Overview of Colorectal Cancer

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Colorectal cancer (CRC) (adenocarcinoma of the large bowel) arises from a neoplastic process involving the epithelial layer of the intestine. In most CRC, the process begins as a benign polyp or adenoma. The adenoma undergoes a transformation to cancer through a series of molecular changes. Early in the process, the cancer can be treated easily with removal of the adenoma or early stage cancer. Thus, as expected from the nature of this disease, prevention and screening have likely reduced the incidence and mortality rates of this disease. The goal of this chapter is to provide an overview of CRC as well as an understanding of the rational for screening for this cancer.

Epidemiology

In the USA, CRC is the third leading cancer-related death for both males and females [1]. The rate for mortality from CRC has been steadily decreasing for the past few decades. However, in the past several years, the mortality rate has decreased at a significantly faster pace, presumably through increased CRC screening [2, 3]. Specifically, whereas the rate was decreasing at 2% per year prior to 2003, the rate decreased by 3% per year in the period from 2003 to 2007 [3]. A recent review of the Surveillance, Epidemiology, and End Result (SEER) mortality database demonstrated that the rates for CRC mortality had decreased to a much greater extent in the Northeastern than in the Southern USA [3]. The authors postulated that the difference in mortality rates between the two geographical regions reflects differences in CRC screening rates, treatment, and risk factors such as smoking and obesity. In addition, the authors attributed the lower screening rates in the southern states to an increased population of poor and uninsured in this region. Furthermore, southern states also have a higher percentage of blacks who have higher rates of CRC mortality than whites [1]. The changes and variation in these mortality rates illustrate the complex factors that can impact the incidence of CRC.

In Europe, CRC is the second commonest cause of cancer-related deaths for males and females [4, 5]. As in the USA, there has been an increase in CRC survival in the past decade [6, 7]. In addition, as observed in the USA, there is a variation in survival trends in Europe [8]. Although Europe has experienced an increase in survival rates for CRC, the improvement has been less pronounced in Eastern

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European countries such as Slovakia [8, 9]. Worldwide, CRC incidence rates make this disease the third most common cancer in females and the fourth most common cancer in men [10, 11]. In some countries such as Israel and Japan, the rates have increased [10, 12].

Anatomy and Embryologic Development of the Colon

There are several layers that comprise the wall of the colon. The innermost layer is the mucosa. This layer consists of the epithelial layer, the lamina propria or connective tissue, and a thin muscle layer called the muscularis mucosae. The next layer is the submucosa, comprised of connective tissue, nerves, lymphatics, and blood vessels. The muscle layer, or muscularis propria, is the next layer and is comprised of two bands, a circular and longitudinal. The outermost layer, the serosa, is present from the sigmoid to the cecum and not below the peritoneal reflection. Knowledge of the layers is important with regard to staging, prognosis, and treatment that will be reviewed later in the chapter.

The colon is comprised of two segments, the proximal and distal large bowel. The proximal colon consists of the cecum, the ascending colon, hepatic flexure, and the transverse colon. The distal colon consists of the descending, sigmoid colon, and the rectum. The proximal colon has its embryonic origin in the midgut, while the distal colon originates from the hindgut. The blood supply for the proximal colon derives from the superior mesenteric artery, while the inferior mesenteric artery supplies most of the distal colon [13, 14]. In addition, there are differences in the capillary network surrounding the colon. While the proximal colon is multilayered, the distal colon is single layered [14]. Furthermore, the crypt length in the distal colon is longer than that of the proximal colon [13]. In addition, there are differences between the enteric flora as well as the metabolism of fatty acids in different anatomic regions of the large intestine [15].

The anatomical and physiological differences between the segments of the colon may play a role in the clinical and molecular differences between proximal and distal colorectal neoplasia [13, 16, 17]. While proximal tumors are more likely mucinous and exhibit both microsatellite instability and methylation defects, distal tumors are more likely to have tumors associated with the chromosomal instability pathway, which lacks these features [18, 19]. In addition, proximal neoplasia is associated with female gender and older age [20–22]. Conversely, smoking and alcohol use are associated with distal neoplasia [23–25]. Morphologically, proximal tumors and polyps are more likely to be flat compared to their distal counterparts [26, 27]. Finally, interval neoplasia or lesions diagnosed between regularly scheduled colonoscopies are more likely to be found in the proximal colon. Issues regarding the molecular, clinical, and morphological presentation of colorectal neoplasia will be further discussed elsewhere in this chapter [28].

Adenoma to Carcinoma Sequence

In most cases of CRC, the disease begins as a benign polyp or adenoma that develops into a tumor. This process is accompanied by a sequence of molecular abnormalities that help to facilitate growth and transformation of the adenoma into a more advanced neoplastic lesion. The first model describing this process was published by Fearon and Vogelstein in 1990 [29]. Their model required seven mutations to occur for a cancer to develop from normal mucosa. This includes initial inactivation of the tumor suppressor gene adenomatous polyposis coli (APC) followed by activation of the oncogene KRAS as well as mutations in TP53 and other pathways. This describes the classic "chromosomal instability (CIN) pathway" [30], but there are two other well-described pathways. Additional detail regarding these three pathways will be discussed in a separate section. It has been estimated that 8–15 years are required for normal mucosa to transform into a cancer [31]. This length of time, also known as "polyp dwell time," has been estimated using different methods [32]. The first method compared the mean age of patients with small adenomas to that of patients

diagnosed with CRC and observed a difference of 18 years [33]. Koretz used the relationship of prevalence = incidence × duration to conclude that the transformation time from adenoma to carcinoma must be at least 4.8 years, the so-called latent phase [34]. However, since some cancers are detected in asymptomatic patients and some cancers develop de novo from the mucosa, adenoma dwell time is likely longer. The strategy of CRC prevention through adenoma detection and removal is based on this lag time and is the basis for current screening strategies [35].

Molecular Pathways of CRC Development

The development of CRC from normal tissue is a result of an accumulation of multiple genetic mutations. These genetic abnormalities decrease cell death and increase the likelihood of clonal expansion. Although there may be many genetic mutations in a single adenoma, only a small proportion will be responsible for neoplastic transformation. In this section, the three major pathways responsible for CRC will be discussed.

Chromosomal Instability

This pathway was first described approximately 20 years ago by Fearon and Vogelstein and is manifested through the traditional adenoma to carcinoma sequence [29, 36]. The CIN, or suppressor, pathway is characterized by aneuploidy or an abnormal number of chromosomes [37, 38]. The first mutation occurs in the APC gene which is responsible for the APC protein [30]. This protein plays a significant role in cell development and the Wnt signaling pathway by binding to beta-catenin. APC mutations are found in over two-thirds of CRC and most commonly in distally located lesions. In the familial cancer syndrome, familial adenomatous polyposis (FAP), the affected individual has a germline mutation in one copy of the APC gene. Any somatic mutation that inactivates the remaining gene will facilitate the development of adenomas. Mutations of an oncogene, usually KRAS, are another development that promotes growth of an adenoma. Another important step in the CIN pathway is the inactivation of the TP53 gene, which is responsible for the p53 pathway. The inactivation of this gene occurs as a result of a mutation and a deletion. The loss of this key tumor suppressor aids in the transformation of an adenoma into invasive carcinoma. Other genes involved in this pathway are SMAD2 and SMAD4, which are part of the TGF-beta signaling pathway involved in cell growth, migration, and apoptosis [37]. There is also mutation of the DCC gene that produces a membrane receptor aiding in promoting apoptosis.

