% for PVE) and a higher rate of completion of stage 2 hepatectomy (100% vs. 77% for PVE) are the other benefits of ALPPS [155].

ALPPS may offer alternative approach in case of preexisting portal vein thrombosis or invasion. ALPPS can be used as a salvage procedure to improve FLR for patients where sufficient FLR volume cannot be obtained after PVE [153].

Portal vein ligation (without liver partition) is similar to PVE with respect to FLR hypertrophy. In a meta-analysis of seven studies aimed to review the percentage increase in FLR and perioperative outcomes after portal vein ligation and PVE before liver resection, portal vein ligation and PVE were found to result in comparable percentage increase in FLR with similar morbidity and mortality rates [156].

Radiation lobectomy is unilobar transarterial radioembolization of the liver with yttrium (90Y)-labeled microspheres. It can induce contralateral hypertrophy. It is reported that radioembolization induces hypertrophy at a slower rate than PVE over a shorter time [157]. In presence of a large, bulky tumor adjacent to major vascular or biliary structures which must be conserved or when the ability to achieve adequate oncological margins are a concern, Y90 radioembolization can be preferred because of the advantages of both controlling and downsizing tumor while increasing the FLR [158].

Complications

Most of the complications are minor, pain, fever, and nausea, and occur in 20–25% of PVE cases [135]. Conservative approach is sufficient. Major complications are rare, occurring in less than 5% of cases. Major complications are usually related with either access or nontarget embolization. Vascular injury-related hematoma and hemobilia, bile leak and bilioma due to bile duct injury, infections (liver abscess and cholangitis), and embolization of main portal vein or portal branches of future liver remnant due to nontarget embolization are the major complications of PVE.

Injury to intercostal artery, hepatic artery, and portal vein may result in subcapsular hematoma, intraperitoneal hemorrhage, arteriovenous fistula, pseudoaneurysm, and transient hemobilia. Pain and hypotension are the most common symptoms. CT imaging can help to relieve the source and extent of bleeding. Conservative management is usually adequate, whereas transarterial embolization may be required for massive bleeding. US-guided approach prevents passage of the needle through hepatic artery, biliary tree, and metastatic tumors on the way to portal vein access. Access from a portal vein branch within the middle third, not central or exceedingly peripheral, also helps to avoid major vascular bile duct injury [159].

Biliomas occur due to bile duct injury and cause persistent abdominal pain. If it is infected, symptoms of sepsis accompany. Bile leak can also cause biliary peritonitis. CT examination can reveal low-attenuating collection. Collections can be drained percutaneously. Surgery may be required for loculated collections. Cholangitis and liver abscess may occur but rare.

Thrombus in the main portal vein (0.5–4%) or portal vein branches in the FLR (1%) may occur due to nontarget embolization [128]. Total occlusion of the portal

vein can lead to hepatic infarction and acute liver failure. Nontarget embolization of FLR portal branches may occur especially during segment 4 embolization and cause a decrease in the FLR hypertrophy. Excessive manipulation of reverse catheters may also cause thrombus formation.

If very sluggish flow inside the main portal vein is seen during PVE, embolization should be discontinued. Bland thrombus may be aspirated, or in case of nontarget glue embolization, glue cast can be retrieved by loop snare catheter [160]. Catheter-directed thrombolysis with tissue plasminogen activator can be performed. Care should be given to monitor signs of hepatic bleeding [159].

Outcomes

Portal vein embolization is overall a safe and effective technique. Technical success is close to 100% [137, 161, 162].

In patients with normal liver and liver metastases, the increase of the FLR ratio is between 8% and 25%, and regeneration is always observed after PVE [137]. Absence of hypertrophy is rare, <10% in metastatic liver, but it can reach 20% in cirrhotic patients [122, 135]. In a 23-year analysis about natural history of PVE before liver resection, sufficient FLR volume was obtained in 96% of patients after embolization [163].

PVE allowed the resection of 70–80% of participants with initially unresectable colorectal cancer metastases. Postoperative liver failure risk is 10%. The main reason for inability to undergo surgery was tumor progression [164–166].

Although PVE patients had inferior disease-free survival and a trend toward a low overall survival in the overall cohorts [167], it should be remembered that patients with colorectal cancer metastases requiring PVE for resection differ significantly from patients who underwent resection without PVE. They have a significantly higher number of metastases preoperatively (3 vs. 1; $p < 0.001$), a higher prevalence of bilateral metastases (23.5% vs. 8.8, $p = 0.028$), and a higher courses of neoadjuvant chemotherapy compared to patients who underwent surgery without PVE [165]. Therefore, adjusted or matched models are required when comparing the clinical outcomes of patients who operated with and without preoperative PVE.

In adjusted analysis the overall survival was similar in both PVE and non-PVE groups (44.7 vs. 49 months), and the disease-free survival of resected PVE patients was higher than non-PVE patients (33.2 months vs. 23.4 months, $p = 0.991$), and this suggests that PVE was not a significant predictor of a lower overall survival or disease-free survival [165].

In another study, no difference was found in terms of disease-free survival and overall survival between PVE and non-PVE groups when patients were matched to create comparable cohorts (3-year disease-free survival 16% vs. 9%, $p = 0.776$, 5-year overall survival 14% vs. 14, $p = 0.866$). Thus, there is no negative impact of PVE on long-term outcomes after liver resection in patients with colorectal cancer metastases in matched analysis [167].

Any adverse effect of PVE on postoperative hepatic recurrence and overall survival was not found in a systematic review and meta-analysis comparing outcomes of patients undergoing major liver resection with or without PVE in six non-randomized studies [168].

PVE has low morbidity and mortality rates. In a study composed of 431 patients, morbidity and mortality rates of PVE were 16.7% and 0.2%, respectively. Curative resection was not possible only in 5% of patients due to PVE-related complications [163].

Complication rates are exceedingly low. In one meta-analysis from data of 37 studies including 1008 patients, the overall complication rate was 2.2% [169].

Postprocedural Follow-Up

If no complication occurred, PVE is usually a well-tolerated procedure. Twentyto thirty percentage of patients may complain about mild to moderate pain which is relieved by oral analgesics and disappears in less than 3 days. Patient can be discharged on the same day with the procedure [135]. Repeat CT is performed after 2–4 weeks to assess FLR hypertrophy, and disease spread. If liver regeneration occurs and there is no spread of disease that would contraindicate the procedure, resection is performed. Otherwise, follow-up CT is performed at monthly intervals [137].

Lung Metastasis

Ablative Therapy

The lung is the second most common metastasis localization in colorectal cancers, with an incidence of watches between 10% and 15% [170, 171]. Metastasectomy or ablation procedure in patients with distant metastasis may increase 5-year survival rates up to numbers which vary between 27% and 68% [17, 21, 172]. However, a small number of patients with pulmonary metastasis are suitable candidate for surgery [173]. In addition, the frequency of recurrence after surgery is 20–68%, and additional surgical interventions may be challenging due to decreased pulmonary reserve [174, 175]. The advantage of ablation therapy to surgery is being a protective approach to reserve pulmonary parenchyma and pulmonary functions, and also new or recurrent metastases can be treated again [176–179].

Ablation is recommended in patients whose extrapulmonary disease or extrahepatic disease is under control. In patients who are not suitable for surgical metastasectomy, life expectancy is longer than 6 months, with lesions less than 3.5 cm in diameter, less than six metastases for each hemithorax and located more than 0.5 cm from large vascular structures are candidates for ablation [180, 181]. Although RF is widely used in tumor ablations, MW has advantages such as the fact that RF cannot provide in some ways, it can provide a more homogeneous and wide ablation

area in a shorter time, and it is less affected by the heat sink phenomenon [26, 42, 182, 183]. In addition, MW appears to be more advantageous in maintaining constant intra-tumor temperatures in tissues with high impedance and water content, such as lung metastases [42, 184].

In a study by Vogl et al., local tumor control rates were reported as 88.3%, 68%, and 69.2% for MWA, LITT (laser-induced thermotherapy), and RF, respectively. In the same study, the progression-free survival rate was reported as 54.6%, 29.1%, 10%, and 1%, respectively, in 1-, 2-, 3-, and 4-year follow-ups [182], and in the 1,-2-, and 3-year follow-ups reported by Lu et al., 47.6%, 19%, and 14.3% progression-free survival rates are similar, respectively [26]. For RF, progression-free survival rates are reported as 77.3%, 50.2%, 30.8%, and 16.4%, respectively, in 1,- 2-, 3-, and 4-year follow-ups. Although there was a statistically significant difference in local tumor control rates, no significant difference was found between ablation methods in time to progression and survival rates [182].

In a study by Kurilova et al. using the microwave technique, LTPFS (local tumor progression-free survival) progression was reported as 93%, 86%, and 86%, respectively, in 1-, 2-, and 3-year follow-ups. In the same study, it is stated that LTPFS is directly related to the minimal ablation margin, tumor size, and location, and the rate of LTP in tumors ablated with an ablation margin of less than 5 mm is 24%. It is stated that LTP rate is 19% in tumors larger than 1 cm and LTP rate is 40% in tumors larger than 1 cm and whose ablation margin is below 5 mm. The risk of LTP is 7.7 times higher in tumors showing pleural-based placement than non-pleural-based tumors [180].

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Radiotherapy in Early-Stage and Local Advanced Rectal Cancer

32

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Rectal cancer is managed by a multidisciplinary treatment approach. Local recurrences (LR) observed during the periods when curative surgery was considered as the primary treatment method have shown the necessity of adjuvant and neoadjuvant treatments in the management of the disease [1, 2].

Radiotherapy (RT) is a treatment method used for neoadjuvant, adjuvant, and palliative purposes in rectum cancer. The primary goal is to control the local disease and thus contribute to disease-free survival and overall survival. Besides, the protection of organ functions and maintenance of the quality of life are aimed in multimodality treatments.

In this section, after answering the question of whether or not there is a place for RT in early-stage rectal cancer, neoadjuvant RT ± concomitant chemotherapy (CRT) which has become the standard procedure in locally advanced-stage disease and adjuvant RT will be discussed.

Since RT is not standard in colon cancer and is not used frequently in our daily practice, it is not mentioned in this section.

The Role of RT in Early-Stage Disease

Local excision (LE) can be used instead of radical surgeries to cause less morbidity in early-stage disease. However, local recurrence (LR) rates have been reported to be higher in patients with LE than in radical surgery. This raises the question of whether RT administration before or after local excision may have a favorable effect on local control or not. The two main factors affecting the success of LE are the surgical technique and tumor pathology. In the surgical technique, the surgeon aims to remove the tumor in one piece (en bloc resection) by full-layer surgery without

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disintegration. Pathologically, the T stage, tumor size, surgical margin, grade, lymphatic invasion, and the perineural invasion status are used to determine the prognosis of the disease and to determine the need for adjuvant RT [3]. The risk of LR after local excision increases as the T stage increases. In a review of 22 studies evaluating the effectiveness of adjuvant RT after local excision, the LR rates of T_1, T_2, and T_3 cases were reported as 5.8%, 13.8%, and 33.7%, respectively [4]. In the CALGB phase II study, T_1 patients were followed up conservatively after full-layer surgery and T_2 patients had received 54 Gy adjuvant RT. After 4 years of follow-up, the local recurrence rate was 5% in T_1 patients and 14% in T_2 patients [5].

There is little experience with neoadjuvant RT in early-stage disease. There was no significant superiority of preoperative CRT in terms of LR compared to surgery alone [6]. In the multicenter, phase II, single-arm ASOSOG 06031 study, 72 patients with T_2 distal rectal cancer underwent local excision after neoadjuvant RT. The mean follow-up duration was 56 months. The 3-year disease-free survival and overall survival were not significantly different from the stage I rectal cancer who underwent total mesorectal excision (TME). The authors emphasized that local excision following neoadjuvant CRT for organ preservation is a treatment option in this group of patients [7].

In conclusion, "local excision" may be the option of surgery in selected cases. However, the type and quality of surgery affect the local disease control. Adjuvant or neoadjuvant RT is not a standard approach in early-stage disease. Pathological prognostic factors should be considered in decision-making. Patients without additional treatment should be followed up for LR.

The Role of Radiotherapy in Locally Advanced Disease

Neoadjuvant Radiotherapy

Neoadjuvant RT has become the standard treatment approach, because it is well-tolerated, increases the resectability by downstaging, and, thus, provides a chance of preserving the sphincter. The application is performed as short-course RT (25 Gy/5 fractions) and long-course RT (45–50.4 Gy/25–28 fractions) with/without chemotherapy (CT).

Neoadjuvant Short-Course Radiotherapy (SCRT)

It is the preferred treatment scheme, especially in Northern Europe and Scandinavian countries, due to a short time requirement for completion, ease of application, and cheapness. Initial studies were performed with low doses of 5 Gy in a single fraction [8, 9], but because of its ineffectiveness, it was revised to five fractions with a total dose of 25 Gy over time.

There are 12 randomized controlled trials in which SCRT was evaluated, including cornerstone studies, such as Stockholm I/II, Sweden, the Netherlands, and MRC CR 07 (Medical Research Council). In five of these studies, the local recurrence rates statistically significantly decreased with radiotherapy [10].

The Netherlands and MRC studies make a difference with TME that is the standard surgical procedure [11, 12]. Surgery following SCRT (5 × 5Gy) RT was compared with surgery alone. In both studies, although adjuvant RT and chemoradiotherapy (CRT) were applied to high-risk patients undergoing TME alone, the local recurrence rates were significantly lower in the neoadjuvant SCRT arm ($p < 0.001$, for both studies).

The results of the two meta-analyses, in which approximately 6000 patients were evaluated, contradict each other. In the meta-analysis of 14 studies by Camma et al., the 5-year overall survival ($p = 0.0003$) and cancer-related survival ($p < 0.001$) of neoadjuvant SCRT were statistically significantly longer, and the local recurrence rate was significantly lower ($p < 0.001$) [13]. In the meta-analysis of the Colorectal Cancer Collaborative Group, the local recurrence rates were decreased with neoadjuvant SCRT without a significant difference in the overall survival rates [14].

The Swedish study was the only study to demonstrate a survival advantage in all subgroups. Patients with clinical stage T_1–T_3 had undergone surgical operation 1 week after 5 × 5 Gy neoadjuvant SCRT. The local recurrence (12% vs. 27%, $p < 0.001$) and the 5-year overall survival (58% vs. 48%, $p = 0.004$) were superior to those in the control group who had undergone surgery alone [15]. At the end of 13 years of follow-up, the survival advantage (38% vs. 30%, $p = 0.0008$) and the local control rate (91% vs. 74%, $p < 0.001$) were significantly superior to in the radiotherapy group [16].

Neoadjuvant Long-Course Chemoradiotherapy (LCCRT)

The favorable results of the postoperative studies raised the question of whether we can use CRT in the preoperative period. This approach, which was accepted in the USA, has led to the design of studies in other European countries to answer the question "Is neoadjuvant CRT or neoadjuvant RT more effective?" Based on the postoperative data, LCCRT schemes were designed, which include the simultaneous addition of CT to neoadjuvant RT. Fractionation was determined as a total dose of 45–50.4 Gy, by 1.8–2 Gy daily [17].

In the French study (FFCD-9203), the patients with operable rectal cancer at a clinical stage T_3 or T_4 had undergone surgical treatment 4–6 weeks following either a total dose of 45 Gy RT alone or simultaneous RT administration with 5-FU (350 mg/m^2) plus leucovorin. Both groups received adjuvant four cycles of CT. There was no 5-year overall survival difference between the groups. However, the pathological complete response (pCR) rate was significantly higher (11.4% vs. 3.6%), and the local recurrence rate was significantly lower (8.1% vs. 16.5%) in the CRT arm. Grade 3–4 side effects were higher in the CRT arm (14.6% vs. 2.7%) [18].

A similar study was conducted by the European Organization for Research and Treatment of Cancer (EORTC). This was a randomized study (EORTC) with 2 × 2 designs in four arms with over 1000 patients. The RT dose was 45 Gy standard. Patients undergoing neoadjuvant RT vs neoadjuvant CRT arms underwent surgery, and they were randomized to adjuvant CT and follow-up arms. The survival advantage could not be demonstrated when the results were evaluated, but in the rate of pCR (14% vs. 5%, $p = 0.0001$) and local recurrence (9% vs. 17%), the results were

in favor of the CRT arm [19]. Adding CT to RT in locally advanced rectal cancer is not a survival advantage, but it is beneficial for local disease control. This makes neoadjuvant CRT a standard treatment modality [20].

Long-Course Chemoradiotherapy Versus Short-Course Chemoradiotherapy

The answer to this question varies according to the clinical stage, disease location, patient performance, surgical plan, and even the health policies of the countries. But, primarily it should be approached from a radiobiological point of view.

In the Colorectal Cancer Collaborative Group meta-analysis, the biological equivalent dose (BED) was calculated for the daily treatment dose fractions, which ranged from 1.8y to 5 Gy, and the doses were classified as lower than 20 Gy, between 20 and 30 Gy, and higher than 30 Gy. The advantage of survival and improved local disease control were shown in patients receiving RT with a dose of BED ≥30 Gy compared to those undergone surgery alone [14]. RT administered at the appropriate BED dose will contribute to local disease control and overall survival. However, it should be noted that increased daily fraction doses may increase the late side effects.

There are two European randomized trials in the literature comparing the SCRT with LCCRT. In the Polish study, a total of 316 patients were randomized into two arms. Surgery was performed 7 days following the completion of 5 × 5 Gy neoadjuvant RT in one arm, and the patients in the other arm underwent surgery after 4–6 weeks of a waiting period following the completion of a 50.4 Gy RT administered with simultaneous 5FU-leucovorin CT. There was no significant difference between the groups in terms of survival, local disease control, late toxicity, and need for permanent stoma in this study where the surgical technique was standard as TME, but the radiotherapy technique and the dose were not standard. Better results were obtained in favor of LCCRT regarding the circumferential margin ($p = 0.017$) [21, 22].

In the Australian Intergroup study, 326 patients with T_3NxM_0 clinical stage were randomized with a protocol similar to that in the Polish study. The tumor location in patients reaches up to 12 cm from the anal access. Adjuvant 5-FU-based CT was administered to both groups. The median follow-up period was 5.9 years. There was no significant difference between the groups in terms of local recurrence, survival, and late toxicity. However, long-term data are needed, especially in terms of late toxicity, in order to name one of these treatment arms a better treatment modality [23].

When evaluated clinically, the efficacy of treatment in the waiting period after RT continues. In this waiting period, downstage can be obtained in the primary tumor and lymph nodes. These responses may contribute to sphincter protection. From this point of view, it seems difficult to use these advantages with surgery after short-term treatments. Therefore, the short-term treatment scheme may be suggested for patients with upper rectal tumors in clinical T_3 stage.

How Long to Wait After Neoadjuvant Radiotherapy

The guidelines have different recommendations for the waiting period between neoadjuvant RT and surgery. For the SCRT, the European Society of Medical Oncology (ESMO) proposes to wait for a maximum of 10 days, the first day of RT being

considered as day 1 [1]; the National Comprehensive National Network (NCCN) recommends waiting for 3–7 days or 4–8 days [2]. ESMO recommends 6–8 weeks for LCCRT, and NCCN recommends 5–12 weeks [1].

According to our classical knowledge, the short waiting period in short-course RT renders the patient to undergo surgery without sufficiently waiting for the tumor response. On the other hand, the long waiting period (especially in SCRT) increases the likelihood of fibrosis development. This may lead to an increase in surgical morbidity [24, 25].

Two new randomized trials argue the prolongation of the waiting period in both SCRT and LCCRT. In the Stockholm III trial, patients with resectable cancer were randomized into three arms: surgery 1 week after 5 × 5 Gy RT, surgery 4–8 weeks after 5x5 Gy RT, and surgery 4–8 weeks after 25 × 2 Gy RT. The primary endpoint was LR in this study, which found similar outcomes in the three arms. Although there was an increase in toxicity due to RT in the delayed surgical arm after SCRT, the number of postoperative complications was lower in this group. As a result, longer waiting periods in short-term RTs may be an alternative to early surgery [26]. In the study of Terzi et al., a total of 330 patients with locally advanced disease were treated with 45 Gy pelvic neoadjuvant RT simultaneously with capecitabine or infusional 5-FU. The patients were then randomized to two arms: those who underwent surgery after a waiting period of 8 weeks and those undergoing surgery after 12 weeks. The primary endpoint of this study was a pCR. The authors found that increasing the waiting period between neoadjuvant RT and surgery from 8 to 12 weeks increased the pCR rate twice. No significant difference was found between the two groups in terms of sphincter preservation, anastomotic leakage, and post-op mortality [27].

The waiting period was prolonged up to 20 weeks in the Dutch colorectal study, which showed that the prolonged interval period did not increase the complications and could be a safe option for the organ protection protocol [28].

Adjuvant Radiotherapy

Adjuvant RT was introduced into clinical practice due to the increase in LRs in the 1990s, when surgery was accepted as the standard treatment method. The most important advantage of this method is to decide the real stage of the patient by the final pathology report after the operation and not to administer overtreatment to early-stage disease. However, the inclusion of the entire scar extending into the perineum in cases with abdominoperineal resection (APR) in the RT area, consequently the large treatment areas, and the increase in the small bowel volume descending into the pelvis in the postoperative period increase the side effects. Furthermore, the tumor bed becomes hypoxic due to surgery; thus, its sensitivity to adjuvant RT and CT decreases [29].

Studies comparing surgery with surgery+adjuvant RT showed a decrease in LR without any difference in survival, disease-free survival, and distand metastasis [14]. These findings suggested that the addition of simultaneous CT to adjuvant RT

may improve the outcomes. The first of two studies showing survival advantage with adjuvant CRT belongs to the Gastrointestinal Tumor Study Group [30]. A total of 227 patients with stage 2 B and C operated rectal cancer (R_0 resection) were randomized into the surgery group, the adjuvant CT (bolus 5-FU-CCNU) group, the adjuvant RT (40–48 Gy split course) group, and the adjuvant CRT (40–48 Gy RT bolus 5-FU) group. The study was terminated early due to the significant superiority in the CRT group. Based on the current results, the 10-year overall survival in the CRT arm versus surgery alone was found to be 45% versus 27%. The local recurrence rate was 10% versus 25% in favor of the CRT arm. The second study is the Mayo-NCCTG study. Two hundred and four T_3/T_4 or N positive patients were evaluated, and the RT and CRT arms were compared. The 5-year overall survival was superior in the CRT arm (55% vs. 40%). The 5-year locoregional failure was higher in the arm receiving RT alone compared to the CRT arm (25% vs. 13%, respectively) [31].

There are studies showing that the simultaneous administration of bolus 5-FU in addition to adjuvant RT has a favorable effect on overall survival [32]. Therefore, adjuvant RT has become a standard approach in the locally advanced-stage disease group (T3–4 or N1–2), who have not received neoadjuvant RT/CRT. It is recommended that this treatment be administered simultaneously with 5-FU or an equivalent CT of 5-FU, such as capecitabine. For patients who are expected to receive adjuvant RT, removal of the small bowel to the outside of the pelvic area with the aid of absorbable mesh or omentum flap during surgery may be a measure that reduces the RT toxicity and facilitates RT planning. Moreover, marking the residual tumor region with metallic clips in cases having surgical margin problem is important in determining the area to receive a high dose of RT [33].

Neoadjuvant RT Versus Adjuvant RT

The CAO/ARO/A10-94 study of the German Rectal Cancer Group is a randomized phase III trial comparing neoadjuvant RT with adjuvant RT. After publication of the results of this study, the role of neoadjuvant RT has been demonstrated, which has become standard clinical practice. A total of 823 patients with rectal cancer who were at T_3/T_4 clinical stage or lymph node positive were randomized into two arms. Simultaneous 5-FU (1/mg/m²/day) was administered to both arms together with 50.4 Gy RT. Furthermore, patients in both arms received adjuvant four cycles of CT. All of the surgical operations were performed by surgeons experienced in TME. The local recurrence rates of the neoadjuvant and adjuvant groups were 6% versus 13%, the regional recurrence rates were 6% versus 13%, the sphincter protection rates were 39% versus 19%, and pathological complete response rates were 8% versus 0% ($p < 0.001$), respectively. No difference in overall survival was found, and the acute and late side effects were less frequent in the neoadjuvant RT arm ($p = 0.001$ for early side effects). In addition, RT and CT completion rates were statistically significant in favor of the neoadjuvant RT arm [34]. According to the 11-year long-term results of the study, the advantage of the neoadjuvant RT arm

Table 32.1 Advantages and disadvantages of neoadjuvant RT and adjuvant RT

	Advantages	Disadvantages
Neoadjuvant RT	– Since the vascular structure is not impaired, RT and CT are more effective – Increases operability by providing tumor shrinkage – Increases the chance of sphincter preservation – Reduces locoregional recurrences – Reduces perioperative cell seeding – Reduces the side effects regarding the small bowel – More easily tolerated	– It carries the risk of overtreatment in early-stage disease – Treatment of micrometastatic disease not reflected in imaging may be delayed – The risk of post-op complications may increase and wound healing may be delayed – There may be a delay in surgery
Adjuvant RT	– Treatment is performed with the true pathological stage – Reduces locoregional recurrences – With the appropriate surgical technique, the small bowel may be left completely out of the RT area – It allows higher doses of RT to be delivered to the residual disease site	– It reduces the efficacy of RT and CT due to vascular damage and consequent reduction in oxygenation – Small bowel toxicity increases due to adhesions – Systemic treatment is delayed – Increased risk of stenosis in the anastomosis

in local disease control is still valid. Overall survival and disease-free survival advantage could not be demonstrate [35].

In a prospective non-randomized study of Akgün et al., 336 patients with locally advanced rectal cancer receiving neoadjuvant and adjuvant RT were evaluated. The mean follow-up period was 60.4 months. The neoadjuvant arm was superior in terms of lower local recurrence, higher cancer-specific survival, higher overall survival, and less adverse events; and the neoadjuvant therapy was superior in the patients' compliance [36].

The advantages and disadvantages of both treatment modalities have been summarized in Table 32.1.

Gray Zone: T3N0 Disease

As with many indications, T3N0M0 is a gray zone in rectal cancer. The question of whether adjuvant RT is necessary or whether neoadjuvant CRT should be offered is still controversial for the operated cases. Although adjuvant RT improves local disease control and survival, complications and toxicity increase after surgical treatment secondary to RT. Therefore, caution should be exercised when making adjuvant RT decision. In this group of patients, risk factors should be evaluated when adjuvant RT is decided. Prognostic factors to be considered include the degree of differentiation of the tumor, presence of lymphovascular space invasion, circumferential margin status, whether a sufficient number of lymph nodes were dissected, presence of perirectal fat tissue invasion, surgical margin status, and the preoperative CEA level (>5 ng/ml) [37].

When deciding the neoadjuvant RT, one should question how the clinical staging of the patient was made. Approximately 22% of the cases staged as clinic T3N0 were found to have metastatic lymph nodes in postoperative pathology reports [38]. While these patients may benefit from neoadjuvant RT, they are forced to receive adjuvant treatment by losing their neoadjuvant chances, since their stage is underestimated. Therefore, neoadjuvant CRT should be considered in T3N0 cases [39].

Gray Zone: Follow-Up After Neoadjuvant RT Without Surgical Intervention "Watch-and-Wait"

It is known that the prognosis of patients with a pathological complete response is better [30]. The pathological complete response is now considered as an independent prognostic factor for stage III disease [40]. Instead of performing surgery, the "watch-and-wait" approach is becoming increasingly popular in patients who showed a complete response confirmed by biopsy after long-term neoadjuvant RT [41]. In distal tumors in particular, the patients are reluctant to undergo a surgical operation due to the need for post-op colostomy. In the Habr-Gamma series, a total of 361 patients with clinical T2–4 stage or lymph node-positive disease received 50.4 Gy neoadjuvant CRT. Complete response was achieved in 34% of the cases, 73% of whom are followed-up as disease-free [42, 43]. The organ protection rate was reported to be 78% at a 5-year follow-up [44].

No statistically significant difference was found in survival and local recurrence rates between the patients with clinical complete response after neoadjuvant CRT and those with pathological complete response after surgery [45]. A thorough evaluation of the clinical complete response criteria in patients to be followed up will provide the maximum benefit from the "watch-and-wait" approach [46].

In a prospective study from Denmark, patients with a diagnosis of T2–3N0–1 distal rectal cancer received 60 Gy external CRT followed by 5 Gy endorectal brachytherapy. Tegafur-Urasil CT was given to the patients simultaneously. During 24 months of follow-up, 78% of the patients, who had achieved complete response, continued complete responsiveness, while only 26% had experienced local recurrence [47].

Although it is not a standard approach, the "watch-and-wait" approach may be an alternative in rectum cancer treatment without surgical intervention conducted by multidisciplinary teams in patients who do not wish to undergo surgery or who cannot undergo surgery due to comorbid diseases or in elderly patients.

Radiotherapy Planning/Techniques and Doses

At present, treatment simulation can be performed by computed tomography and MRI or PET. CT simulation is a widely used method. Figure 32.1 shows a computed tomography simulator and an automatic injector system used to deliver intravenous contrast.

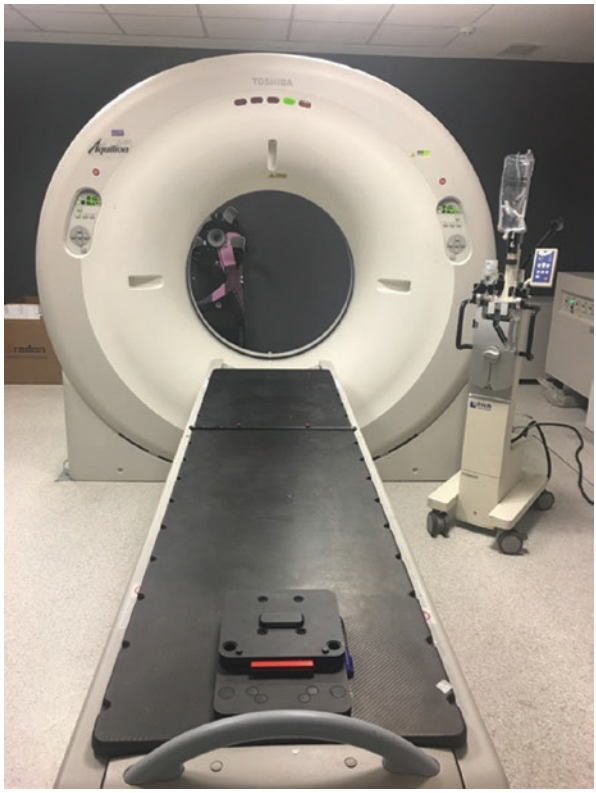


Fig. 32.1 Computed tomography simulator

Simulation

The patient is fixed by the immobilization methods such as vacuum bed and below-knee wedge. The patient can undergo treatment with supine or prone simulation. Figure 32.2a shows patients simulated in the supine position and Fig. 32.2b in the prone position.

Belly board can be used in the prone position to remove small bowel volume from the pelvic field, especially in obese patients [48]. The prone position reduces the small bowel dose by reducing the volume of the small bowel entering the treatment area [49].

Figure 32.3 depicts a belly board. It is aimed that the small bowel falls into the cavity by leaning the pubic roof against the space in the middle of the Belly board. Figure 32.4 shows a patient lying in the prone position on a belly board.

The digital reconstructed radiograph (DRR) images generated from computed tomography images taken in the prone and supine positions of the same patient are shown below. The volume colored with blue indicated the pelvic planned treatment volume (PTV), and the pink is the small bowel volume. Figure 32.5a shows that the small bowel volume has less penetration into the pelvic treatment volume in the

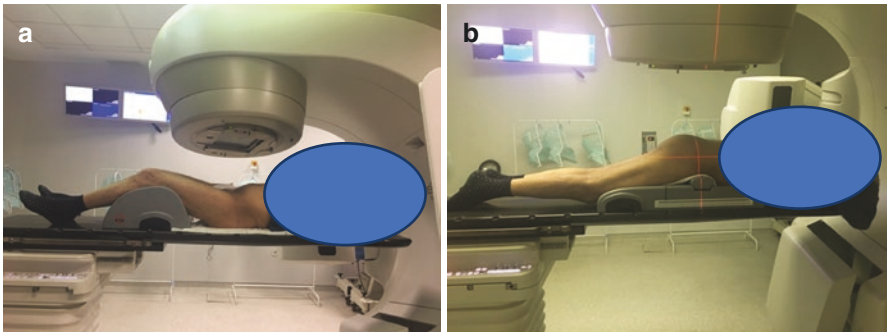
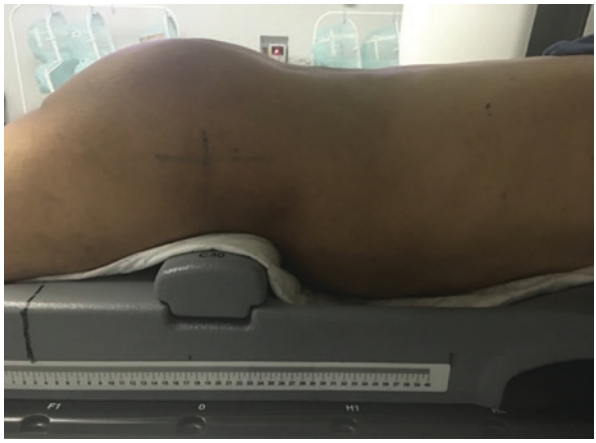


Fig. 32.2 (**a**) Supine position. (**b**) Prone position

Fig. 32.3 Belly board

Fig. 32.4 A patient lying on the belly board



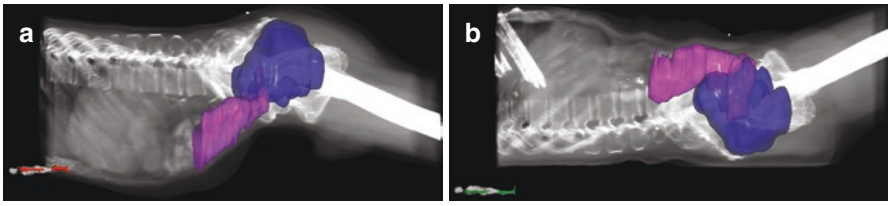


Fig. 32.5 (**a**) Prone DRR. (**b**) Supine DRR. Blue: PTV_pelvis Pink: Small bowel

prone position. In Fig. 32.5b it can be seen the small bowel volume has more penetration into the pelvic PTV.