Microsatellite Instability

DNA replication errors in the form of mismatched nucleotide base pairs occur frequently in microsatellite regions of DNA and can result in transcription errors and altered gene expression [39]. These errors are collectively known as microsatellite instability (MSI). DNA mismatch repair (MMR) enzymes are responsible for the repair of these erroneous segments. There are seven proteins that are involved in the enzymatic repair process: hMLH1, hMLH3, hMSH2, hMSH3, hMSH6, hPMS1, and hPMS2. Two proteins, hMLH1 and hMSH2, are essential parts of the functioning MMR enzyme [40]. There are several key genes involved in CRC development that contain microsatellite regions particularly susceptible to mismatch errors. These include the following: TGFβ2, β-catenin, IGF-2, APC, MSH3, MSH6, Bax, Caspase 5, and E2F4. Adenomas can develop as a result of these mutations.

There are five standard microsatellite patterns that are used to detect MSI in a tumor: BAT25, BAT26, D5S346, D2S123, and D17S250. If none of these are present, then the tissue is considered to be microsatellite stable (MSS). If one of these patterns is present, then the tissue is MSI-L (low), and if two or more are present, then the tissue is MSI-H [41]. About one in five CRC is MSI-H, but only a fraction of these are in the setting of hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, a familial cancer syndrome

that is characterized by colonic adenomas and CRC with high levels of MSI. The majority of MSI-H tumors likely arise from somatic methylation of hMLH1 [42]. Tumors that result from methylation tend to be proximal and less aggressive [39].

CpG Island Methylator Pathway

Methylation of the gene promoter region is associated with epigenetic silencing of gene expression. If there is methylation of CPG promoter regions in genes responsible for hMLH1 and p16, there is an increased risk of CRC [43, 44]. Tumors can be categorized as CIMP+ or CIMP− based on the presence of defined markers: CACNA1G, IGF2, NEUROG1, RUNX3, and SOCS1. CIMP+ tumors present as proximal lesions and occur in older women. CIMP+ tumors that are not MSI-H have a worse prognosis than MSI-H tumors or tumors arising in the setting of the CIN pathway [39, 45]. Since CIMP+/MSI-H tumors are associated with epigenetic silencing of hMLH1, an overlap between the CpG island methylator pathway (CIMP) and the MSI pathway exists in a large proportion of CRC. In some CIMP+ tumors that are not MSI-H, there is a mutation of the oncogene BRAF [46]. These tumors tend to have a poor prognosis [46]. In other CIMP+/non-MSI-H tumors, KRAS mutations are present rather than BRAF mutations [47, 48].

Symptoms and Diagnosis

Presenting complaints for CRC can include rectal bleeding, change in bowel habits such as diarrhea or constipation, abdominal pain, weight loss, and fatigue due to anemia. Many patients with CRC do not have any symptoms. Tenesmus, painful or incomplete defecation, has been associated with rectal cancer. In their review of nearly 200 patients diagnosed with CRC, Majumdar et al. observed that rectal bleeding, abdominal pain, and a change in bowel habits were the most common presenting symptoms [49]. Rectal bleeding and constipation were the strongest independent predictors of distal CRC. Since a delay in diagnosis in symptomatic patients is a concern in clinical practice, these investigators also examined the duration of symptoms and the stage of cancer at diagnosis. They found no significant association between the duration of symptoms and the stage of the disease. In these studies the overall mean duration of symptoms (or delay to diagnosis) was 14 weeks. The mean patient delay was 26 weeks and 11 weeks for the physician delay.

In a study of 349 patients with CRC, Stapley et al. observed that rectal bleeding was associated with a lower cancer stage and higher survival rates. Anemia was associated with more advanced stages and lower mortality [50]. Duration of symptoms was not associated with the stage of cancer. A study of over 4,000 CRC patients in Norway demonstrated that the duration of symptoms was associated with a less advanced disease stage [51]. The authors explain this paradox by postulating that aggressive tumors may be associated with more worrisome type symptoms than less aggressive cancers. Recently, Adelstein et al. performed a systematic review of 62 articles examining symptoms and the diagnosis of CRC [52]. They observed that rectal bleeding and weight loss were significantly associated with CRC. Other symptoms such as change in bowel habit, constipation, diarrhea, and abdominal pain were not associated with CRC. In summary, it appears that a prudent practitioner would refer for evaluation any patient who presented with new complaints such as rectal bleeding, abdominal pain, or fatigue due to anemia.

Risk Factors

There are many known risk factors associated with colorectal neoplasia although age and family history of CRC are the only ones typically considered when screening for the disease. The recent American College of Gastroenterology CRC screening guidelines introduced the concept of using other factors in selecting patients for screening [53]. Considering other risk factors can allow for both tailoring screening recommendations and/or efforts at modifying them to reduce the risk for CRC. In this section, the risk factors

are divided into modifiable and non-modifiable risk factors. In addition, there will be a discussion of the risk factors associated with advanced neoplasia as well as CRC.

Non-modifiable Risk Factors

Age

Age is one of the strongest predictors of colorectal neoplasia in many studies. The high risk observed when examining the association between age and neoplasia likely results at least partially from the number of years of exposure to other factors such as smoking. However, in many studies, the risk remains high even after controlling for many known exposures. The importance of age as a risk factor for CRC is highlighted by the fact that it is used to determine when to start screening. For patients of average risk, the recommended age to start screening is 50 years.

Gender

Most studies of asymptomatic populations have demonstrated an increased risk of developing adenomas and more advanced neoplasia (advanced adenomas) in men [54–56]. A recent meta-analysis by Nguyen et al. found that men were more likely than women to have advanced adenomas (RR = 1.83; 95% CI 1.69–1.97) [57]. While male gender is a significant risk factor for advanced adenomas, the lifetime risk for CRC remains similar for men (5.3%) and women (5.0%) in the USA [1]. The CRC risk for women lags by approximately 5 years that of men such that the risk for a women at 55 is similar to that of a man at 50 years of age [58]. Thus, women have a similar lifetime risk to men with regard to CRC but a substantially lower risk for advanced neoplasia.