Oral contrast helps visualize the intestine, and IV contrast helps to better visualize the bladder and tumoral structures. The full bladder pushes the small bowel out of the pelvic area, thus out of the RT area. However, it may not be possible to ensure the same amount of bladder fullness on each therapy day. The reproducibility with the empty bladder is easier. During the simulation, incision scars and anal entry should be marked with barium or wire.

Target Volume Delineation and Contouring

Neoadjuvant or adjuvant external pelvic RT areas should be designed according to the site of the disease and areas with a high risk of recurrence. Physical examination is important in definition the target volume. The location, the distance to the anal canal, and the size of the palpable mass on rectal examination and the palpable lymph nodes, if any, should be recorded. MRI has become the standard imaging technique for preoperative disease staging. MRI is superior to computed tomography in detecting mesorectal fat tissue invasion in T3 disease and adjacent organ invasion in T4 disease. MRI can be used for contouring of the primary tumor and metastatic lymph nodes by fusion with planning tomography to delineate the target volume. Another standard procedure for imaging is the PET-CT, which helps contour the gross disease. Contouring should be made by combining the physical examination findings and the radiological data. The primary tumor or the postoperative tumor bed, the anastomosis line, the presacral area, the pelvic lymph nodes, and the mesorectum should be included in the treatment area. The distal common iliac and the internal iliac lymph nodes should be included in the pelvic field in all patients. It is recommended that the external iliac, obturator, inguinal, and paraaortic lymph nodes be included in the treatment area under the conditions shown in Table 32.2, despite the fact that there is no clinical or radiological involvement [50, 51].

The upper limit of the pelvic clinical target volume (CTV) is the L5-S1 level. However, if there is a proximal lymph node involved, this limit can be extended upward. The tumor location should be considered when determinating the lower limit. Table 32.3 shows the CTV lower limit recommendations based on tumor localization.

Table 32.2 Criteria for inclusion of external iliac, obturator, inguinal, and paraaortic lymph nodes in the RT area

External iliac ln	– Anterior extension – T4 disease with adjacent organ invasion – clinical T3 disease with marked obturator lymph node involvement
Obturator ln	– Tumors located in the lower/middle rectum with mesorectal fascia invasion – Significant internal iliac lymph node involvement – Posterior clinical T4 disease
Inguinal ln	– Distally located tumors with anal canal involvement – Ischiorectal fossa invasion
Paraaortic ln	– In case of radiologically detectable involvement

Table 32.3 CTV lower limit according to tumor location

Tumor location	CTV lower limit
Tumors starting >1.5 cm above the anal-rectal ring	The lower limit of the mesorectum
Tumors starting <1.5 cm above the anal-rectal ring	It should include 1 cm proximal to the anal canal
Tumors extending along the entire anal canal	Entire anal canal and sphincter complex
Tumors infiltrating the rectal fossa	The lower limit of the ischiorectal fossa

The scars extending to the perineum should be within the treatment area in patients who have undergone APR. The boundaries of the pelvic field were determined under fluoroscopy in the two-dimensional RT era. It used to be planned by four-box (anteroposterior-posteroanterior-right lateral-left lateral) or three-field (posteroanterior-right lateral-left lateral) technique. Treatment area: The upper limit was planned to pass through the L5-S1 level and the lower limit approximately 3–5 cm below the primary tumor/tumor bed depending on the tumor localization. The posterior area should contain the sacrum and envelope the presacral area; the anterior area should cover the mesorectum roughly passing 4 cm in front of the rectum. The area should be modified according to incision scars and extra rectal extensions [29].

With the introduction of three-dimensional conformal RT, the fields to be treated were created within the concepts of gross tumor volume (GTV), CTV (standard and high risk), and PTV by adhering to the abovementioned areas. The target volumes to be generated according to the information above are given in Tables 32.4 and 32.5 [50, 52, 53].

Figure 32.6 shows the pelvic CTV contours of a patient with a diagnosis of cT4N (+) distal rectal cancer.

Fractionation and Doses

In the meta-analysis of the Colorectal Cancer Collaborative Group, a biologically effective dose of 30 Gy or more was shown to statistically significantly reduce local recurrences [14]. It was found that 45–50.4 Gy RT administered at conventional

Table 32.4 Target volumes in neoadjuvant RT

Neoadjuvant RT target volumes	Definitions
GTV	– Primary: Gross tumor volume on physical examination, colonoscopy, and radiologically visible disease – Nodal: All visible lymph nodes involved in the pelvis in the imaging
CTV_Standard risk	– Distal common iliac lymph nodes + internal iliac lymph nodes – Entire rectum + mesorectum + presacral region – External iliac lymph nodes should be included in T4 disease with anterior organ involvement and 1–2 cm margin should be given to adjacent organs – To cover the lymph nodes well, the iliac vessels should be given a margin of 0.7 cm (bone, muscle tissue should be exclude)
CTV_High risk	– GTV should be given a margin of 1.5–2 cm. – Entire rectum + mesorectum + presacral area
PTV	– CTVs are given approximately 0.5–1 cm margin according to the organ movement, set-up errors-portal imaging methods determined by each clinic

Table 32.5 Target volumes in adjuvant RT

Adjuvant RT target volumes	Definitions
CTV_Tumor bed	– Positive surgical margin or gross residual disease
CTV_Standard risk	– Distal common iliac lymph nodes + internal iliac lymph nodes – Entire rectum + mesorectum + presacral region – External iliac lymph nodes should be included in T4 disease with anterior organ involvement and 1–2 cm margin should be given to adjacent organs – To cover the lymph nodes well, the iliac vessels should be given a margin of 0.7 cm (bone, muscle tissue should be exclude) – The lower margin should extend to the pelvic floor or descend 1 cm below the anastomotic stump or rectal stump, whichever is more distal – Incision scar should be included
CTV_High risk	– Entire residual rectum + mesorectal bed + presacral region + tumor bed
PTV	– CTVs are given approximately 0.5–1 cm margin according to the organ movement, set-up errors-portal imaging methods determined by each clinic

doses could eliminate microscopic disease and increase the local disease control [54]. The meta-analysis that evaluated 2000 patients emphasized that RT doses above 50 Gy increased the local disease control rate but negatively affected the sphincter functions in the long term [55, 56].

Hyperfractionated schemes have been tested in phase I and II studies and have been found to lead to an increase in acute toxicity beside an increase in the complete pathological response rate [57]. Doses above 60 Gy are recommended after R1 or R2 resection, but it is not possible to achieve these doses with external beam RT, because it exceeds the limits of normal tissue tolerance doses [58]. Intraoperative RT may be considered as the solution to this problem [59].

The dosing schemes used in daily practice have been presented in Table 32.6 [60].

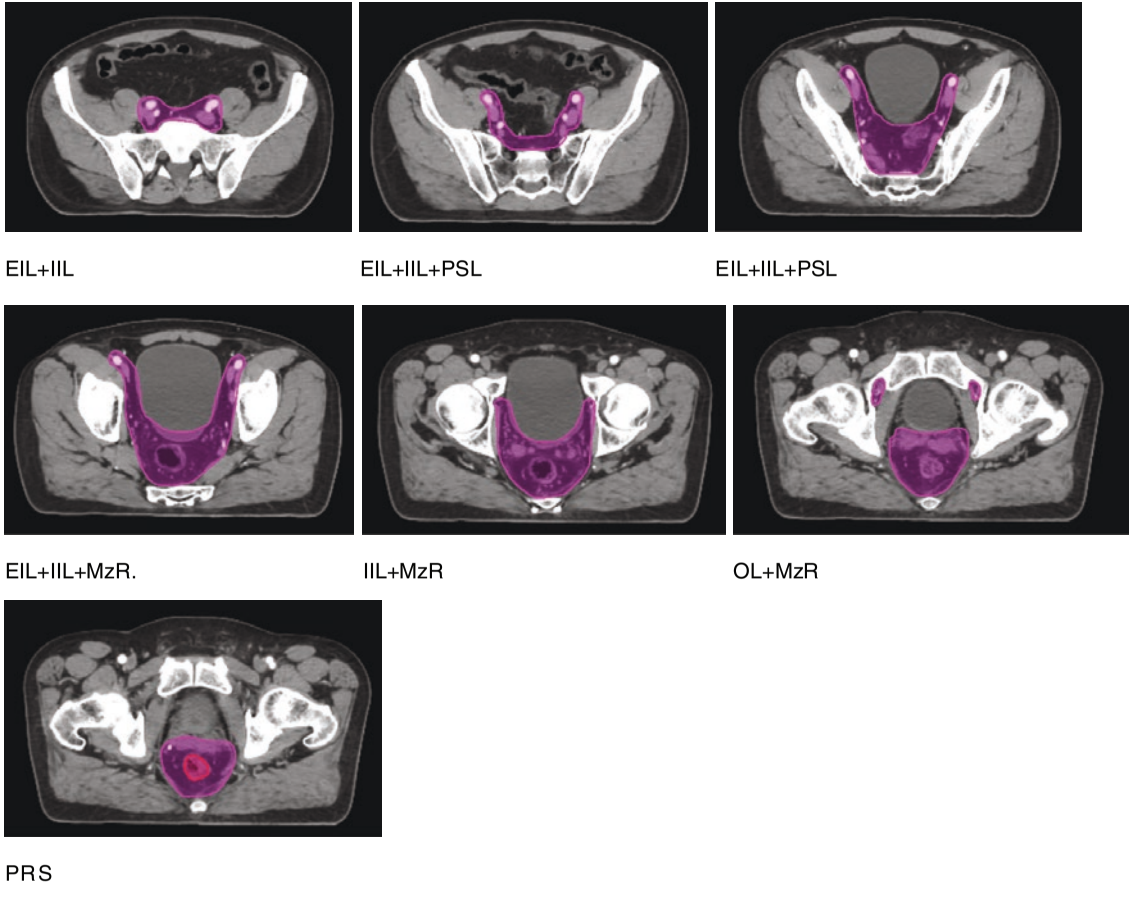


Fig. 32.6 Contouring of pelvic CTV. *EIL* external iliac lymph node, *IIL* internal iliac lymph node, *PSL* presacral lymph node, *MzR* mesorectum, *OL* obturator lymph node, *PRS*, perirectal space

Table 32.6 Dose scheme

		Conventional	SIB (Gy)
Preoperative T3N0/T1–2N+	SR HR	45 Gy/1.8 Gy fx 50.4 GY/1.8 Gy fx	45 Gy/1.8 Gyfx 50 Gy/2 Gy fx
Preoperative T4	SR HR	45 Gy/1.8 Gy fx 54–55.8 Gy/1.8 Gy fx	45.9 Gy/1.7 Gy fx 54 Gy/2 Gy fx
Preoperative short term		25 Gy/5 fx	
Postoperative (surgical margin(−))	SR HR	45 Gy/1.8 Gy fx Min 50.4 Gy, 54–55.8 Gy/1.8 Gy/fx	45.9 Gy/1.7 Gy fx 54 Gy/2 Gy fx
Postoperative (surgical margin (+))	SR HR	45 Gy/1.8 Gy fx 54- ≥59.4 Gy/1.8 Gy/fx	45.9 Gy/1.7 Gy fx 54–60 Gy/2 Gy fx

SIB simultaneous integrated boost, *Gy* gray, *fx* fraction, *SR* standard risk, *HR* high risk

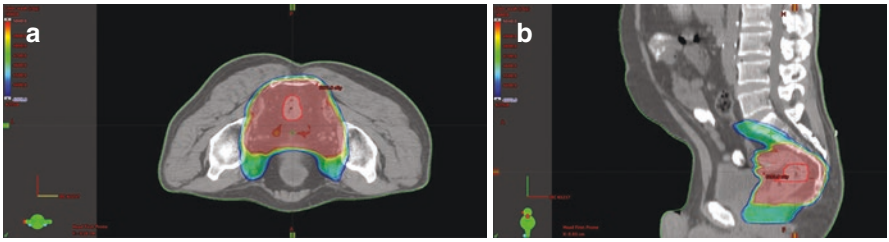


Fig. 32.7 (**a**) Dose distributions of 4275–5040 cGy in the axial plane of CT scan performed in the prone position. (**b**) Dose distributions of 4275–5040 cGy in sagittal plane

Figure 32.7a, b shows cross-sectional dose distribution images (color wash) from a treatment plan using the volumetric arc technique in a patient with stage III disease. 45 Gy was administered to the PTV_pelvis (standard risk); 5.4 Gy was administered to the mesorectum+GTV + presacral space (high risk).

Dose Limitations

The dose limitations in normal tissues have been displayed in Table 32.7 [61, 62].

Figure 32.8 shows the dose-volume histogram (DVH) values of the IMRT plan, which was designed to have a pelvic 45 Gy with a 5.4 Gy boost (total dose: 50.4 Gy) in patients with cT3N1M0 rectum cancer.

Nowadays, the intensity-modulated radiotherapy (IMRT) method is used for the treatment plans due to its superiority [63]. Besides, the simultaneous integrated boost technique provides treatment at normal tissue doses and acceptable acute side effects.

Table 32.7 Dose limitations in normal tissues

Small bowel	V15 < 120 cc V45 < 195 cc
Bladder	Dmax ≤65 Gy, V65 ≤ 50%
Femur heads	Dmax<50 Gy, V40 Gy ≤ 40%, V45 Gy ≤ 25%

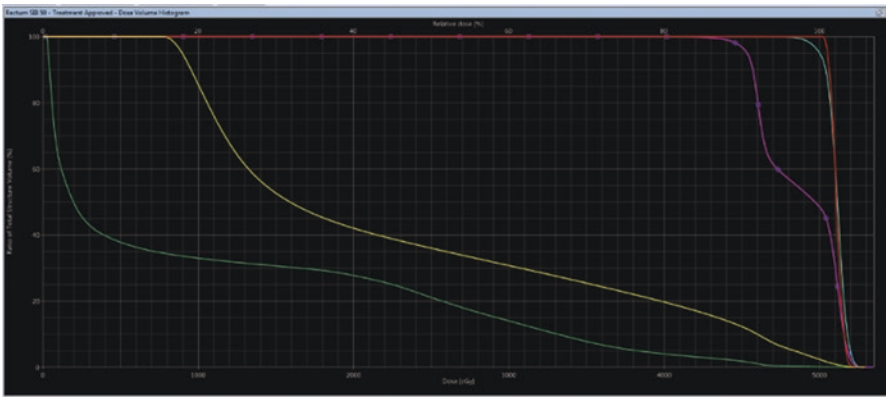


Fig. 32.8 DVH example. *Red* GTV, *light blue* PTV_50.4, *Magenta* PTV_45, *Yellow* bladder, *Green* small bowel

Side Effects

RT-related side effects can be grouped as factors related to patient and to treatment. Comorbid diseases involving all organ systems such as diabetes, obesity and vascular problems, and a previous history of pelvic surgery, as well, lead to more intense and prolonged side effects secondary to treatment. CT added to RT increases this situation. The extent of the treated area, the fraction dose, the total dose, and the technique used are important parameters for the development of early and late side effects [64]. Dysuria, proctitis, and diarrhea are the most common acute side effects [65]. The simultaneous administration of chemotherapy aggravates these side effects. These symptoms disappear in a few weeks after completion of the treatment. Symptomatic therapies, simple dietary recommendations, and hydration are usually sufficient to manage these side effects. Antispasmodic and anticholinergic drugs may be prescribed.

Late-term side effects usually develop 6–18 months later and are more severe and last longer. Persistent diarrhea, proctitis, perineal tenderness, urinary incontinence, anastomosis stricture, and bladder atrophy are the most common ones. These side effects may require long-term symptomatic treatment and sometimes surgical intervention [33].

The therapeutic effects of sucralfate for acute radiation-related proctitis, mesalazine for enteritis, and diarrhea and butyric acid for chronic radiation proctitis have been investigated in randomized trials, but their efficacy has not been established [66]. However, they continue to be used in daily clinical practice for the symptomatic treatment of these conditions.

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Radiotherapy in Recurrent and Metastatic Rectal Cancer

33

Zeliha Guzeloz Capar

Introduction

Radiotherapy (RT) has a role in recurrent disease and metastatic disease besides neoadjuvant and adjuvant purposes in rectal cancer.

We may use RT more safely in recurrent disease through newly developing techniques today. Higher doses may be reached through second-line irradiation, both with external RT and intraoperative RT.

It will be better to evaluate metastatic disease as oligo-metastatic and disseminated metastatic disease, because the curative approach has nearly become standard in patients with limited number of distant metastases through the concept of "oligo-metastatic disease," which has developed in recent years.

On the other hand, RT is a good treatment option in the treatment of symptoms like hemorrhage and pain, both in local and distant metastases in patients who have lost the chance for curative treatment.

Radiotherapy in Recurrent Disease

Local recurrences (LR) have a more heterogenous and aggressive nature compared to the primary disease. Multiple treatment modalities including surgery, RT, and CT are recommended for increasing survival [1]. Recurrences may occur in the pelvic region, tumor bed, and also in organs such as the prostate and the uterus. The recurrence rate is about 10% in patients in early stage, like T1-T2N0, who have undergone local excision, but have not undergone sufficient lymph node dissection and meso-rectal surgery [2].

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The course is more aggressive, and surgery is more difficult in recurrences. The treatment strategy should include surgery following neoadjuvant chemoradiotherapy (CRT) in the absence of previous RT. In this group, 50–54 Gy neoadjuvant CRT and subsequent surgery are recommended [3].