This paradox was recently highlighted in review by Bianchi and Roy [59]. They noted that there was a higher rate of interval cancers in women [28]. Interval cancers are lesions that are diagnosed between regularly scheduled colonoscopies, typically every 5 or 10 years. The authors postulated that colonoscopy may be less effective in women than men. They also hypothesized that women may have a different clinical presentation of CRC due in part to the higher proportion of proximal neoplasia in women, the chemoprotective effect of estrogen, and an increased sensitivity to risk factors such as smoking. One possible explanation that was proposed suggests that women may have a higher rate of adenomas that progress to advanced lesions. The Women's Health Initiative demonstrated a higher rate of metastatic lymph node involvement, but a lower rate of CRC in women who had been treated with estrogen/progesterone [60]. Another explanation was that women may harbor more flat colorectal neoplasia. Recently Johnson et al. observed that adenomas greater than 5 mm in size were more likely to present as flat and proximal in women than men [61]. Despite these observations, there are no differences between screening recommendations for men and women in the current guidelines.

Race

African Americans have a higher rate of CRC incidence and mortality than any other racial or ethnic groups. Disparities in mortality rates from CRC due to racial differences increased from 1960 through 2005, even as the overall CRC mortality rate declined in the same period [62]. Recent data from the SEER database show age- and gender-adjusted CRC incidence and mortality rates to be higher for African American than whites [63]. In addition, African Americans may be diagnosed at a younger age than whites [64]. Reasons for the higher rates in African Americans include lower CRC screening rates [65–67] and higher exposure rates to risk factors such as cigarette smoking or type II diabetes mellitus [67–70]. A recent analysis of the Clinical Outcomes Research Initiative (CORI) database demonstrated an increased prevalence of polyps larger than 9 mm in African Americans compared with that of whites [71]. This relationship was stronger for women than men. In addition, for patients older than 60 years of age, black patients were more likely to have proximal polyps that were larger than 9 mm. The authors concluded that there might be a need to alter the guidelines to screen black patients prior to the age of 50 years.

They did note that this could add to the complexity that exists in the current multi-society guidelines. The American College of Gastroenterology, however, recommends that African Americans begin screening at the age of 45 years of age [53, 72].

Modifiable Risk Factors

Smoking

Tobacco exposure in the form of cigarette smoking has been identified as a major risk factor colorectal neoplasia [24, 27, 73–77]. Smokers may be at an increased risk for MMR defects, and this may play a role in the development of neoplasia in this group [78, 79]. In addition, tobacco exposure may increase the risk for BRAF mutations. An increased association between the point mutation of the oncogene BRAF (V600E) has been seen in people who smoke [80]. BRAF has been shown to be tightly correlated with the CIMP CRC phenotype [81, 82]. Increased methylation defects are the hallmark of a recently described pathway that is also seen in serrated lesions. Accordingly, Anderson et al. observed an increased risk of smoking for sessile serrated adenomas as well as serrated aberrant crypt foci [83].

Smoking may account for 20% of all cancers in the USA [84]. Smoking is associated with as much as 30% increased risk for CRC for men and women [85–90]. In addition, smoking may account for 12% of all CRC-related deaths [91, 92]. Smoking has been observed to be associated with an earlier age of CRC diagnosis than in nonsmokers, and smokers present with a more advanced stage of disease than nonsmokers [93]. A recent study demonstrated an increased mortality in smokers after the diagnosis of CRC [94]. This finding was most pronounced in patients who had tumors with high MSI.

With regard to advanced adenomas, smoking has been consistently associated with an approximately twofold increased risk compared with nonsmokers [95]. Based on colonoscopy findings in nearly 2,500 asymptomatic patients, Anderson et al. concluded that 30 pack years of exposure or more was associated with an increased risk for advanced neoplasia [73]. In a separate gender analysis, they observed that women had an increased risk for advanced neoplasia if they smoked 10–30 pack years [74]. Men required more than 30 pack years to have an increased risk. In addition, while both genders had an increased risk for distal advanced adenomas in smokers, only female smokers had an increased risk for proximal advanced lesions. In this population, there was a distinct difference between men and women with regard to tobacco exposure. The authors postulated that the anatomical differences could be due to increased methylation and MMR defects seen in women [78, 96–98].

Obesity

Obesity is defined as a body mass index (BMI) ≥ 30. An increased waist circumference or waist to hip ratio has been proposed as a more accurate measure of visceral adiposity, which is felt to be important in carcinogenesis. Insulin resistance may play an important role in the development of colorectal neoplasia in obese patients. Elevated insulin levels along with hyperglycemia and increased free insulin-like growth factor (IGF-1) can increase the risk for colorectal neoplasia [99–102]. Insulin resistance can lead to increased cellular proliferation and reduced apoptosis [103–105]. The increased risk of CRC associated with type II diabetes mellitus has been observed in large case control studies [106, 107].

Several studies have demonstrated that obesity is associated with an increased risk for CRC, and the risk appears to be stronger in men than in women [108–112]. In the Health Professionals Follow-Up Study (HPFS), men with the highest BMI had a twofold increased risk compared with the thinnest men [113]. In a comparable study, participants in the Nurses' Health Study (NHS) who were obese were one and a half times as likely to have CRC as the thinnest women [114]. Other longitudinal population studies have observed that an increased risk for CRC is correlated with an increased waist circumference [115].

Obesity is important since it is a modifiable risk factor, and there is data to suggest that weight loss can decrease the risk for colorectal neoplasia [116]. There is an increasing prevalence of obesity in the USA, and it has been shown that obese

patients may be less likely to be screened for CRC than nonobese patients [117]. In its 2008 CRC screening guidelines, the American College of Gastroenterology introduced obesity as a potential risk factor that identifies patients who may need screening earlier than age 50 [53]. However, their enthusiasm for this recommendation was tempered by the recognition of the attendant comorbidities associated with obesity that may limit the benefits of screening.

Alcohol

There are several large studies that demonstrate an increased risk for colorectal neoplasia associated with alcohol intake [118–120]. Mechanistically, the increased risk associated with alcohol has been attributed to abnormal DNA methylation and repair, induction of cytochrome p450 enzymes, and altered bile acid composition [121, 122]. The NHS observed a direct increased risk related to alcohol intake of colorectal neoplasia in the colon but not the rectum of women [118]. The HPFS demonstrated an increased risk in men for an intake of 15 grams or more of alcohol per day [123]. One study that combined eight large prospective longitudinal populations observed an increased risk for patients who drank ≥2 alcoholic beverages per day [120]. Most studies have observed an increased risk for all types of alcoholic beverages. However, one study examining CRC [124] and another examining adenomas [23] found a decreased risk associated with wine intake. Overall, it appears that avoiding alcohol would decrease the likelihood of developing colorectal neoplasia.

Diet

Much of the emphasis in the literature regarding diet has focused on the CRC risk associated with red meat consumption and the potential reduction of risk with fiber intake. With regard to red meat consumption, the increased risk of CRC may result through several mechanisms. These included the production of heterocyclic amines, increased animal fat intake, increased heme absorption, and stimulation of insulin [125–127]. In the HPFS study, there was an increased risk of CRC in men who consumed more than five servings of red meat per week [118]. A recent meta-analysis by Alexander et al. observed a modest increased risk for colon cancer and a trend toward an association with the consumption for red meat [128]. The authors concluded that the association was not strong enough to discount potential confounders that may explain any positive correlation.