Being curative surgery is among the most important prognostic factors that increase the survival [4]. Intraoperative RT is an option that could contribute to local control in these patients [5].

Radiotherapy is recommended to be combined with CT in rectal cancer with local recurrence. In the study of Hegemens et al., while the median survival has been reported as 14 months in the group receiving RT only, it was found to be 29 months in the group receiving CRT [6].

Second-line RT may be tried in patients with LR who have previously received RT. Concomitant CT may be recommended in selected patients [7]. Treatment is challenging, and late toxicity rate is high in this group. Therefore, it should be preferred in experienced centers and selected patients. Chemotherapy may be used for palliation and tumor down-staging in patients for whom salvage surgery is not planned [8].

In the study of Mohuiddin et al. investigating 103 patients, who were determined to have LR and previously received RT, the re-irradiation dose was a median 34.8 Gy (15–49.4 Gy). Surgery was performed in 34 patients after re-irradiation. The median survival was found to be 26 months, and the 5-year overall survival was found to be 19%. In the subgroup analysis, median survival between those who underwent surgery following re-irradiation and did not go to surgery following re-irradiation was 44 months vs 14 months, respectively, and 5 years overall survival were found to be higher for surgery group (22% vs. 15%, $p = 0.001$). Late complications were reported in 22 patients [9].

In a study retrospectively investigating 147 rectal cancer patients with LR, 30.6 Gy re-irradiation was administered to 57 patients, and the 5-year overall survival was found to be 32% in patients who had subsequently undergone surgery and intraoperative RT and 48% in patients who could undergo R0 resection [10].

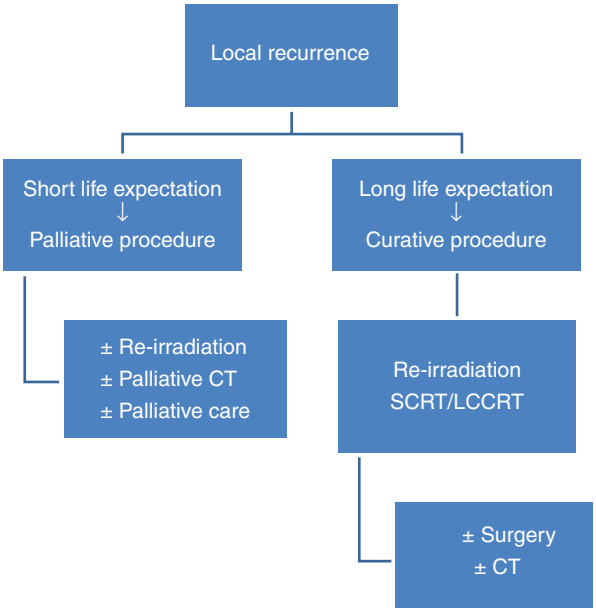
The recommended re-irradiation dose is 30–40 Gy in patients who have previously received RT [7]. Care should be taken for small bowel toxicity. Survival and local control of the patients are better in patients who have undergone R0 surgery, although this is not very clear. Table 33.1 depicts the treatment algorithm in patients who were determined to have LR.

Radiotherapy in Metastatic Disease

Survival has prolonged up to 2 years through the developments in systemic treatments in metastatic colorectal cancers [11]. Surgery, radiofrequency ablation, cryosurgery, and stereotactic body RT (SBRT) have increased the survival in liver metastases [12]. Also metastases can be controlled with surgery and SBRT in lung metastases.

Synchronized metastatic foci are present in 2–5% of colorectal cancers at the time of the diagnosis. Most of these foci are in the lungs and the liver. Metastatic

Table 33.1 Treatment algorithm in local recurrence



CT chemotherapy, *SCRT* short-course radiotherapy, *LCCRT* long-course chemoradiotherapy

disease, which has a maximum number of 5 or is at a limited number, which does not progress during treatments, and which is limited to one organ, is defined as "oligo-metastatic disease" [13, 14]. A small number of metastatic foci are staged as "oligo-metastatic," and a chance for curative treatment is given to the patient [15]. This group of patients should be differentiated from widespread metastatic stage. The crucial point for making a decision for treatment is performing R0 resection or not. In this context, the patients should be supported with local ablative treatments (i.e., radiofrequency ablation, cryotherapy, microwave ablation, brachytherapy, external RT, radioembolization, chemoembolization) and systemic treatments. Single organ metastases (mostly liver) or few metastases in a few organs (like lungs) or isolated bone metastases should be considered for curative therapy as complete response may be achieved at a rate of 20–50% in many serials if R0 resection can be performed [16].

Guidelines such as NCCN [17] and ESMO [18] recommend beginning the treatment with systemic treatment despite the absence of a standard approach. Short-term RT may be preferred for not prolonging the surgery time. Single-center studies report that capecitabine-oxaliplatin-bevasizumab combinations could be added to short-term RT [19]. Timing of surgery is still of debate. Removal of synchronized metastases together with the primary tumor is preferred. On the other hand, some studies recommend the "watch-and-wait" approach, particularly for lung metastases with better course [20].

SBRT has gained popularity due to being an alternative to surgery for ablative treatment of synchronized metastases and also for being noninvasive and easily available. Stereotactic RT was proven to increase survival in oligo-metastatic disease in phase II randomized studies [21]. Franzese et al. reported the 1-, 3-, and 5-year overall survival rates as 88.5%, 56.6%, 37.2% and local control rates as 95%, 73%, and 73%, respectively, in their oligo-metastatic colorectal cancer series of 270 patients with synchronized lung and liver metastases who underwent SBRT [22].

Most publications report oligo-metastatic rectal cancers with liver and lung metastases presentation. Favorable local control outcomes were obtained with SBRT administered to metastatic liver and lung metastases in oligo-metastatic rectal cancer. Local failure was associated with lesion size and insufficient dose [23, 24]. In the study of Thompson et al., better local control was reported with high-dose SBRT administered to the colorectal cancer patients with liver metastases [25]. Hence, SBRT may be a good treatment option for patients for whom surgery cannot be performed [26, 27]. The ESMO metastatic colorectal cancer guidelines also recommend SBRT as an applicable and safe treatment method with evidence level of IV-B in patients who cannot be operated or applied the other ablative methods [18]. Figure 33.1 shows the SBRT plan for liver metastasis in a patient who has

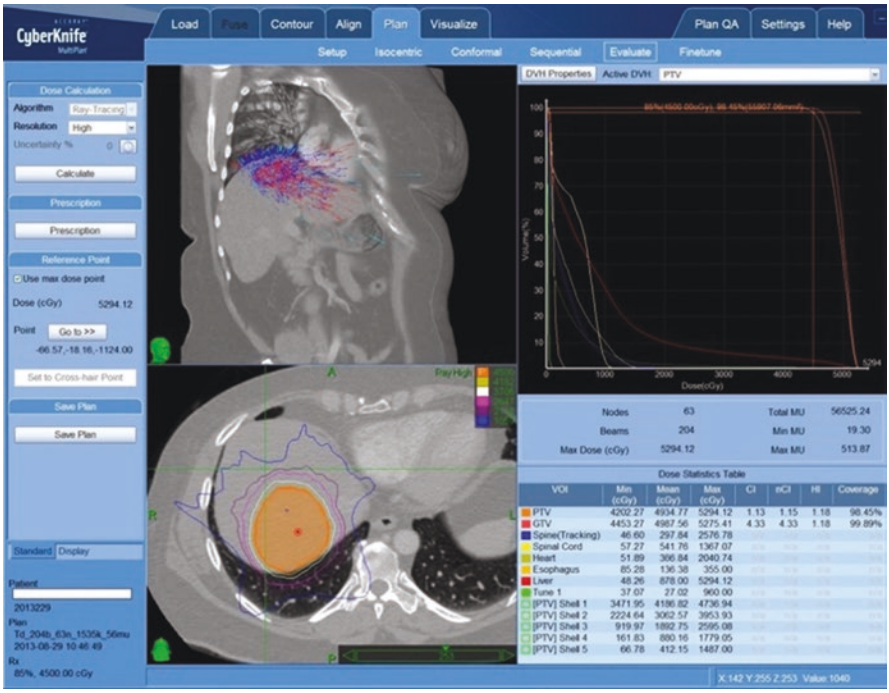


Fig. 33.1 SBRT plan of a single liver metastasis (Planning photo was used with permission from Adem Sengul, MD from the Katip Celebi University Atatürk Research and Training Hospital, Department of Radiation Oncology)

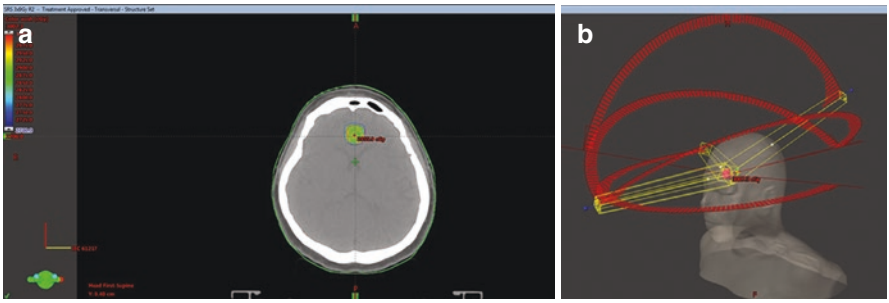


Fig. 33.2 (**a**) Operated rectal cancer patient, 46 years old. The patient underwent surgery due to detection of isolated cerebral metastasis on the follow-up. (**a**) Tomography contour image of the patient who was administered 27 Gy in three fractions to the tumor cavity with stereotactic RT, (**b**) stereotactic RT plane of the same patient

oligo-metastatic rectal cancer with liver metastasis. A total of 45 Gy/3 fractions were administered to a single liver metastasis.

SBRT may also be applied in oligo-metastatic bone, cerebral metastases besides the liver, and lung metastases. Figure 33.2a, b shows images of the cranial SBRT plan.

It is the best to determine the treatment strategy according to the patient in multidisciplinary councils. Table 33.2 shows the treatment algorithm and options in metastatic colorectal cancer.

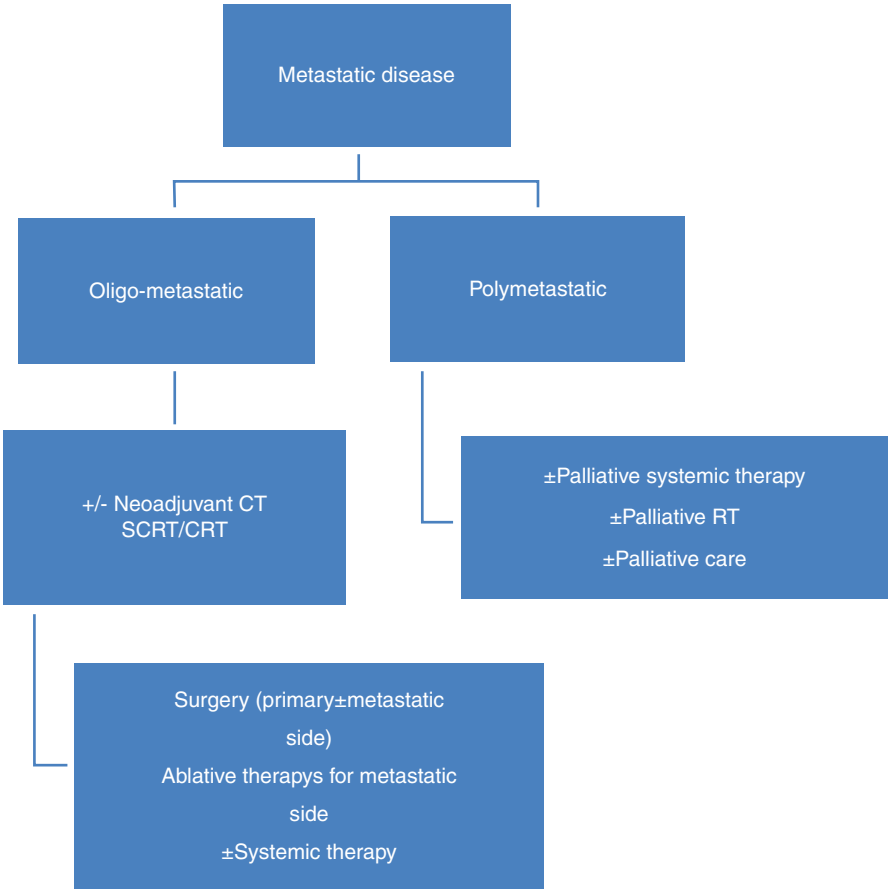
In colorectal cancers palliative RT can be applied for bone, soft tissue, lymph node, and solid organ metastases as in other organ cancers. RT is used for different purposes including pain palliation, reducing the compressive effect, and stopping hemorrhage in widespread metastatic and recurrent disease.

Figure 33.3 shows the magnetic resonance imaging and RT plan in the axial and sagittal plain of patients who was a 64-year old with rectal cancer and who has metastatic disease and local recurrence. Palliative RT was applied to the recurrent primary tumor due to rectal hemorrhage. Rectal hemorrhage could be completely palliated. The patient is being followed up with systemic treatment.

Table 33.3 below shows an example dose-fractionation scheme for SBRT and conventional palliative treatment applied in our clinic. The doses may be modified by the physicians according to patient and planning characteristics.

SBRT: stereotactic body radiotherapy; *fr:* fraction

Table 33.2 Treatment algorithm in metastatic colorectal cancer



SCRT: short-course radiotherapy, *CRT:* chemo-radiotherapy, *CT:* chemotherapy, *RT:* radiotherapy

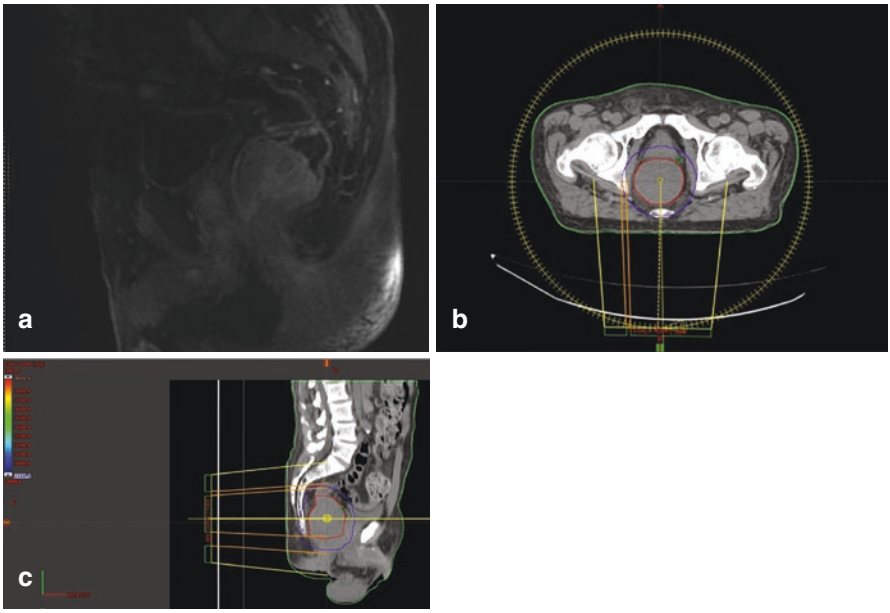


Fig. 33.3 (**a**) MRI shows local recurrence findings. (**b**) Radiotherapy plan in the axial plain, red, primary tumor; purple, planned treatment volume. (**c**) Radiotherapy plan in the sagittal plain, red, primary tumor; purple, planned treatment volume (MRI image was used with permission from the Radiology Clinic of Tepecik Research and Training Hospital, Health Sciences University)

Table 33.3 Radiotherapy doses applied in our clinic for re-irradiation, SBRT and palliative irradiation

Pelvic re-irradiation	30–40 Gy/1.8–2 Gy fr
Liver SBRT	45 Gy/3 fr
Lung SBRT	25–34 Gy/1 fr, 54 Gy/3 fr, 48 Gy/4 fr, 50 Gy/5 fr, 60 Gy/8 fr
Bone SBRT	16–18-24 Gy/1 fr, 24 Gy/2 fr, 30 Gy/4 fr, 24Gy/3 fr
Cerebral SBRT	16–20 Gy/1 fr, 24 Gy/2 fr, 27 Gy/3 fr (cavitary irradiation)
Palliative irradiation	20 Gy/4–5 fr, 30 Gy/10–12 fr, 8 Gy/1–2 fr

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Systemic Chemotherapy in Colorectal Cancer

34

Olcun Umit Unal, Murat Keser, and Baran Akagündüz

Abbreviations

5-FU	5-Fluorouracil
BSC	Best supportive care
CRC	Colorectal cancer
DFS	Disease-free survival
EGFR	Epidermal growth factor receptor
FGFRs	Fibroblast growth factor receptors
FGFs	Fibroblast growth factors
HR	Hazard ratio
IV	Intravenous
LV	Leucovorin
mCRC	Metastatic colorectal cancer
MOSAIC	Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer
nCRT	Preoperative concomitant radiochemotherapy
OS	Overall survival
PFS	Progression-free survival
VEGF	Vascular endothelial growth factor

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O. Engin (ed.), *Colon Polyps and Colorectal Cancer*,
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Chemotherapy Definitions

Chemotherapy covers a wide range of treatments. Terms such as "adjuvant," "neoadjuvant," and "palliative" generally contribute to confusion surrounding chemotherapy if not properly defined and described. The purpose of this page is to increase the level of understanding of the various chemotherapy protocols currently in use.

Adjuvant chemotherapy: Chemotherapy given to destroy any remaining (microscopic) cells that may be present after removal of the known tumor by surgery. Adjuvant chemotherapy is given to prevent a possible cancer recurrence.

Neoadjuvant chemotherapy: Chemotherapy given before surgery. Neoadjuvant chemotherapy may be given to reduce cancer, so that the surgical procedure does not have to be so comprehensive.

First-line chemotherapy: Research and clinical studies have shown that chemotherapy is most likely to treat a particular cancer. This can be called standard therapy.

Secondary chemotherapy: Chemotherapy given if a disease does not respond or recur after primary care chemotherapy. Secondary chemotherapy has been found to be effective in the treatment of a certain cancer that does not respond or recur after standard chemotherapy through research and clinical research. In some cases, this may also be called recovery therapy.

Palliative chemotherapy: Palliative chemotherapy is given specifically to address symptom management without waiting to significantly reduce cancer.

Chemotherapy treatment should be performed in centers where doctors, nurses, and health personnel are trained. Chemotherapy drugs can be given intravenously, orally or into body cavities [1]. Intravenous chemotherapy drugs are mixed into the serum and given for various periods. Chemotherapy should be prepared in a closed system safe cabinet. The chemotherapy unit should be planned separately in other departments, and a suitable infusion pump set should be available for each patient. Long-term applications may require hospitalization. Some chemotherapy medications (e.g., infusion 5-fluorouracil) may require long-term intravenous administration. For this type (long term infusional) of drug, called port, the drug directly to the main vein devices that provide chemotherapy is inserted. How to use them is very important and must be taken under expert control. There should be sufficient bone marrow reserve and adequate liver and kidney function to give chemotherapy to a patient [1–3].

Neoadjuvant Treatment in Colorectal Cancer

In colorectal cancer, neoadjuvant therapy is used as neoadjuvant chemoradiotherapy or only neoadjuvant radiotherapy in rectal cancer [2]. Intravenous 5-fluorouracil or oral capecitabine is used as chemotherapy [3]. The locoregional recurrence rate of resectable stage II–III rectal cancer patients was between 15% and 65% [4]. Even with total mesorectal excision, the local regional recurrence rate of stage III patients is about 20–30% [5]. Resectable stage II–III patients should receive neoadjuvant therapy before surgery to improve local control rate and long-term survival rate [6]. Preoperative concomitant radiochemotherapy (nCRT) has become the standard

treatment for resectable stage II–III patients [7]. Preoperative concomitant chemoradiotherapy is the only standard treatment for nonresectable locally advanced rectal cancer, and most of these patients become resectable after nCRT [8]. This is explained in detail in the section on radiotherapy.

Adjuvant Therapy

Patients with stage III colon cancer and selected patients with stage II disease benefit from adjuvant chemotherapy. Stage 2 colon cancer may benefit from treatment: T4 tumors or poorly differentiated histology or intestinal perforation during presentation or sampled less than 12 lymph nodes or lymphovascular invasion or perineural invasion [9]. Stage II patients with microsatellite instability do not benefit from adjuvant therapy, and adjuvant therapy is not recommended for these patients [10]. Adjuvant therapy is not recommended in patients with stage I disease [11]. 5-Fluorouracil-based therapies form the basis of current adjuvant therapy. Oxaliplatin has no utility in stage II disease but has been shown to be beneficial in stage III disease. The following describes the agents used in adjuvant treatments and their studies, respectively.

FU-Based Treatment

Bolus 5-fluorouracil (5-FU) and leucovorin (LV) improved patient outcomes and became the standard of care in the early 1990s for patients with high-risk colon cancer (T4 tumors, poorly differentiated, etc.) with postoperative adjuvant chemotherapy [12]. Continuous infusion used in metastatic disease shows a better toxicity profile and at least similar efficacy results compared to bolus 5-FU/LV combination regimens. Comparing these two regimens in adjuvant therapy, disease-free survival (DFS) and overall survival (OS) results are not statistically different between treatment groups [13, 14].

Oral Fluoropyrimidines

First oral fluoropyrimidine is capecitabine. Capecitabine examined X-ACT study in adjuvant therapy. The findings of the study showed that capecitabine was at least as effective as IV bolus 5-FU/LV and had a better toxicity profile [15]. 5-Year OS data showed similar efficacy for both treatments [16]. Second agent is UFT [17]. UFT was compared to bolus 5-FU/LV [18]. The results were similar in a 5-year DFS (68.3–66.9%) and OS (78.7–78.7%), with a similar toxicity profile and improved quality of life for patients treated with UFT/LV. Third agent is S1. S-1 is approved for CRC treatment only in Japan and Korea. This fluoropyrimidine has not been optimally developed in the Western world, and data from well-designed clinical studies are lacking [19].

5FU-Based Combination Regimens with Oxaliplatin

It has been shown that 5-FU-based combination regimens containing oxaliplatin prolong survival in patients with metastatic disease [20]. These combinations have also been studied in adjuvant therapy. The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) in Colon Cancer Adjuvant Treatment compared the bolus and infusional 5-FU regimen combined with LV with the same regimen plus oxaliplatin (FOLFOX4). Significant improvement was observed in 3-year DFS for the oxaliplatin-containing regimen. DFS rates at 3 years were 72.9% and 78.2%, respectively [21]. Based on these findings, the FOLFOX4 regimen was the standard adjuvant treatment for patients with stage III colon cancer [22]. Additional follow-up showed that the advantage of FOLFOX4 was maintained [23].

After the successful FOLFOX regimen, a phase 3 study comparing the capecitabine-oxaliplatin combination with this regimen showed that both regimens were equal. After a mean follow-up of 74.7 months, both DFS and OS were equal. Nowadays, stage III colon cancer adjuvant therapy is FOLFOX or capecitabine-oxaliplatin combination regimen [24].

Targeted Treatments

To date, adjuvant studies with both EGFR- and VEGF-targeted therapies have been negative [25, 26]. Therefore, this group of agents is not recommended for adjuvant treatment of colorectal cancer [27, 28].

Adjuvant Chemotherapy Duration

In the earliest adjuvant chemotherapy studies for colon cancer, patients were treated for 12 months [29]. Subsequent studies compared 12- and 6-month treatments in stage III colon cancer, and treatments given in both periods were equally determined [30]. However, 6-month oxaliplatin-based chemotherapy can cause permanent neurotoxic side effects that may affect the patient's daily functioning [31]. A shorter duration of adjuvant chemotherapy was investigated due to the oxaliplatin cumulative neurotoxicity.

Study was carried out in 12 countries simultaneously to investigate 3 or 6 months of adjuvant FOLFOX or CAPOX chemotherapy with 6 randomized phase III (SCOT, TOSCA, Alliance/SWOG 80702, IDEA France, ACHIEVE, HORG). This prospective, pre-planned, International Duration Evaluation of Adjuvant Chemotherapy (IDEA) international resulted in a time assessment, a pooled analysis of 12,834 patients with stage III colon cancer over 6 studies [32]. It has been shown that a 6-month adjuvant chemotherapy provides a <1% benefit over a 3-month adjuvant therapy. In the subgroup analysis of the IDEA study, it was divided into two risk groups. Low-risk patients were identified as T1–3 and N1, and high risk was defined as T4 and/or N2. In patients at low risk, CAPOX chemotherapy

regimen showed noninferiority for 3 and 6 months (3-year DFS HR 0.85, 95% CI 0.71–1.01; the 3-year DFS rate is 85.0% vs. 83.1%). However, it was found that there was no noninferiority in low-risk patients treated with FOLFOX in the low-risk group (3-year DFS HR 1.10, 95% CI 0.96–1.26; 3-year DFS rate 81.9% vs. 83.5%). Similarly results, 3-month treatment versus 6-month treatment in high-risk patients receiving CAPOX (3-year DFS HR 1.02, 95% CI 0.89–1.17; The 3-year DFS ratio was 64.1% vs. 64.0%). Similarly, it was found that there was no inferiority 6 months treatment versus 3-month treatment in high-risk patient receiving FOLFOX (3-year DFS HR 1.20, 95% CI 1.07–1.35; the 3-year DFS rate was 61.5% vs. 64.7%). As a result, adjuvant chemotherapy duration in colorectal cancer is 6 months [32, 33]

Follow-Up in Operated Colorectal Cancer Patient

Follow-up programs for patients with curatively resected colorectal cancer increase survival [33]. Patients should be informed about the risk of disease recurrence or secondary bowel cancer, the potential benefits of follow-up, and uncertainties that require further clinical research. In patients with a high risk of recurrence (stage IIb and III), clinical evaluation is recommended when symptoms occur or at least every 6 months for the first 3 years and at least 5 years annually [34]. During these visits, blood CEA, chest x-ray, and liver imaging are recommended in patients [35]. For patients with a lower risk of recurrence (stage I and Ia) or concomitant diseases that disrupt future surgery, control is recommended only annually or when symptoms occur [36]. All patients should undergo colonoscopy before the first surgery or within 6 months and should be repeated once a year if villous or tubular adenomas greater than 1 cm are found; otherwise, repetition is recommended every 3–5 years [37]. All patients with recurrence should be evaluated by a multidisciplinary team in a cancer center [38].

Systemic Therapy in Metastatic Colorectal Cancer

Approximately 20% of patients with colorectal cancer are at metastatic stage at the time of diagnosis. With the regular use of current treatment options, it is possible to achieve a 3-year survival in mCRC patients. This section describes current treatment regimens, new potential targets, and treatments in mCRC patients [38, 39].

First-Line Chemotherapy Protocols

In the 1990s, 5-fluorouracil/leucovorin was a standard treatment for mCRC treatment with approximately 10 months of survival [39]. In the 2000s, approximately 20 months survival was achieved with irinotecan or oxaliplatin [40, 41]. FOLFOX and FOLFIRI chemotherapy regimens were created by adding irinotecan or oxaliplatin to infusional 5-fluorouracil/leucovorin. These two chemotherapy regimens emerged as standard first-line chemotherapy options in the 2000s in the treatment of mCRC [41].

First-Line VEGF-Based Treatment Protocols

One of the well-defined targets in mCRC is angiogenesis [42]. The most important factor controlling angiogenesis is vascular endothelial growth factor (VEGF) [43]. Bevacizumab is a humanized monoclonal antibody that targets VEGF-A. The addition of bevacizumab to different first-line chemotherapy regimens showed significant survival results. The AVF 2107 study showed that the addition of bevacizumab to IFL resulted in significantly longer mOS (20.3 vs. 15.6 months, $p < 0.001$) [42]. Intergroup N9741 study also showed that the addition of bevacizumab to FOLFOX chemotherapy increases survival [43]. In later studies of bevacizumab, it was studied in combination with FOLFOX, FOLFİRİ, and XELOX chemotherapy regimens. Survival results were similar in these studies [44, 45]. As a result, bevacizumab is used in the first-line treatment with both irinotecan- and oxaliplatin-based treatments in mCRC.

First-Line EGFR-Based Treatment Protocols

Epidermal growth factor receptor (EGFR) plays a role in autocrine and paracrine control of colorectal cancer cell development and development of angiogenesis and metastasis. Two monoclonal antibodies targeting EGFR in the treatment of mCRC are cetuximab and panitumumab. Cetuximab is human/mouse chimeric monoclonal antibody that binds to the extracellular part of EGFR. Panitumumab is a humanized antibody. Both agents are effective only in mCRC with wild-type RAS. The efficacy of cetuximab in first-line therapy was investigated in the CRISTAL study. In this study, a total of 1198 patients were randomized to compare FOLFIRI and FOLFIRI plus cetuximab. In KRAS-WT patients, FOLFIRI plus cetuximab significantly prolonged mOS (23.5 and 20.0 months, $p = 0.0093$) and mPFS (9.9 and 8.4 months, $p = 0.0012$) compared to FOLFIRI alone [46]. The efficacy of panitumumab in first-line therapy was investigated in the PRIME study [47]. In the PRIME study, panitumumab was added to FOLFOX in the first-line treatment. The KRAS-WT cohort, PFS in panitumumab plus FOLFOX compared to FOLFOX alone (9.6 vs. 8.0 months, HR 0.80, 95% CI 0.66–0.97, $p = 0.02$) without significant increase in OS ($p = 0.02$). In contrast, the KRAS-MT group had PFS ($p = 0.02$) and a tendency towards poor mOS (15.5 vs. 19.3 months, 95% CI 0.98–1.57) ($p = 0.068$) in the group receiving panitumumab. Today, cetuximab or panitumumab plus FOLFIRI or FOLFOX chemotherapy is accepted as standard treatment in KRAS wild-type mCRC [46, 47].

Second-Line Treatment Options

Whether progression has been observed on the first line with oxaliplatin- or irinotecan-based chemotherapy regimens, it is an appropriate approach to evaluate the other combination regimen. The response rate with the second-line FOLFIRI chemotherapy regimen was 4–12% and PFS 2.5–4 months [41]. Similarly, the response rate with the second-line FOLFOX chemotherapy regimen was 9–15% and PFS 4.2–4.7 months [41].

Aflibercept is a recombinant fusion protein that prevents binding to VEGF-A, VEGF-B, and placental growth factor receptor. This agent has been evaluated in the VELOUR study in mCRC patients who have previously progressed with oxaliplatin-based regimens with or without bevacizumab. In this study, FOLFIRI plus aflibercept and FOLFIRI were compared. FOLFIRI plus aflibercept achieved a 1-month survival increase in both PFS and OS [48].

Ramucirumab is a human monoclonal antibody that targets VEGFR2 and is located on the surface of endothelial cells. In the second-line treatment, FOLFIRI plus ramucirumab achieved a 2-month survival increase in both mOS and mPFS [49].

Anti-EGFR agents were evaluated in the second-line mCRC treatment. The combination of irinotecan and cetuximab in the second line of treatment in mCRC was compared with single-agent irinotecan. In this study better response rate (16–4%) and better PFS (4–2.6 months) were found in the combination arm [50, 51]. Similarly, it has been observed that FOLFIRI plus panitumumab combination provides better response rates and PFS than FOLFIRI chemotherapy regimen in second-line mCRC treatment.

Microsatellite instability (MSI) is due to incomplete mismatch repair system (dMMR), which is responsible for correcting nucleotide base errors during DNA replication. The most commonly affected mismatch proteins include MLH1, MSH2, MSH6, and PMS2. MSI-high (MSI-H) status is found in 3–5% of mCRC cases. Evidence from previous studies of anti-programmed cell death protein 1 (PD-1) checkpoint inhibitors has demonstrated that dMMR/MSI-H status is a biomarker predictive of response to anti-PD-1 therapy. Nivolumab and pembrolizumab, two anti PD-1 antibodies, were evaluated by studies in second-line mCRC therapy [51–53]. Thirty to fifty percentage of response rate was detected in both agents and approved by the Food and Drug Administration in 2017.

Third-Line Therapy

Today, there are two agents and studies in third-line therapy. The first one is trifluridine-tipiracil (TAS-102). TAS-102 is an oral nucleoside antitumor agent consisting of trifluridine and tipiracil hydrochloride. TAS-102 evaluated by a study among patients thought to be resistant to conventional chemotherapy and biological agents and was associated with a 2-month prolongation of mOS [54]. The second one is regorafenib. Regorafenib is a multimolecular targeted drug inhibiting angiogenesis and apoptosis. Regorafenib shown to improve OS compared with placebo in patients with mCRC refractory to standard chemotherapy in a randomized phase III CORRECT trial [55].

Treatment of Rare Conditions

BRAF Mutation

The BRAF gene is located on human chromosome 7 and encodes the BRAF protein, also known as serine/threonine protein kinase. Activating BRAF mutations often occur at codon 600 and are known as the V600E mutation; this is found in less than 10% of sporadic CRC cases [56]. BRAF mutants mCRC were significantly

associated with poor survival. mCRC patients with BRAF V600E mutation were evaluated by the BEACON study in combination of binimetinib, encorafenib, and cetuximab. For this poor group of tumors, 48% response rate, PFS was 8 months, and mean OS was 15 months. With this study, this combination has become the standard treatment for BRAF mutant mCRC tumors [57].

Her2

Her2 amplification is overexpressed in breast and stomach cancer [57, 58]. Her2 mutations were detected in 5% of CRC patients [59]. In addition, Her2 amplifications were most common in KRAS and BRAF wild-type patients. HERACLES-A study investigating the combination of trastuzumab and lapatinib was performed after failure of standard treatments in EGFR-resistant KRAS wild-type (exon 2 codons 12 and 13), metastatic CRC patients [60]. The majority of patients (74%) received higher or equal treatment than the previous four treatment sequences. The ORR of 27 patients was 30% (n = 8; 4% complete response and 26% partial response), and 44% had stable response. In general, disease response and/or disease control lasted 4 months or longer in 59% of patients. Thus, the disease was controlled at 74% and followed for a mean of 94 weeks. The most common side effects of treatment are well tolerated with diarrhea, rash, dry skin, fatigue, and paronychia, but fatigue is the only grade 3–4 side effect seen in more than 10% of patients. Studies for similar targeted therapies (pertuzumab, trastuzumab emtansine, and the like) for Her2-positive mCRC are ongoing [58–60].