There are currently conflicting data with respect to fiber intake a risk of CRC. A possible protective effect of fiber intake in the form of fruits and vegetables on the risk for CRC has been examined in many large prospective studies [129, 130]. Some of the proposed mechanisms include increased folate consumption, binding of carcinogens, lower colonic pH, decreased colonic transit time, beneficial effects of micronutrients found in fruits and vegetables, and an increased production of short-chain fatty acids [131, 132]. A meta-analysis of 16 case control studies found a 50% reduction in CRC risks associated with fiber consumption [133]. Randomized controlled studies of fiber in the form of cereal or fruits and vegetables found no effect on the recurrence of colorectal adenomas [134, 135]. In the USA, studies that have examined both male and female health professionals have observed no effect of fiber on CRC risk [136, 137]. One large study did show an increased risk of CRC, but higher amounts of fiber intake did not offer any protective effect [138].

Family History of Colorectal Cancer

In current guidelines [53, 139], a family history of CRC has been used to inform the decision regarding when to start CRC screening. Having a first-degree relative (FDR) with CRC can increase the risk up to three times that of an average risk individual [140]. Johns and Houston performed a meta-analysis of 27 studies regarding CRC risk in patients with relatives with CRC and nine studies of patients with a family history of adenomas [141]. They observed that the relative risk for having an FDR with CRC was 2.25 (95% CI = 2.00–2.53). If a patient had more than one FDR with CRC, the risk was 4.25 (95% CI = 3.01–6.08). If the relative was diagnosed before the age of 45 years, the risk for the affected individual

was 3.87 (95% CI = 2.40–6.22). If the relative had a colorectal adenoma, the risk for CRC was 1.99 (95% CI = 1.55–2.55). Although it is well accepted that a family history of CRC significantly increases the risk for CRC, there is less data for a family history of an adenoma. One study by Cottet et al. observed an increased risk of large adenomas or CRC in patients with an FDR with a large adenoma [142]. Based on these data as well the lack of data for small adenomas, the ACG dropped a family history of any adenoma as an indication for earlier screening in its most recent guidelines. Based on available data, patients with second- or third-degree relatives with a history of CRC should receive average risk screening [140, 143].

Familial Syndromes

CRC in the setting of a familial syndrome represents less than 10% of all CRC. However, the identification of patients with these syndromes is important for surveillance of the affected individual as well as for screening of the relatives. Some important clues that an individual may have a familial syndrome include an early age of onset of the CRC, multiple adenomas, more than one affected relative with colorectal neoplasia, and successive generations with colorectal neoplasia. In addition to a family history of colorectal neoplasia, the practitioner should ask the patient about other cancers in first-, second-, and third-degree relatives. The United States Surgeon General's web site has an online tool for patients to collect a family history of diseases including cancer (https://familyhistory.hhs.gov/fhh-web/home.action). In this section we will briefly describe the common syndromes and the colorectal cancer screening guidelines for these patients.

Hereditary Nonpolyposis Colorectal Cancer

This familial syndrome, also known as Lynch syndrome, is responsible for less than 5% of all CRC [144]. The common features of this syndrome include young age of onset and predisposition for proximal tumors. The lifetime CRC risk for patients with the HNPCC mutation is about 50–80% [145]. These tumors are often mucinous, poorly differentiated, and contain infiltrating lymphocytes. The most common extracolonic tumor observed in HNPCC is endometrial cancer with the hMSH6 mutation conferring the greatest risk [146]. Other common sites for tumors include ovaries, small bowel, stomach, brain, skin, pancreas, hepatobiliary system, and the urinary tract. The Muir-Torre variant of HNPCC includes skin lesions such as sebaceous adenomas.

HNPCC occurs in the setting of germline mutations in the MMR genetic code. These genes are responsible for the production of DNA repair enzymes: hMLH1, hMLH3, hMSH2, hMSH3, hMSH6, hPMS1, and hPMS2 [39, 40]. The target of these repair genes is mismatch errors that occur in the microsatellite regions of the genome where there are tandem nucleotide base repeat sequences. When these microsatellite repeats cannot be repaired, MSI ensues.

There are multiple clinical guidelines to assist in the identification of HNPCC. The first set of guidelines was known as the Amsterdam Criteria-I [147]. These guidelines required that an individual have at least three relatives with CRC. One had to be an FDR of the other two with at least two successive generations affected and one individual diagnosed at less than 50 years of age. The second set of guidelines, Amsterdam Criteria-II, was developed to be more sensitive and allowed the relatives to have a diagnosis of an extracolonic HNPCC-associated tumor [148]. The current recommendations are the Revised Bethesda Guidelines for testing CRC for MSI [149]. These criteria recommend MSI testing when any of the following clinical scenarios are present: CRC diagnosed in a patient younger than 50 years, the presence of synchronous or metachronous CRC, the presence of another HNPCC-related tumor, CRC with MSI-related histology in a patient younger than 60 years, CRC diagnosed in an individual with an FDR with an HNPCC-related tumor or CRC less than 50 years of age, and CRC diagnosed in a patient with two or more FDR or second-degree relatives of any age with HNPCC tumors.

Testing for MSI involves a panel of five DNA markers. If two or more of these five markers are present, then an immunohistochemistry (IHC)

analysis can be done to confirm the presence of the protein products of the repair genes, which include MSH2, MSH6, MLH1, and PMS2 [150]. Any absence of the proteins in the tumor specimen, when compared to normal cells obtained in a blood sample, suggests that a germline mutation is present. When present, 90% of germline mutations in HNPCC are located in hMSH2 and hMLH1, while hMSH6 and hPMS2 account for the remaining 10% [151]. hMSH6 mutations carry a lower cancer risk than the other abnormalities [152]. A review by Koornstra et al. reported that the risk for endometrial cancer was the highest for hMSH6 and the lowest for hMLH1 [146].

The recommendation for an individual suspected of having HNPCC is a colonoscopy every one to 2 years. In a study by Stupart et al., 129 subjects with an hMLH1 defect underwent surveillance colonoscopy every 2 years until age 30 and then annually after that age, while 49 patients refused surveillance [153]. Patients who refused surveillance had a higher risk of death from CRC as compared to the group who had surveillance. The age recommended to begin screening in HNPCC patients is at 20–25 years of age or 10 years younger than the youngest affected individual with CRC. A flexible sigmoidoscopy is not recommended, given the proximal nature of the colon tumors associated with HNPCC. There is little evidence to support screening for the other HNPCC-related tumors.

Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is an autosomal dominant syndrome that is caused by a genetic mutation of the APC gene on chromosome 5. Unlike HNPCC, the penetrance of FAP is complete and is accompanied by a nearly 100% chance of developing CRC when the genetic mutation is present. APC mutations occur in approximately 1 in 10,000 births [154]. There are two phenotypes of the disease, classic and attenuated FAP. Classic FAP presents with thousands of adenomas in the colorectum by the time an affected individual is 10–12 years of age. The average age at which the individual develops CRC is less than 40 years of age [140]. Most patients with classic FAP will have duodenal adenomas by their fifth decade [155, 156], and duodenal or peri-ampullary cancer is the leading cause of death after a colectomy is performed [157]. These duodenal adenomas occur in the second portion of the duodenum or around the papilla. Many patients with classic FAP have polyposis of typically benign fundic gland gastric polyps that some studies have demonstrated to have a high rate of dysplasia [158]. Gastric adenomas can occur in less than one-fifth of all FAP patients and are usually located in the antrum [140]. Other manifestations include desmoid tumors, which are usually intra-abdominal. In addition, patients with FAP are at risk for endocrine tumors such as adrenal gland tumors and thyroid papillary carcinoma. Attenuated FAP (AFAP) differs from FAP in that these patients have a later onset of CRC.

The diagnosis of FAP is made by the initial observation of multiple colorectal or duodenal adenomas followed by confirmation with genetic testing for mutation of the APC gene. If the test for the FAP gene is negative, then a test should be performed for the MYH-associated polyposis (MAP) gene. An individual with an APC mutation should have a flexible sigmoidoscopy starting at 10–12 years of age [159–162]. If an adenoma is detected, surgery should be considered in the patient. In AFAP, screening should start at age of 18 years since the disease has a later onset. If an adenoma is detected, the individual should be placed in a yearly colonoscopy surveillance program. With regard to the surveillance of duodenal carcinoma, endoscopy with both forward and side-viewing scopes should begin at the age of 20.

Polyps

Polyps can be classified in several ways that include size, histology, anatomic location, morphology, and degree of dysplasia. In this section, there will be a discussion of traditional adenomas, which are considered neoplastic. In addition, hyperplastic or serrated lesions will be discussed in light of recent data suggesting their prominent role in carcinogenesis.

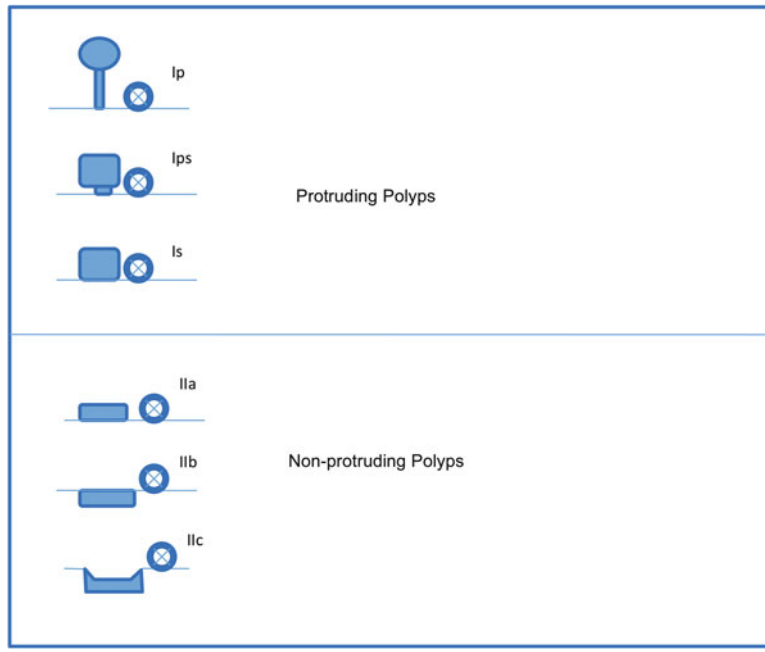

Fig. 1.1 The Paris classification divides polyps into protruding and non-protruding lesions

Traditional Adenomas

Histology

Adenoma histology has classically been described as tubular, villous, or tubulovillous. Over 90% of adenomas will have tubular pathology with less than 10% having some villous elements [55]. The majority of the tubular adenomas will be less than one centimeter in diameter as demonstrated in endoscopic studies of asymptomatic patients [24, 55, 163]. Although the majority of adenomas will be tubular adenomas, villous adenomas are of greater interest with regard to screening. Villous adenomas pose a challenge to the endoscopist since there is great variability to the pathologist's interpretation with regard to presence and extent of villous tissue. Rex et al. suggested that one quality indicator should be that villous adenomas account for less than 10% of all adenomas found [164]. In a study of 3,121 asymptomatic veterans, Lieberman et al. observed that 1,171 patients had adenomas [55]. There were 93 (93/1,171; 7.9%) patients who had adenomas with at least 25% villous elements. The primary importance of villous histology is in its role in defining an advanced adenoma.

Morphology

Adenomas can be classified as flat or protruding, and there are two schemes by which these morphologies can be described. The Japanese Research Society Classification (JRSC) defines flat lesions as those where the height is less than one-half the measured diameter [165–167]. The Paris classification divides lesions into those that are protruding versus those that are non-protruding [168, 169]. This is based on whether the lesion protrudes into the lumen a distance of at least 2.5 mm or the approximate width of a standard snare catheter. Adenomas are categorized into protruding which included pedunculated (Ip), sessile (Is), and mixed (Ips). The non-protruding or flat adenomas include elevated (IIa), flat (IIb), and depressed (IIc). A representation of the Paris classification is shown in Fig. 1.1.

Over the last decade there has been a significant amount of speculation regarding adenoma morphology and its possible association with

advanced neoplasia or frank malignancy. Soetikno et al. reported that while less than 15% of 1,819 patients from a veteran's hospital population demonstrated flat adenomas, 6.6% of these lesions had high-grade dysplasia or more ominous features [170]. These data suggested that while only a fraction of adenomas were flat, these lesions had a higher rate of advanced pathology than protruding adenomas. However with the advent of high-definition endoscopy, there are more data to suggest that non-protruding adenomas are common and that among these lesions, depressed morphology is the most important predictor of advanced pathology.

In a study by Kahi et al., there were 780 adenomas found, of which 338 (43.3%) were non-polypoid [171]. Most of the flat lesions were classified as IIa. Among the advanced lesions, only two protruding carcinomas were detected. In an Italian population of 27,400 patients, there were 4,154 patients with adenomas [172]. There were 25.9% of the patients who had non-polypoid adenomas, with a total of 1,121 flat adenomas detected. Among the 176 adenomas with HGD or greater, there was no difference in the prevalence of flat versus polypoid adenomas. The size of the polyp was the most important factor of advanced histology in this study. However, there was a higher rate of HGD or greater in the depressed (IIc) group compared with adenomas that were flat (IIb) or elevated (IIa). In summary, recent data suggests that IIa lesions are the most common morphology and that flat adenomas have high risk of advanced pathology if they present as IIc lesions [173].

Prevalence and Location of Adenomas

Adenomas can be located throughout the colon in at least 20% of all patients older than 50 years. However, there can be great variation with regard to anatomical location and prevalence. With regard to anatomic location, two separate studies examining female and male veterans observed that women [56] were more likely to have proximal neoplasia than men [55]. Anderson et al., in a study of nearly 2,000 screening patients, observed that age greater than 60 years, smoking, and a family history of CRC increased the likelihood of isolated proximal neoplasia [174]. This is neoplasia that would not have been detected on flexible sigmoidoscopy because it was proximally located and had no index distal lesion that would have prompted a full colonoscopy.