Fibroblast Growth Factor Receptor

Fibroblast growth factor receptors (FGFRs) include 18 secreted glycoprotein ligands and four tyrosine kinase receptors (FGFR1, 2, 3, and 4) that bind to any of the fibroblast growth factors (FGFs) [61]. FGFR overexpression has been identified in CRC samples and is assumed to play an important role in this disease. FGFR may represent a potential therapeutic strategy to overcome resistance in CRC [62]. There is now ponatinib with anti-FGFR activity in various malignancies in clinical trials. In addition, regorafenib, an oral multikinase inhibitor with relative activity against FGFR 1 and 2, has been approved for the treatment of refractory metastatic CRC [63].

Conclusions

5-FU-based chemotherapy is the gold standard for adjuvant treatment of colorectal cancer. Only 5-FU-based chemotherapies are in the foreground in stage II disease, whereas 5-FU and oxaliplatin combinations are standard treatment for stage III disease. There are many treatment options for the metastatic stage. The sequential use

of these treatment options is important. Agents from eight different classes (fluoropyrimidines, irinotecan, oxaliplatin, anti-EGFR agents, anti-VEGF agents, regorafenib, TAS-102, anti-PD-1) show anti-tumoral activity at this stage.

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Urological Manifestations of Colorectal Malignancies and Surgical Management of Urological Complications During Colorectal Cancer Surgeries

35

Zafer Kozacioglu and Erdem Kisa

Introduction

The close relation between the colorectal and the urogenital organs may lead to direct invasion. Besides, although it is rare, urogenital organ involvement may occur through distant metastasis of colorectal cancers. Whether the urogenital organ involvements are diagnosed during the primary diagnosis of colorectal cancer or its recurrence, the primary purpose is both to optimize the oncological status and to develop a treatment plan to maintain urological function.

The objective of this review is to serve as a guide for the diagnosis and treatment planning of urogenital organ involvement through distant metastasis of colorectal cancers or invasion in locally advanced stage. It is also intended to create a diagnosis and treatment algorithm in iatrogenic urogenital organ injuries which may occur during colorectal cancer surgery.

Renal Metastasis

Renal metastasis of colorectal cancer is very rare, while it constitutes 2.8% of the secondary renal cancers in postmortem series [1]. Local or distant metastases of colorectal cancers generally occur as a lymphatic or venous spread. Arterial dissemination in these cancers is around 3% which is the main route of spread of colorectal cancers to the kidneys [2–4]. Renal invasion of colorectal cancers through extraluminal dissemination is also reported in the literature [5]. Patients may apply with flank pain or hematuria, or they may be asymptomatic.

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While most of the metastatic lesions are multifocal during imaging, in some cases, they may mimic renal cell carcinoma lesions which may be solitary and large [6]. In suspicion of renal metastasis of colorectal cancers, renal biopsy may be used for diagnosis [7]. Treatment may vary between radical nephrectomy or, in suitable cases, partial nephrectomy based on the size and location of the metastatic lesion and the prognosis of the primary colorectal disease [6–8].

Ureter Metastases

Ureteral metastases caused by primary colorectal cancers may occur as distant metastasis via lymphatics/venous route. These metastases are very rare, and they are generally in the form of case presentation in the literature. Ureteral metastases of colorectal carcinoma may rarely occur and can be extraluminal or intraluminal and imitate urothelial carcinoma. Ureteral metastases of these cancers may be asymptomatic, or they may have symptoms such as hydronephrosis due to extraluminal or intraluminal pressure, lower quadrant pain, or colic pain. It may be diagnosed while screening the metastasis of primary colorectal tumor or with symptoms associated with renal pelvis or ureter involvement years after the treatment of primary tumor [9]. It is reported that diagnosis in intraluminal lesions is possible with ureteroscopic cold cup biopsy [10]. However, it is difficult to distinguish the ureter metastasis of primary colorectal tumors from the primary urothelial carcinoma of the ureter with the macroscopic ureteroscopic image or through imaging methods. Sometimes even the ureteroscopy-guided biopsy materials may not distinguish colorectal carcinoma metastasis from the primary urothelial carcinoma of the ureter [11]. Therefore, there are cases among the case presentations in the literature which are reported as colorectal cancer metastasis upon radical nephroureterectomy due to primary ureter tumor. If there is an intraluminal lesion before the treatment and if it is possible to make a diagnosis of "adenocarcinoma metastasis" by distinguishing it from urothelial carcinoma through cold cup biopsy and if proper treatment for primary metastatic colorectal cancer is administered, draining the hydronephrotic kidney by a double j catheter or nephrostomy tube may be sufficient.

Bladder Invasions

Almost 5–22% of the colorectal cancers are locally advanced stage without distant metastasis at the time of diagnosis. 3–10% of these locally advanced cancers have already invaded the adjacent organs (such as bladder, prostate, ureter, and vagina) at the time of diagnosis, and the bladder is the most frequently invaded organ [12–14]. 21–73% of these bladder invasions consist of malignancies, while some of the remaining bladder invasions and adhesions may be due to the inflammatory process [15–17].

The presence of dysuria and hematuria complaints in the detailed anamnesis of these patients should raise suspicion of bladder involvement. Patients complaining of presence of feces in their urine is a sign of sigmoid/rectal-bladder fistulae. During the physical examination of such patients, especially large and palpable masses may

be observed. The local dissemination and bladder involvement should be evaluated by preoperative imaging methods (computed tomography (CT) or magnetic resonance (MR)). Colon/rectum-bladder fistulae tract should be carefully evaluated by means of CT urography or MR urography. However, it may not always be possible to distinguish peritumoral inflammation from direct tumor infiltration by using imaging methods. If necessary, the spreading of the tumor into the bladder may be evaluated preoperatively with cystourethroscopy under anesthesia to have a more accurate treatment plan [13, 14].

Survival after wide resection in patients with local advanced stage colorectal cancer depends on the stage and the negative surgical margins obtained [15–18]. In these tumors with bladder involvement, there are controversies in the literature in terms of the required surgery for bladder resection and the oncological outcomes [14, 17, 19, 20]. In the study conducted by Carne et al., patients with colorectal tumors invading the urinary bladder were retrospectively evaluated for a period of 15 years. During that period, urinary bladder invasion and adhesion were detected in 53 patients. 4 (7.5%) of those patients underwent total cystectomy, and 45 (84.9%) of them underwent partial cystectomy, while 4 (7.5%) patients had an adhesion between the urinary bladder and primary tumor which was detached with blunt dissection without bladder resection. While none of the patients who underwent total cystectomy developed local recurrence, all patients who had adhesions disrupted without bladder excision developed local recurrence [14]. In another study conducted by Winter et al., 63 patients who had concurrent bladder resection due to local advanced colorectal cancer were evaluated. In 48 patients (76%), the remaining bladder tissue was primarily repaired after partial bladder excision, five patients (7.9%) had bladder augmentation following partial bladder excision, and ten patients (15.8%) had urinary diversion together with cystectomy. In 54% of these patients who underwent bladder resection, bladder invasion of the primary colorectal cancer was demonstrated histologically. In patients with negative surgical margins, 5-year survival was 72%, while this ratio in patients with positive margins was 27% [19]. In the study by Nyam et al., 27 patients underwent concomitant partial cystectomy due to locally advanced colorectal tumors. Histological bladder invasion of primary colorectal cancer was found only in seven of these patients (26%). In the mean 40.2 months of follow-up, 20 patients (74%) did not develop local or distant metastasis [20]. Also in the study of Talamanti et al., partial or total bladder excision was performed in patients with local bladder invasion of primary colorectal cancer, and no difference in local recurrence or survival could be found between the two surgical procedures if negative surgical margins were obtained [17]. However, it was emphasized that, whether surgery is performed or not, the most proper treatment in terms of oncological and local control was not to leave any tumor behind [17, 19, 21].

In patients with locally advanced stage colorectal cancer, in cases with suspicion of preoperative invasion or where perioperative urinary bladder invasion was observed, total pelvic exenteration (TPE) together with urinary diversion or partial cystectomy together with wide tumor excision may be required oncologically [22, 23]. In some cases, urinary bladder reconstruction (urinary bladder augmentation)

may be required due to inadequate bladder capacity after partial excision [24]. There is no single standard treatment modality for every patient. Patients should be notified in detail of all postoperative possibilities following total or partial cystectomy with a preoperative multidisciplinary approach and without compromising oncological outcomes. Patients who had non-continent ileal diversion with cystectomy should be informed that they will live on with a urostomy bag from that day forward or, if ileal augmentation is required following partial cystectomy, they may need clean intermittent catheterization and/or they may have incontinence complaints [24].

Cystectomy

In patients with locally advanced colorectal cancer invading into the urinary bladder, urinary diversion may be required with radical cystectomy. Many factors should be considered in choosing the type of the urinary diversion (ileal conduit or orthotopic diversion). Factors such as the patient's age and comorbidities, surgical history, expectations of the patient, and the preference of the surgeon affect the selection of the type of diversion. Today in urology clinics around the world, particularly non-continent ileal conduits are among the most preferred options following radical cystectomy [25]. Especially in locally advanced colorectal cancers, it is a safe option in patients with a history of radiotherapy after total pelvic exenteration or earlier. In studies comparing ileal conduit and orthotopic urinary diversion after radical cystectomy, there are conflicts regarding the superiorities of the options in terms of quality of life [26].

Bladder-Sparing Techniques

It was found that bladder-sparing techniques in patients with locally advanced colorectal cancers with urinary bladder involvement have equivalent outcomes with cystectomy with less morbidity [14]. The most ideal option is primary closure of the bladder wall, if sufficient amount of bladder tissue is remaining after primary tumor excision, but it may not always be possible. It is difficult to predict the bladder capacity remaining after the surgical resection of the primary tumor from the bladder preoperatively or intraoperatively. During the postoperative period following partial cystectomy, urinary bladder storage symptoms (pollakiuria, urgency, nocturia) associated with decreased bladder capacity may occur which may lead to the need for bladder augmentation during follow-up. Bladder augmentation surgery is a procedure that increases the bladder capacity and compliance of the patient. On the other hand, augmentation requirements concurrent with the primary colorectal tumor surgery should be considered in patients with inadequate preoperative bladder compliance who have overactive bladder symptoms due to radiotherapy and/or in patients who would no more have sufficient tissue for primary closure of the bladder following bladder excision. It should be noted that bladder augmentation is

a good alternative for urinary diversion. However, the patient should be informed about the necessity to use clean intermittent catheterization before this surgery and that he/she should have the hand skill to perform this. Moreover, it should be kept in mind that those who will undergo bladder augmentation should have a functional urethral sphincter and an intact urethra [14, 24].

Prostate-Seminal Vesicle Invasions

Prostate and seminal vesicle invasions occur only in 10% of the patients who require pelvic exenteration for colorectal cancers [27]. In the preoperative staging or during the re-stating of the recurrent disease, prostate and/or seminal vesicle invasions may be suspected by imaging methods (Fig. 35.1). Although only radical prostatectomy and rectal resection were performed with bladder-sparing surgery in isolated prostate invasion in the literature, the overall approach is to perform TPE in such cases [22, 28].

Urethral Invasions

Posterior urethral injury may occur due to urethral invasion of the locally advanced colorectal cancer, or during surgery for tumor excision. Primary repair over a catheter should be performed, if applicable, in intraoperatively diagnosed cases. If the diagnosis is not made intraoperatively, the urethral injury should be suspected in prolonged drainage postoperatively and when drain biochemistry matches the urine. Retrograde urethrogram (RUG) is a standard method in the diagnosis of urethral injuries [29, 30]. Opaque extravasation during RUG is

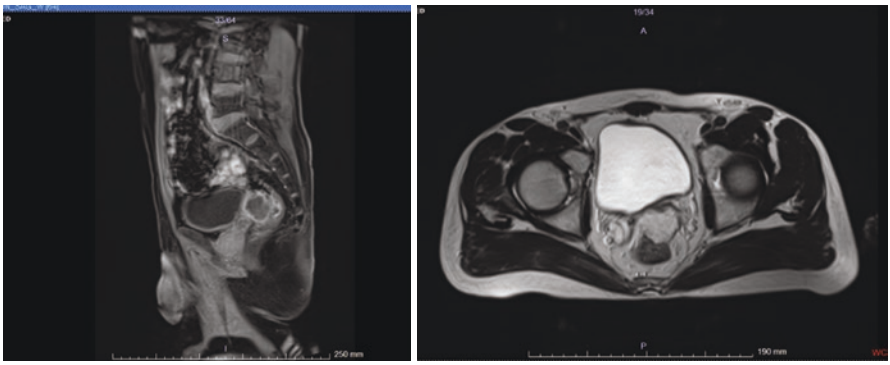

Fig. 35.1 (**a**, **b**) Mass with local recurrence and left seminal vesicle invasion during follow-up after colon tumor resection. Septate fusiform cystic mass lesion of sizes 44 × 29 mm with peripheral contrasting in post-contrast series is observed at the left seminal vesicle level. The pathology of the cystic mass on the seminal vesicle was reported as "Mucinous adenocarcinoma" after resection

pathognomonic for diagnosis. If deferred treatment will be administered in urethral injuries, the combination of RUG and antegrade cystourethrography would provide more detailed information about the final status of the posterior urethral stricture before repair [31]. Another method for diagnosis in the case of urethral injury is cystourethrography. It may particularly provide valued information when RUG is suspicious and in distinguishing between complete-partial urethra disruption [30].

Urethroplasty may be performed on cases whose urethral injuries are diagnosed at an early stage (up to week 6) during the postoperative period. Deferred surgery (after month 3) is another approach for patients with urethral injuries. This method may require a combination of abdominoperineal approaches [31]. Both approaches may lead to urethral stricture, erectile dysfunction, and incontinence at varying ratios [31–33].

Penile Metastases

Penile metastases of colorectal cancers are very rare, and these generally originate from rectum and rectosigmoid area [34–36]. These tumors mainly metastasize through the retrograde venous transport system. The primarily involved region in the penis is corpus cavernosum. Patients may mostly apply with perineal pain, urethral obstruction, priapism, and hematuria. Penis metastases may present clinical symptoms such as penile plaque, nodule, and erythematous ulcer during physical examinations [37, 38]. After primary rectoadenocarcinomas, penile metastases generally occur 2 years postoperatively and typically, there is dissemination to other organs of the body. Prognosis in these metastases is mostly poor, and the treatment is palliative rather than curative. This palliative control may be achieved through radiotherapy, systemic chemotherapy, or surgery [37–39].

Iatrogenic Ureteral Trauma (IUT) in Colorectal Surgeries

Given all surgeries, the incidence of this trauma is approximately 0.5–10% [40]. Colorectal surgeries rank as the second cause of IUT after gynecological surgeries, with the incidence of 0.2–2% [41, 42]. These IUTs may specifically occur during abdominoperineal resection and low anterior resection [41]. Ureteral injury may occur due to various mechanisms such as ligation with suture, damage during clamping, partial or complete transection, thermal damage, or ischemia associated with devascularization [43–45]. IUTs most frequently occur in the distal segment of the ureter [44–46]. Various risk factors that may lead to IUT are given in the literature. Previously impaired normal anatomic structure, locally advanced stage malignancies, previous surgeries or radiation exposure, diverticulitis, anatomic abnormalities, and major hemorrhages during surgery may be listed among these risk factors [41, 43, 47, 48].

Diagnosis Algorithm in IUT

IUT may be diagnosed intraoperatively or during the postoperative period. Ureteral injury may be directly visualized during surgery. If IUT is not detected in direct examination but there is a suspicion, it may be diagnosed by injecting intravenous indigo carmine dye to exclude it or in patients who don't have an opaque CT scan before exploration like in trauma patients, particularly a single-dose intravenous pyelography (IVP) may be taken intraoperatively to exclude urethral injury [43, 46].

If it occurs in the postoperative period, it is generally diagnosed with urinary tract obstruction, urinary fistule, or symptoms secondary to sepsis. IUT diagnosis is supported by the occurrence of complaints such as flank pain, fever, hematuria, and symptoms associated with uremia together with extended drainage of urine. Hydronephrosis is determined by USG and the location of the injury by IVP or by CT urography by scanning opaque extravasation at the level of the injury. In laboratory analysis, while the peritoneal fluid collected from the drain shows the biochemical characteristics similar to the serum, those with high creatinine levels confirm urine leakage [43–46].

Prevention of Iatrogenic Trauma

The most important phase of preventing IUT during operation is to visualize the ureters and dissect them carefully from the proximal end [43–45]. In the relevant literature, various methods are practiced both in gynecologic surgeries and before colorectal surgeries. The overall approach is to use a prophylactic preoperative temporary ureteral stent before complicated cases with a ratio in the literature as 4.4–27% [49, 50]. This practice helps the visualization and palpation of the ureters intraoperatively [49, 50]. The predictive factors to place a prophylactic stent are indicated as the presence of diverticular disease for colorectal surgery, performing radical resection instead of segmental colectomy and history of radiotherapy [49].