With regard to the prevalence of adenomas, there is also great variation. Although the quality benchmark for the percentage of patients with adenomas detected on a screening exam is 20% [164], many recent studies using high-definition colonoscopy have demonstrated higher detection rates. For example, in their study comparing white light to narrow band imaging, Rex and Heilbig found that over 50% of screening patients had adenomas [175]. In their study of over 600 asymptomatic patients, Kahi et al. examined the difference between white light high-definition colonoscopy versus high-definition colonoscopy plus chromoendoscopy with indigo carmine [171]. The percentage of patients with at least one adenoma detected was 55.5% for the chromoendoscopy arm and 48.4% for the white light-only group. Another recent study of 600 asymptomatic patients demonstrated an adenoma detection rate of approximately 40% [176].

Advanced Features

Advanced adenomas are lesions that have been identified as important targets with regard to screening. Adenomas with features such as size equal to or exceeding one centimeter, containing villous histology, high-grade dysplasia, and/or adenocarcinoma can qualify as an advanced adenoma. These lesions are important due to their malignant potential as well as their association with future neoplasia. Good evidence to support the role of advanced adenomas in the development of CRC can be found in a British study that followed 1,618 patients [177]. Patients who had polyps that were large (>1 cm) or had villous tissue were more likely to develop CRC than the general population (OR = 3.6; 95% CI: 2.4–5.0). Recently, Lieberman et al. examined the 5-year follow-up after a baseline screening examination in 3,121 male veterans [178]. This study examined the risk for developing an advanced adenoma depending on the baseline findings. The relative

Table 1.1 Prevalence of advanced adenomas in screening populations

Study	Year	Country	Population	Advanced adenomas
VA 380 [55]	2000	USA	3,121 male veterans aged 50–75 years	10.5% (329/3,121)
University of Navarra [186]	2003	Spain	Asymptomatic patients ($n=2,210$) older than 40 years	7.0% (156/2,210)
Eli Lilly [163, 188]	2003	USA	Asymptomatic patients ($n=3,025$) older than 50 years	6.0% (181/3,025)
CONCeRN [56]	2005	USA	1,463 asymptomatic female veterans aged 50–79 years	4.9% (72/1,463)
Tel Aviv Sourasky Medical Center [187]	2006	Israel	1,177 people aged 40–80	6.3% (74/1,177)
Rockford Gastroenterology [183]	2006	USA	2,053 patients with no previous screening	5.2% (107/2,053)
Maria Sklodowska-Curie Memorial Cancer Center[185]	2006	Poland	50,148 patients ages 40–66. Those less than 50 had a family history of CRC	5.6% (2,796/50,148)
University of Wisconsin [184]	2007	USA	Study compared screening with CTC ($n=3,120$) and OC ($n=3,163$)	CTC: 3.2% (100) OC: 3.4% (107)
CORI [71]	2008	USA	Asymptomatic patients from 17 sites ($n=11,854$)	5.9% avg risk 5.7% Fam Hx CRC or adenoma

risk in patients was 6.40 (95% CI: 2.74–14.94) with tubular adenomas at least 10 mm in size, 6.05 (95% CI: 2.48–14.71) for villous adenomas, and 6.87 (95% CI: 2.61–18.07) for adenomas with high-grade dysplasia. Conversely, the risk was only 1.92 (95% CI: 0.83–4.42) with one or two tubular adenomas <10 mm in size. One corollary was that the risk of CRC in patients with three or more tubular adenomas <10 mm in size was almost as high as the advanced adenomas (RR = 5.01; 95% CI: 2.10–11.96). Many other trials such as the National Polyp Study [35, 179], the pooled chemoprevention trials [180], and European calcium trial [181] have reported that adenoma multiplicity is a strong predictor of advanced neoplasia on follow-up exam [182]. Thus although they are not considered an advanced adenoma, the presence of multiple (at least 3) adenomas of any size is an important predictor of future advanced neoplasia.

With regard to the prevalence of advanced adenomas, there are several factors that can affect these rates. These include age, gender, family history of CRC, as well as other lifestyle factors such as smoking and BMI. The overall rates can vary from 3 to 10% [55, 56, 71, 81, 163, 183–188]. Screening studies provide the most reliable data for prevalence of these lesions, and results from some of the more notable studies are shown in Table 1.1. It is important to note that most of these studies do not comment on sessile serrated adenomas.

Size

Size is an important characteristic for adenomas as the risk for high-grade dysplasia is directly related to this measurement. Although, there are many endoscopists who measure polyp size with an open forceps method, there is data to suggest that the pathologist's measurement is more accurate [189]. Muto et al. observed that the rate of high-grade dysplasia in polyps <1 cm in size was 1.1% compared with larger polyps that had a rate of greater than 10% [190]. One analysis from the National Polyp Study found that the prevalence of high-grade dysplasia was 1.1% in adenomas less than 5 mm in size, 4.6% in patients with 5–9 mm adenomas, and 20.6% in patients with adenomas at least 1 cm in size [191]. Butterly et al. examined 1,933 adenomas resected from 3,291 colonoscopies for evidence of advanced pathology defined by the presence of villous elements, high-grade dysplasia, or adenocarcinoma [192]. In that analysis, they observed that the rate

of advanced pathology was 1.7% for adenomas 4 mm or smaller and 10.1% for adenomas that were 5–10 mm.

A similar study was performed by Tsai and Strum on adenomas resected from nearly 5,000 patients who had received a screening colonoscopy [193]. In that population, there were 930 patients with at least one adenoma, 248 with advanced adenomas, and 8 with adenocarcinoma. With regard to size, there were 89 polyps one centimeter or larger, and 76 (85%) had advanced pathology. In this study, advanced pathology is defined as the presence of villous tissue, high-grade dysplasia, or adenocarcinoma. Among the 6–9 mm polyps, 67 (27%) were advanced and 105 (10%) of 1,025 polyps ≤ 5 mm had advanced histology. These rates of advanced pathology are much higher than previous studies. In Table 1.2, the results of other selected studies demonstrating the risk of advanced histology relative to adenoma and polyp size are shown.

Size is not only important with regard to the risk of malignancy. The increasing detection rate of diminutive polyps (<5 mm) may force endoscopists to alter how they treat these small lesions in the course of colon cancer screening. As previously noted, studies that have employed high-definition colonoscopes [27, 171, 175, 176, 191] have yielded adenoma detection rates in screening populations that are much higher than in previously published studies [24, 55, 56, 163]. Resection of these polyps can be associated with complications and substantial pathology costs. Therefore, the benefit from removal is small given the low risk of malignancy. In response to these issues, some experts have recommended a "resect and discard" policy which is designed to decrease cost while maintaining the efficacy of cancer prevention with colonoscopy [196]. While this recommendation appears to address the concern of cost, there are other concerns such as patient acceptance of this policy that require further examination. Another issue is how to deal with multiple polyps. Specifically, while it is recognized and accepted that small adenomas individually pose a small risk with regard to malignant potential and metachronous lesions [178], multiple adenomas have been shown to be predictive of future adenomas [197, 198]. Although discarding one or two small polyps is unlikely to change surveillance recommendations for the patient, detection of more than two adenomas may change the interval of surveillance by several years. Thus, histologic confirmation by a pathologist may be needed for patients with multiple polyps. Finally, with an increasing detection rate for these small adenomas, we may want to consider raising the threshold for shorter surveillance intervals from three adenomas to a higher number. Thus, more studies evaluating these issues are required.

A study by Rex et al. demonstrates the significance of lesions less than one centimeter in size [195]. In that study, they examined the "high-risk adenoma" rates in patients who underwent an endoscopic examination. High-risk adenomas were defined as advanced adenomas and multiple adenomas. Of the 10,034 patients, there were 5,079 who had at least one adenoma and 1,001 patients with high-risk adenomas. Among patients with high-risk adenomas, 293 (29%) had three adenomas less than 5 mm ($n = 267$) or advanced pathology ($n = 26$). Of the 774 patients with one or two adenomas 6–9 mm in size, 184 (18%) had multiple adenomas ($n = 149$) or had an adenoma with advanced pathology ($n = 35$). This study reinforces that adenomas less than 1 cm can have significant pathology. However, this study also demonstrates the number of patients with multiple adenomas that are either less than 9 mm (18% of the 1,001 high-risk patients) or less than 5 mm (27%).

Serrated Pathway

In 1990, Longacre and Fenoglio-Preiser published data on polyps that had features of both hyperplastic polyps and adenomas [199]. The authors believed that these polyps represented a variant of a villous polyp rather than two separate polyps juxtaposed together. These polyps were denoted serrated adenomas because of the pattern of the architecture.

Since their initial description, these polyps have gained a great deal of interest because of the many challenges that they pose. The first challenge lies in the rapidly changing nomenclature

Table 1.2 Prevalence of advanced histology as a function of adenoma and polyp size

	0–5 mm		6–9 mm		≥10 mm	
Study	Adenomas	Polyps	Adenomas	Polyps	Adenomas	Polyps
Butterly et al. [192]	2.7% (35/1,305)	N/A	8.2% (40/487)	N/A	25.8% (35/141)	N/A
Lieberman et al. [194]	2.5% (46/1,880)	1.2% (46/3,744)	7.9% (64/811)	5.3% (64/1,198)	35.2% (274/778)	28.9% (274/949)
Rex et al. [195]	1.9% (79/4,211)	0.9% (79/8,798)	9.9% (68/689)	5.3% (68/1,282)	N/A	N/A
Tsai et al. [193]	16.0% (105/656)	10.2% (105/1,025)	3.4% (67/198)	27.1% (67/247)	59.2% (45/76)	50.1% (45/89)

of these lesions. Recently, these lesions have been divided into hyperplastic polyps (HP), sessile serrated adenomas (SSA), and traditional serrated adenomas (TSA) [200]. Another recognized, but less commonly used, category is the "mixed polyp" with adenomatous tissue juxtaposed next to hyperplastic tissue. Another challenge lies in the pathologic interpretation of serrated polyps as there are several studies that have demonstrated significant variability among pathologists in interpreting and classifying these lesions [201, 202].

The classification of HP can be divided into two subgroups: the microvesicular serrated polyps (MVSP) and the goblet cell serrated polyps (GCSP), which are primarily located in the distal colon [203]. The GCSP have enlarged distended crypts with many goblet cells in the upper half of the crypts and prominent tufting of the epithelium. Conversely, the MVSP have long funnel-shaped crypts with prominent serration in the upper portion of the crypt. The MVSP appear to have similar molecular abnormalities to SSA and may evolve into these more advanced lesions. On the other hand, it is not known if GCSP progress to SSA or another advanced lesion. An excellent study that demonstrates this divergence is an examination by Rosenberg et al. of the molecular profile of aberrant crypt foci (ACF). ACF are small lesions, one or two crypts in size, that were used by this group as models of carcinogenesis. In this study, Rosenberg et al. observed that ACF with distended crypts were more likely to have KRAS abnormalities, while serrated ACF were more likely to have BRAF mutations. The KRAS lesion is mutually exclusive with BRAF mutations and rarely found in SSA [204].

Sessile serrated adenomas (SSA) are characterized by similar features to MVSP in the upper crypts, but irregularity of the architecture of the lower crypts. This gives the crypts the appearance of an upside "L" or "T." With regard to molecular abnormalities, SSA have BRAF mutations and are CIMP-H lesions [205, 206]. SSA are often proximally located and are often difficult to detect as they often present as flat (IIb) or superficially elevated (IIa) lesions [207]. They frequently can be detected by the presence of a yellowish mucous cap covering the polyp [208]. SSA usually exhibit a type II pit pattern or stellate-shaped pattern due to their serrated crypt formation. In addition, some SSA may develop dysplasia and therefore exhibit a type III or IV pit pattern seen in adenomas.

Another important feature of SSA is their strong association with advanced neoplasia. A few studies have demonstrated that large serrated polyps are likely to have synchronous advanced neoplasia [209, 210]. Hyperplastic polyposis syndrome (HPS) is characterized by multiple HP throughout the colon. In SSA that are adjacent to carcinoma, the transition zone is dysplastic. In addition, Goldstein et al. examined eight serrated polyps with a focus of malignancy [211]. They observed that these serrated polyps averaged 8.3 mm in size, that the carcinoma in these polyps averaged 2.8 mm in size, and that it invaded the submucosa without spreading laterally. Thus SSA appear to have a proclivity to become advanced lesions and could be considered precursors of CRC.

Another group of serrated lesions is TSA which are characterized by serration and a uniform population of dysplastic cells which are columnar with eosinophilic cytoplasm. These polyps tend to be protuberant, unlike SSA which are typically flat. TSA are believed to be a separate entity from SSA with dysplasia, despite both having serration and dysplasia. One important distinguishing factor between the two histologic types is the observation that ectopic crypts are found in TSA. These are crypts whose bases are adjacent with the muscularis mucosa [212].

Another challenge that endoscopists face is the difficulty in detecting serrated polyps. As previously noted, serrated polyps are often proximally located and flat in morphology. A recent study by Kahi et al. observed a marked variation of 1–18% for the prevalence of serrated lesions in nearly 7,000 patients undergoing colonoscopy [213]. Furthermore, the detection rate of serrated lesions correlated with the detection rate of traditional adenomas. The authors concluded that successful detection of serrated polyps is likely dependent on adherence to quality indicators in the performance of colonoscopy.

Interval Cancer

Recently published data have suggested an anatomical difference with regard to the protective effect from colonoscopy. While the risk for distal advanced neoplasia and CRC is reduced in patients who have received a colonoscopy, the risk for proximal CRC is not reduced [214, 215]. Interval CRC is diagnosed between regularly scheduled screening or surveillance colonoscopies. Many studies have demonstrated a proximal proclivity for interval tumors. A study by Bressler et al. demonstrated that older age and female gender are risk factors for interval cancers [28].