Although this practice helps intraoperative identification of the ureter, it is shown that it does not minimize ureteral injury during surgery [44, 51]. However, it should be noted that preoperative ureteral stent placement minimizes ureter mobilization and changes the ordinary anatomic pathway of the ureter. Moreover, minor complications associated with postoperative ureteral stent (hematuria, pain, dysuria, urgency, frequent micturition, and vesical tenesmus) and the cost should be kept in mind [44, 52, 53]. Besides, in a 10-year retrospective cohort study, it was indicated that both unilateral and bilateral ureteral stenting before colorectal surgeries increased acute renal insufficiency by 1.75 and 3.82 times postoperatively, respectively, and uretral stenting increased the operation time, hospitalization time, and costs [51]. Increased surgical experience with the recent technological and instrumental developments led to the decreased incidence in IUT [43, 54].

Classification of Ureteral Trauma

- *Grade I*: Only hematoma
- *Grade II*: Laceration <50% of ureteral diameter
- *Grade III*: Laceration >50% of the ureteral diameter
- *Grade IV*: Complete tear <2 cm of devascularization
- *Grade V*: Complete tear >2 cm of devascularization

Management and Treatment Algorithm of Intraoperative Injury in IUT

Iatrogenic ureteral trauma management may vary based on the nature, grade, and level of the ureteral trauma (Fig. 35.2). If the ureter is ligated intraoperatively, it may be treated by reversing the ligation and placing a temporary ureteral stent. In minimum injury of the ureteral mucosa, short ureteral strictures associated with injury or in partial ureteral injury less than 50% of ureter diameter, it may be sufficient to place a temporary stent with endoscopic methods or insert a nephrostomy

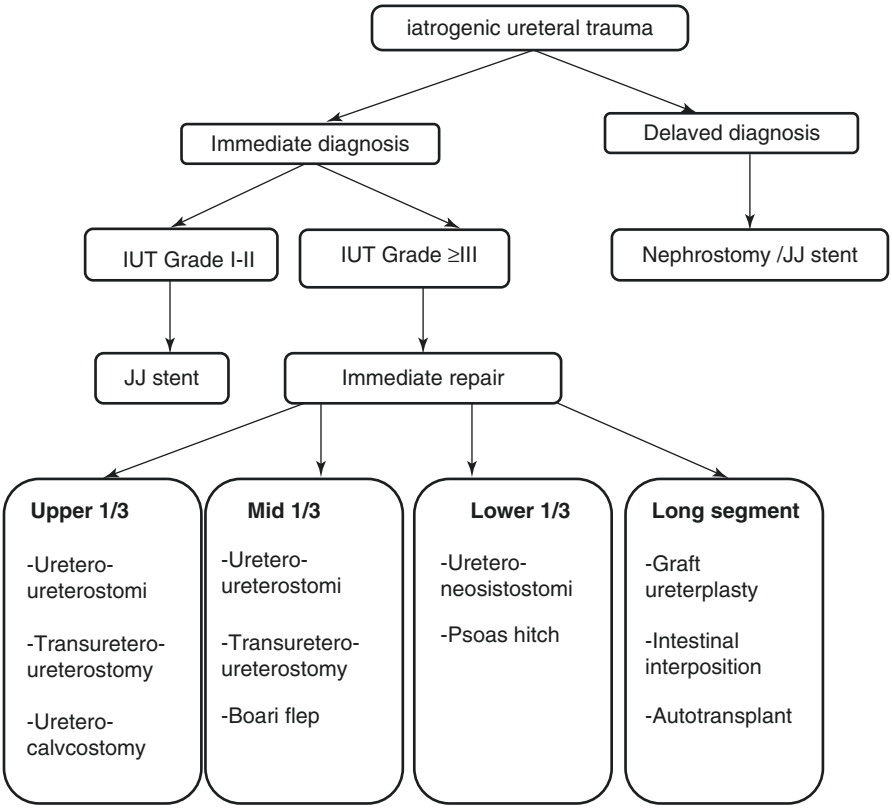

Fig. 35.2 Iatrogenic ureteral trauma treatment algorithm

catheter. Ureter stent placement may both accelerate ureter canalization and minimize the risk of developing stricture after injury [43]. However, in cases where the endoscopic methods failed or in complete ureteral injury, intraoperative repair should be immediately performed.

What Should Be the Timing of Repair of IUT?

If ureteral injury is not noticed intraoperatively or if the diagnosis is late, the overall approach should be to attempt ureteral stenting or to place a nephrostomy tube. It was shown in the literature that retrograde (from the ureter to the kidney) ureteral stent placement or antegrade (from the kidney to ureter) percutaneous nephrostomy tube placement was performed with 14–19% success. The method to be used in case these treatments fail is surgical exploration, and this exploration differs in surgical repair based on the degree of ureteral injury [55–57]. In a prospective study conducted regarding the elimination of ureteral obstruction associated with IUT, patients who underwent early (within first 15 days) and delayed (15–120 days) repair procedures were compared in terms of estimated creatinine clearance (eCrCl) and mercaptoacetyltriglycine (MAG3) clearance which are the markers that indicate renal functions in long term. In the group with the early repair of ureteral obstruction, both eCrCl and MAG3 clearances are detected as statistically better compared to the group with delayed repair [57].

Early diagnosis following IUT is also important for the later morbidities. A failure in early diagnosis increases the complication ratios [46, 58, 59]. There are several studies in the literature that compare early repair and delayed repair. They indicated that early repair led to better outcomes than delayed ones [57, 60]. In a prospective study conducted by Lucarelli et al., a total of 76 patients with ureteral injury were enrolled. Thirty-six (47%) of these patients underwent surgical repair within the first 2 weeks, while 40 patients were repaired after week 2 (median 85 days, days 20–120). When the postoperative MAG3 results and eCrCl are compared, it was detected that the group which underwent repair after 2 weeks had lower MAG3 and eCrCl compared to the other group, which underwent repair within the first 2 weeks (25.6% ± 9.2% vs. 48% ± 3.2%, $p < 0.0001$, 103 ± 15.7 vs. 68.1 ± 13.9 ml/min, $p < 0.001$, respectively) [57].

Proximal and Mid-Ureteral Injury

Ureteroureterostomy

If the length of defect is shorter than 2–3 cm, ureteral injuries at such degrees may be typically treated with primary ureteroureterostomy. During repair, both ureter ends should be dissected; necrotic tissues should be debrided and spatulated. Then, distal and proximal ureter ends should be mobilized, and ureteral ends should be anastomosed, avoiding stretching the ureter ends, in form of end-to-end mucosa-to-mucosa in a "watertight" fashion with absorbable suture and by placing an internal ureteral

stent. Where necessary, peritoneum or omentum should be isolated. The internal stent is left in the ureter for 4–6 weeks on average. A drain is placed around the repair, but care should be taken to avoid placing the drainage tube directly on the anastomosis line. A Foley catheter is placed into the urinary bladder to ensure drainage. Foley catheter is removed on the postoperative day 3–4. If the amount of drainage increases after Foley removal, it is required to place it again. If there is no drainage within 24 h after removing the Foley catheter, the drain may be removed [61].

Ureterocalicostomy

Ureterocalicostomy is another option especially in proximal ureteral injury in cases where primary ureteroureterostomy is not suitable. An oval opening is made in the kidney lower pole calyx system, and once the ureter is spatulated, tension-free and watertight anastomosis is performed using absorbable sutures. A double j catheter is placed, and drainage from the bladder is provided with the Foley catheter [61].

Transureteroureterostomy

In case of long ureteral injuries that may not be repaired by primary ureteroureterostomy, transureteroureterostomy is another alternative when the distal ureter is not suitable for repair or when it is obliterated. The contraindication of this procedure is the risk of disease or obliteration on both kidneys. These risks include a history of nephrolithiasis, upper urinary system transitional cell carcinoma, infectious diseases such as tuberculosis, and bilateral ureteral strictures. This method involves finding of the injured proximal ureter segment; to help ureter's mobilization and to identify the anterior part during reconstruction following mobilization, a suspension suture is placed on the mobilized anterior part of the ureter. A posterior retroperitoneal tunnel is formed posterior to the inferior mesenteric artery, and the ureter is moved to the other side. The ureteric end to be anastomosed into the normal ureter is spatulated by 1.5 cm, medial ureterostomy is performed to the receiving normal ureter, and a tension-free, watertight end-to-side anastomosis is performed with absorbable suture from the medium part of the ureter. For 6 weeks, 6 Fr double j stent is left in the kidney with a drain placed around the repair and a Foley catheter inserted [61]. The stenosis and revision ratios are approximately 4% and 10% with this method, respectively [62].

Boari Flap Repair

This is another method that may be used in middle ureter strictures. Prior to the Boari flap technique, the surgeon must be sure that the urinary bladder of the patient has sufficient volume and the patient should not have a history of urinary bladder surgery, pelvic radiation, or neurogenic bladder. The proximal portion of the ureter is suspended with a vessel loop or Penrose drain, and the distal end of the ureter is dissected as much as possible. If practical and required, defective distal ureter

segment and distal ureter can be removed. Bladder flap is prepared by freeing peritoneum from the posterolateral surface of the bladder. The bladder should be fully mobilized at the opposite side of the planned Boari flap. For bladder mobilization, the superior vesicle pedicle on the other side is dissected, and the bladder is fully mobilized. When the bladder is distended, the flap size required to eliminate the ureteral defect reaching to the end of the posterior section of the posterior bladder wall is measured with an umbilical tape, and the flap line is marked with a surgical pen. Flap length would depend on the size of the ureteral defect, and it should be slightly wider than the apex as it would also be used in base tubularization. To prevent ureter stricture after tubularization, the base should be at least 4 cm wide, and the end should be 2–3 cm (or three times the ureter diameter). If the flap will be longer, the base should be wider. If a longer size is required, oblique or S-shaped incision is possible. Once the bladder is drained, flap sizes are controlled again. Ureter portion is anastomosed to bladder flap with continuous absorbable sutures by forming a submucosal tunnel, if possible. Before closing the bladder, a double j catheter is placed into the ureter. A Foley catheter is placed for bladder drainage. Drain is placed in the retroperitoneal region. On postoperative day 10–14, a cystogram is taken, and the Foley catheter is removed if there is no leakage. The double j stent is removed from ureter 4–6 weeks later. On the third month in postoperative follow-up, renal scintigraphy and a CT urography may be taken [63, 64].

Distal Ureteral Injury

Ureteroneocystostomy

As the primary trauma in distal ureteral injuries may impair the distal ureteric blood flow in general, this is best managed by ureteroneocystostomy. This method may be applied together with psoas hitch, or it may also be used with the "Lich-Gregoir" technique, which is defined as an extravesical technique, after IUT. Once the bladder is filled with saline, extraperitoneal approach is used. The ureter is identified and isolated, and a vessel loop is placed at the posterior of the ureter to ensure atraumatic traction. The bladder is dissected caudally toward hiatus. The detrusor muscle is incised along the required submucosal tunnel with electrocautery. Dissection of the ureter is continued outside the Waldeyer sheath toward the urothelium, and it is seen in the whole bladder as a translucent bluish layer. Detrusor flaps are dissected from urothelium to submucosal tunnel with perpendicular, blunt, and electrocautery dissection combination. The ureter is placed in the tunnel, and the detrusor muscle is closed over the ureter with absorbable sutures [65].

Psoas Hitch

Ureteroneocystostomy technique may not always be possible, or particularly in cases where ureteral anastomosis to the bladder may not be tension-free, "psoas hitch" method may be used. There are no preoperative contraindications for this procedure.

The bladder is filled with saline at the beginning of the surgery. The healthy ureter is identified from the proximal of the obstruction, and a vessel loop is placed around it. Ureteral dissection is continued until the distal end; distal ureteral stump is typically tied and obliterated. Bladder dome traction and mobility are inspected. Once the mobility is confirmed, suspension sutures are placed above the mid-point of the anterior bladder wall. An oblique bladder incision is made with a cautery between the suspension sutures equal to the maximum dimension of the ureter. Bladder mobility may be increased by freeing the peritoneal and contralateral perivesical attachments. In general, these maneuvers provide sufficient bladder mobility, and if required, a contralateral superior vesical artery may be ligated. Two fingers are placed on the bladder dome through a cystotomy, and the bladder is pulled toward the psoas muscle anterior to the iliac veins. Three to five slowly absorbable 2/0 sutures are placed between the detrusor muscle of the bladder dome and psoas minor muscle tendon. Before the psoas sutures are tied, the ureter is approached to the bladder, and the tension is checked. The ureter is placed into the bladder by forming a tunnel to the superolateral portion of the bladder dome and anastomosed by absorbable sutures. A double j stent is placed in the ureter, the bladder is closed, and a Foley catheter is placed. A cystogram may be taken to check the recovery of the bladder in the postoperative period, and the Foley catheter is removed. Dj catheter may be removed on postoperative week 4–6. The success rate with this method is very high in the literature (96%) [66]. Another method that may be used in long strictures where both middle and distal sections of the ureter are injured and especially in cases where psoas hitch method may lead to stretched anastomosis is the Boari flap method explained above. The success rate of this method in the literature is 81–88% [64].

Long-Segment Strictures

The ureter may be replaced by using an ileum segment in long strictures or big amount of tissue loss. However, these patients should be free of renal dysfunction or any known intestinal diseases [67]. Complications such as stricture and fistule may also occur in this surgery in long term [68]. If the ureteral injury cannot be repaired in long and wide ureteral losses or despite repeated interventions, another option is the autotransplantation of the kidney to the pelvis. Renal veins are anastomosed to iliac veins, and the ureter is re-implanted to the bladder [69, 70].

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Gynecology for Metastatic Colorectal Cancer

36

Mehmet Gokcu

Gynecology for Metastatic Colorectal Cancer

Epidemiology

Ovaries are not unusual sites for cancer metastasis. Tumors metastasize to the ovaries from many organs, mainly from gastrointestinal system including the stomach, small intestine, colon, rectum, gall bladder, appendix, and pancreas and also from the breast, uterus, fallopian tube, and peritoneum. Frequency of metastatic ovarian tumors varies from region to region among the incidence of cancer type in that population. In Japan, gastric tumors are frequent, and the incidence of Krukenberg tumors in all ovarian cancer was 17.8%, mainly of gastric type [1]. In a study from Turkey, nongenital cancers metastatic to the ovaries constituted 9% of all malignant ovarian neoplasms, and the primary cancers were breast 23%, stomach 22%, and colorectal (CRC) 22% [2]. The prevalence of metastatic ovarian tumors appears to be associated with the incidence rates and spread patterns of primary malignancies. But in western world, CRC (colorectal cancer) is the most common cancer metastasizing to the ovaries [3].

Many tumors arising from primary organs spread to the ovaries by various routes. Via direct spread cancer invades the neighboring organs, in this situation CRC cancer directly invades the adjacent ovary. Spread from more distant sites is mainly by other routes such as blood vessels, lymphatics, and via peritoneal route by the help of intraabdominal fluid circulating inside peritoneum. However, in many cases cancer metastasis through more than one route, because many of cancers are at advanced stage when diagnosed. It is very difficult to determine the exact pathway of tumor spread. In a clinical study of pathways of metastases from primary organs to the ovaries, it was found that the main route of metastasis from colon to ovaries is via

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hematological spread (67%) and direct invasion (33%) [4]. Hematogenous spread is the most likely cause, as ovarian metastases are often seen in the absence of peritoneal disease. Also it is seen that laterality of the metastasis to the ovary in colon cancers does not correspond to the side of the primary lesion [5]. Risk of ovarian metastasis is higher in premenopausal women due to high vascularity and raw surface after ovulation attracting surface deposits.

Metastasis to uterus from extragenital sites is seen in less than 10% of cases of those affecting female genital tract with breast and colorectal cancers being the most common. Uterine involvement usually involves ovary as the first site of metastasis, and further involvement of the uterus has been proposed as secondary to lymphatic spread from ovaries. Within the uterus, metastasis involves myometrium in 96.2% cases and only endometrium in 3.8% cases [6].

Secondary malignancies that metastasize to the uterine cervix from extragenital sites are very rare, comprising about 3.4% of cases of metastasis to female genital tract. Possible reasons for infrequent involvement of cervix are due to its hard nature because of high fibrous content, small size, and limited blood flow.

Clinical Symptoms

The symptoms of metastatic colon cancer to the ovaries are non-specific and related to the presence of a pelvic mass. Sometimes patients are asymptomatic and diagnosed at a routine follow-up examination. Metastatic ovarian tumor can be discovered as an adnexal mass in a patient with a prior history of colon cancer, and this metachronous recurrence is more likely to be accurately diagnosed before surgery. It has been reported that 2% of the patients with primary CRC develop metachronous ovarian metastases within 2 years after the primary resection [7].

Otherwise, CRC with synchronous ovarian metastasis are often discovered at the time of surgery as an ovarian cancer by a gynecological oncologist or incidentally as an adnexal mass in CRC operation by a general surgeon. Isolated ovarian metastases occur in approximately 3–8% of women with colon cancer, both at the time of CRC diagnosis and as a site of metachronous disease spread [8].

In a clinical study of CRC with synchronous ovarian metastasis, it was found that abdominopelvic pain and increased abdominal girth of 61% were the most frequent presenting symptoms; 21% of patients complained of a pelvic mass, with only 17% patients complaining rectal bleeding. Twenty-six percentage of the patients presented as acute abdomen with suspected tumor rupture and emergent laparotomy was performed with the suspicious of ovarian carcinoma. These findings well illustrate the difficulty in differential diagnosis of pelvic mass in CRC because presenting symptoms point more to a gynecological primary tumor rather than to CRC. Some of this can be explained by the fact that the size of the ovarian metastasis is often much larger than the primary tumor. It is estimated that up to 45% of colon cancer metastases to the ovary are clinically mistaken for primary ovarian tumors because of their large size [9]. In pathological evaluation, the median ovarian tumor size was 10 cm, significantly larger than the median colon tumor size of 4.5 cm [10].

Metastasis to only uterine corpus or cervix without metastasis to ovaries is very rare. They are usually involved secondary to lymphatic spread from ovaries. But in a patient presenting with postmenopausal bleeding following treatment of colorectal malignancy, metastasis to uterine corpus or cervix should be considered.

Clinicopathological Features of Metastatic Ovarian Tumors

Kim et al. recruited 103 CRC patients who were diagnosed with ovarian metastasis and subjected to surgery between 1989 and 2005, mean age at diagnosis was 46 years (range 14–72 years), and 65% of the women were less than 50 years old at diagnosis (Table 36.1). Synchronous ovarian metastases (defined as ovarian metastases diagnosed at the same time) occurred in 75% of the patients; metachronous ovarian metastases occurred in 25%. Eighty-two percentage of metachronous metastases was within the first 3 years. 41.7% of the patients had bilateral involvement, whereas 35% had right; 23.3% had left side involvement. Bilateral ovarian involvement occurred more in synchronous metastases than in metachronous lesions (48.6% vs. 24.1%). The mean size of the primary tumor was less than that of the ovarian metastatic lesion [11].

Morphologic Features of Metastatic Ovarian Tumors

Pathological reports describe 60% of metastatic tumors being bilateral lesions that appear as diffusely solid tumors, multiple solid nodules, and partly cystic masses [12]. According to pathology textbooks, most ovarian metastases originating from the stomach, breast, lymphoma, and uterus are solid, whereas most ovarian metastases originating from the colon are cystic in nature. In a clinical study, 82% of

Table 36.1 Clinical characteristics of primary tumors with ovarian metastases

	%
Age at Dx of primary tumor (years)	
≤50	65
>50	35
Location of primary tumor	
Right colon(caecum/distal transverse colon)	40.8
Left colon(splenic flexure/sigmoid colon)	40.8
Rectum	18.4
Bilateral ovarian involvement	
Bilateral	41.7
Right	35
Left	23.3
Combined extra-ovarian metastasis (EOM)	
Peritoneal involvement	42.7
Liver metastasis	9.7
Periton+liver met.	9.7
Paraaortic node metastasis	1.9

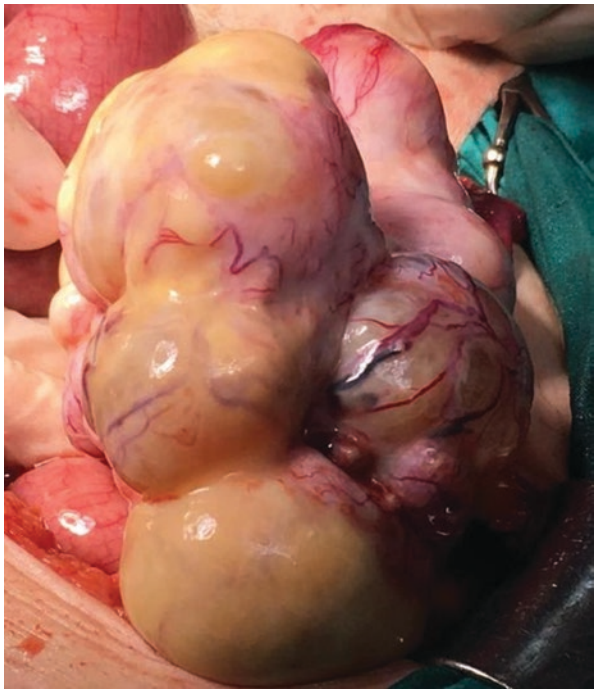

Fig. 36.1 Ovarian metastasis of CRC

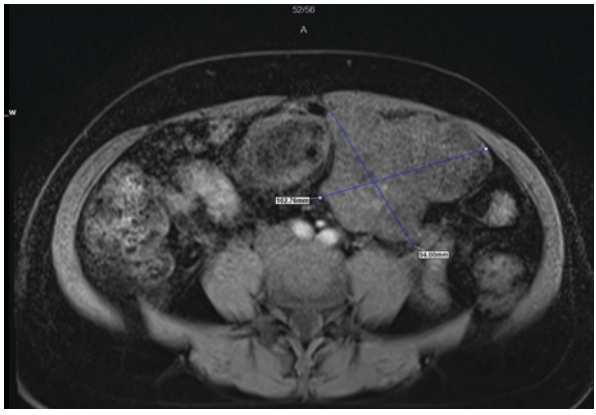

Fig. 36.2 MRI image of left ovarian metastasis from colon (same patient)

metastases from the colon, rectum, appendix, or biliary tract were most often multilocular or multilocular solid. Also metastases in the ovaries that were derived from the colon, rectum, and appendix were larger than were those derived from the stomach, breast, lymphoma, or uterus (median maximum diameter, 122 mm vs. 71 mm). Cystic fluid in ovarian metastases (OM) from the colon is usually serous or mucinous (anechoic or low-level echogenicity of cystic fluid) and that ovarian metastases from the colon are often large. It is possible that mucin production explains the large tumoral diameter and cystic pattern in ovarian metastases (Figs. 36.1, 36.2, and 36.3)

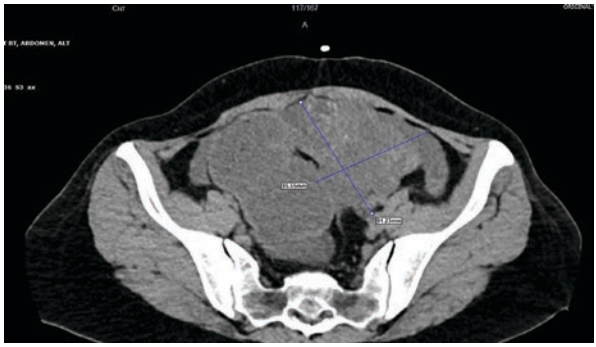

Fig. 36.3 CT image of left ovarian metastasis from colon (same patient)

from CRC. Also, in these metastases, irregular external borders were more common 86% vs. 46% [13].

Ovarian metastasis originating from CRC are usually bilateral, multiloculated, cystic, and around 100 mm lesions. This is in contrast with primary ovarian tumors of endometrioid, mucinous, and clear cell types which are pathologically mixed up with ovarian metastasis of CRC, since they are 90% unilateral.

Diagnostic Workup

Carcinoembryonic antigen (CEA) historically has been a valuable marker in identifying gastrointestinal tumors and their metastases, but it was also secreted in patients with inflammatory diseases and in benign and/or malignant tumors of the gastrointestinal tract, breast, urothelium, ovary, uterus, and cervix. Therefore, CEA only cannot be used independently to distinguish primary ovarian carcinoma from metastatic CRC to ovaries. Thirty years after its discovery, CA 125 antigen level is still widely used in both detection and disease follow-up in ovarian carcinomas (OC). But serum CA 125 levels can also be elevated in both malignant and benign numerous conditions. High CA 125 levels in other malignant diseases other than ovarian and tubal carcinoma are breast cancer, mesothelioma, non-Hodgkin lymphoma, gastric cancer, and leiomyoma of gastrointestinal origin. Endometrioma, pregnancy and liver diseases are benign conditions that increase Ca 125 levels. So CA 125 alone cannot be used to distinguish primary ovarian carcinoma from metastatic CRC to ovaries. It has been reported that using CA 125/CEA ratio appeared to be more valuable than CEA alone for diagnosis of CRC or CA 125 for differentiation of ovarian carcinoma from CRC. In a large clinical study, a sensitivity of 91% and a specificity of 100% for detection of ovarian cancer from CRC have been reported by using the CA 125/CEA ratio with the value exceeding 25 [14]. But although this is a good clinical parameter for differentiation between CRC and ovarian carcinomas, the problem is that CEA is not a typical marker for ovarian cancer and most primary CRC with definitive diagnosis do not check the marker of CA 125. So we should workup both CEA and CA 125 in suspicious ovarian and CRC patients.

It still remains controversial whether colon screening should be considered as a part of preoperative workup for gynecologic oncologic patients. In NCCN ovarian cancer guideline, gastrointestinal system evaluation is indicated if there is a clinical suspicion for metastatic carcinoma or mucinous type ovarian cancer, but routine screening with colonoscopy or barium enema is not indicated in recommended workup. Saltzman et al. have concluded that colon screening is not needed in the asymptomatic patient with age below 50 years old, but a full colonoscopy should be considered for those older than 70 years [15]. Colon screening with colonoscopy is indicated when there is any suspicion for metastatic carcinoma to ovaries.

When we consider appendiceal carcinomas, they are rare and usually cannot be diagnosed prior to surgery. A study by Dietrich III et al. revealed that only two out of 48 patients with CRC had the diagnosis of appendiceal cancer prior to surgery [16]. Although the sensitivity of colonoscopy for the diagnosis of CRC is almost 95%, CRC with flat, scirrhous, or lateral tumor spreading type (Fig. 36.4) is still more likely to be missed by colonoscopy. Also in diffuse metastasis and peritonitis carcinomatosis due to obstructions and peritoneal adhesions, preoperative diagnosis can be difficult [17].

The role of frozen sections in distinguishing between primary and secondary ovarian malignancy is important because the surgical management of primary and metastatic ovarian cancer is different. However, it is difficult to differentiate metastatic CRC from primary ovarian cancer. Lee et al. report that 43% of metastatic ovarian malignancies would be correctly identified on frozen sections [17]. They concluded that poorly differentiated high-grade serous carcinomas, primary

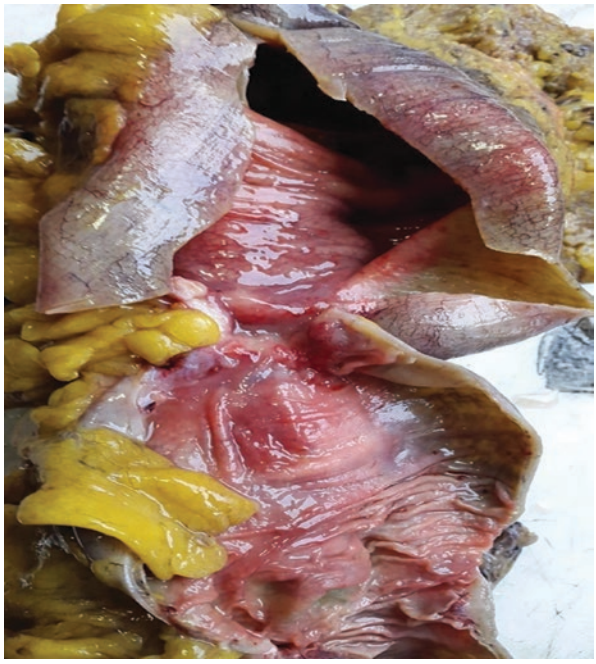

Fig. 36.4 Scirrhous, lateral spreading-type colon cancer

endometrioid, and mucinous adenocarcinoma were more difficult to be distinguished from primary ovarian malignancy and metastasis from a CRC. Frozen section analysis of bilateral tumors is more accurate than unilateral tumors when this consultation is made between the pathologist and the surgeon during the surgery.

Treatment

Synchronous and metachronous OM occur more frequently in patients with colon cancer than in those with rectal cancer. Patients with CRC who developed OM were younger and had a more advanced tumor stage and more oftenly synchronous than metachronous. Among women with colon cancer, survival of those who developed metachronous OM was as poor as that of patients with extra-ovarian recurrences [8].

Ovarian metastases from primary CRC are known to present a poor prognosis. The median survival time of 6–18 months in CRC patients with ovarian metastases has been described by Yang et al. [18]. Recently, better 5-year survival rates such as 78–80%, after ovarian metastasectomy in CRC patients without peritoneal dissemination, have been reported [7, 19]. But also in a study with a large series of patients, it was found that, in contrast to other reports, only 43% of patients with OM had concurrent peritoneal carcinomatosis and that peritoneal involvement was not associated with worse OS. In this study of Ganesh et al., 195 patients who had undergone oophorectomy and had a pathological diagnosis of parenchymal OM-CRC OM were present at the time of the initial CRC diagnosis in 44% of patients and were bilateral at the time of presentation in 45% of patients [20].

The majority of patients (63%) received chemotherapy before undergoing oophorectomy, with 81% of these patients experiencing discordant growth of OM in comparison with EOM (extra-ovarian metastasis). Macroscopic surgical cytoreduction of OM and other metastases are strongly associated with better progression-free survival (PFS) and OS [21, 22]. Peritoneal dissemination is an adverse prognostic factor, but an increased OS was associated with an R0 resection. Ganesh et al. concludes that, when achieved, cytoreduction has equivalent outcomes in patients with or without extra-ovarian disease [20].

So the most important prognostic factor for OM-CRC is RO resection of tumors. In synchronous OM-CRC, if the patient is premenopausal, effected ovary should be removed if R0/R1 resection could be achieved. The other ovary should be carefully inspected and can be preserved if there is no sign of metastasis in premenopausal patient. In a postmenopausal patient, if there is metastasis in one ovary, both ovaries should be removed because in patients who initially presented with unilateral OM, 13% eventually developed metachronous metastases in the unresected ovary within 3 years [20].

Hysterectomy is not indicated if there is only OM in CRC. CRC rarely metastasize to the uterus, cervix, and vagina. If they are involved, in this case usually involved ovary is the first place of metastasis, and further involvement of the uterus has been proposed as secondary to lymphatic spread from ovaries. In uterine and cervical metastasis, total hysterectomy and bilateral salpingo-oophorectomy should

be preferred. İf there is vaginal involvement, effected vaginal section should also be involved in the specimen. In metachronous OM, ovary is the sole metastatic place in only 24% of the patients, whereas in 76% of patients, other sides like the peritoneum (43%) and liver (49%) are also involved. Although the peritoneum and liver capsule/parenchyma are most common places, every organ in abdominal cavity may be involved in metachronous OM. In this situation patients with EOM are expected to have unresectable disease as there may be many sides of metastasis, so if we only analyze the subgroup of patients with extra-ovarian metastasis to whom R0 cytoreduction could be achieved and the patients with solely metachronous ovarian metastasis, we see that they have equivalent OS. Metachronous OM-CRC compromise a clinical subgroup characterized by younger women with poor overall clinical prognosis and discordant ovarian response to chemotherapy. OM occurred in younger women, frequently displayed disproportionate growth during chemotherapy. Surgery should be the prior treatment in solely OM and also in patients with extra OM in which RO cytoreduction could be achieved. Chemotherapy should be postponed after surgery. Bilateral salpingo-oophorectomy is preferred in surgery of metachronous ovarian metastasis. If the uterus, cervix, and vagina are also involved by metastatic disease, total hysterectomy and bilateral salpingo-oophorectomy with vaginal metastasectomy should be performed if R0 resection can be achieved. In conclusion, aggressive resection for ovarian metastases from primary CRCs is associated with good OS. The analysis of prognostic factors showed that the presence of peritoneal dissemination is associated with a poorer survival, but R0 resection significantly improves OS [20–22].

Ovarian Transposition Before Pelvic Radiation for CRC

Patients with pelvic cancer frequently require radiotherapy, which causes infertility even at low dose. Oocytes are uniquely sensitive to radiation injury. Ovarian transposition is performed for preventing menopause in reproductive aged women that will receive radiation therapy to pelvic area for CRC. Several factors should be taken into account before coming to a conclusion, including the patient's age, ovarian reserve, desire for future pregnancy, medical condition, and prognosis. Women aged more than 40 years and in menopause are not good candidates for transposition because of decreased ovarian reserve and are at high risk for ovarian failure even with the procedure. For women over 35 years of age ovarian reserve should be evaluated by basal serum follicle-stimulating hormone (FSH) (on cycle day 3) and anti-Müllerian hormone (AMH) levels and antral follicle count (AFC). AMH is the most sensitive test and can be performed at any time in menstrual cycles, and low AMH (<0.5 ng/mL) level strongly indicates poor ovarian reserve. Ovarian transposition can be performed both by laparotomy and minimal invasive approaches, but outcomes are better with laparoscopy and have less complications, also allowing earlier onset of radiotherapy. For patients who will have laparotomy for primary treatment of their disease, ovarian transposition should be performed at the same time. Radiation can be started within a day or two following laparoscopy and 1 week

after laparotomy. Ovarian transposition is performed to protect the ovaries from radiation and thus preserve endocrine function. Pelvic radiotherapy with fertility preservation is not yet available for women with pelvic tumors, not even with the intensity-modulated radiation therapy or other techniques. In such cases, the limited options are oocyte and/or embryo freezing and ovarian transposition, which might preserve reproductive and hormonal function, respectively. Although ovarian tissue cryopreservation and transplantation are possible, they are still experimental. It should be kept in mind that uterus is also in radiotherapy field which could affect its function. Recently new surgical techniques are developed for laparoscopic transposition of the uterus and ovaries to the upper abdomen, outside of the scope of radiation, to preserve fertility. After the end of radiotherapy, rectosigmoidectomy was performed, and the uterus and ovaries were repositioned into the pelvis. This technique offers a valid option for fertility preservation in women who require pelvic radiotherapy and want to bear children [23, 24].

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