There have been several explanations proposed to explain interval neoplasia. Interval CRC may arise from previously resected polyps. Cancers arising from inadequate resection of adenomas may account for a large percentage of interval cancers. Another possibility includes the potential differences in the biology between right- and left-sided neoplasia. The methylation pathway may provide an answer with regard to biological explanations given the proximal location, accelerated path to advanced pathology, and difficulties in detection of interval CRC. One study by Arain et al. observed that interval CRC has a higher rate of CIMP than non-interval cancers [216]. As previously discussed, this molecular abnormality is the hallmark of SSA.

Missed lesions are also likely to play an important role in interval CRC. Major reasons for missing lesions during colonoscopy involve technical performance issues that limit intubation and visualization of the right bowel. The study by Bressler et al. observed that factors affecting performance of colonoscopy can be associated with interval CRC [28]. These include the presence of diverticular disease or pelvic surgery in women [217, 218]. Furthermore, these investigators also observed that having a colonoscopy in an office or performed by an internist or by a family practitioner is also an independent risk factor for interval CRC.

Other factors may result in missed lesions even when the cecum is intubated. Inadequate preparation of the colon as well as quick withdrawal time may result in colorectal neoplasia going undetected. Rex has published multiple papers recommending quality indicators to maximize adenoma detection during colonoscopy [173, 219, 220]. These included adequate withdrawal time, adequate preparation time, and a minimum cecal intubation rate of 90%. Following these recommendations should result in overall adenoma detection rate (ADR) of 20%. Adenoma detection rate is the percentage of all patients in whom an adenoma was detected and is considered the main benchmark with regard to quality of colonoscopy. The importance of two of these quality indicators was validated in landmark colonoscopy studies. The first was an analysis by Barclay et al. of the adenoma detection rate in a population of nearly 8,000 patients who had an endoscopy by one of 12 experienced gastroenterologists [183]. They compared the adenoma detection rate between the endoscopists who used more than 6 min to withdraw the colonoscope versus those who used less than 6 min. Compared with endoscopists with shorter withdrawal times, those with longer withdrawal times had higher rates of detection of any neoplasia (28.3% vs. 11.8%, $P<0.001$) and more importantly of advanced neoplasia (6.4% vs. 2.6%, $P=0.005$). A second study was performed by Kaminski et al. in a population of over 45,000 patients who received a screening colonoscopy [221]. There was a higher rate of interval CRC among endoscopists with an ADR of less than 20%. Thus, one could conclude that better technique such as longer withdrawal time should result in a higher ADR and subsequently lower interval CRC rate.

Pohl and Robertson designed a novel analysis to estimate the frequency of missed interval cancers [222]. They calculated the proportion of missed lesions that resulted from missed adenomas at baseline. Key assumptions based on the literature included published adenoma miss rates, adenoma prevalence rates, and adenoma–carcinoma transition rates. Their analysis demonstrated that the rate for interval CRC within 5 years of screening could range from 0.5/1,000 interval CRC for the lowest adenoma miss rates to 3.5/1,000 for the highest adenoma miss rates.

Staging of CRC

The Dukes' classification was the earliest form of CRC staging. Originally published in 1929, the Dukes' classification has been the most widely used and accepted CRC staging scheme. This classification used intraoperative findings and was based on patients who had undergone a potentially curative resection [223, 224]. The first stage was A for any tumor confined to the submucosa or the muscularis propria. Stage B was for any tumor that penetrated the muscularis propria and invades directly into the peri-colorectal tissue, the surface of visceral peritoneum or adjacent organs or structures. The modified Astler–Coller classification was different in that it subcategorized the Dukes' stages (ABC) into numbered categories to differentiate tumor penetration levels. In addition, tumors penetrating the muscularis propria were taken out of the "A" category and classified as B2. Since this classification, the TNM or tumor-node-metastasis classification has been used by the Union Internationale Contre le Cancer (UICC) and the American Joint Committee on Cancer (AJCC) [225]. The most important aspect of the staging for CRC pertains to the treatment, which will be discussed in the next section. In the TNM classification, the N category is divided into N0, N1, and N2 depending upon the number of positive lymph nodes. The M category is categorized by the number of organs that the tumor has involved.

The following is the breakdown for the T staging:

- Tis: Tumor confined to the mucosa.
- T1: Tumor extends through the muscularis mucosa into the submucosa.
- T2: Tumor extends through the submucosa into the muscularis propria.
- T3: Tumor extends through the muscularis propria into serosa but not through the bowel wall.
- T4a: Tumor extends through the serosa.
- T4b: Tumor extends though the wall of the colon and invades nearby structures/organs.

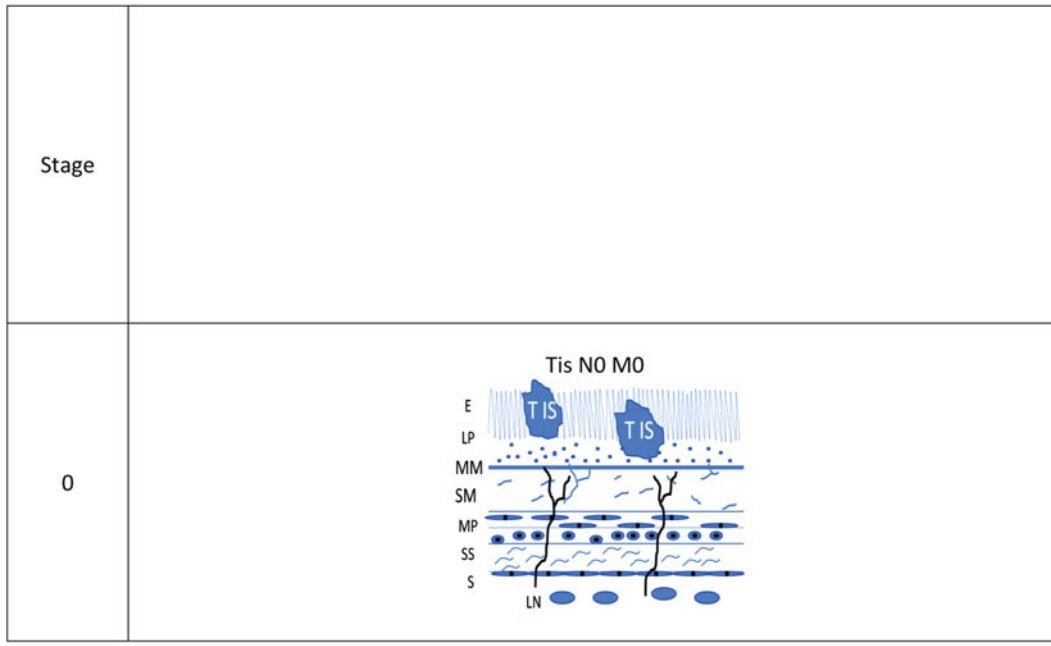

Fig. 1.2 A representation of the stages for colorectal cancer according to the American Joint Committee on Cancer (AJCC)

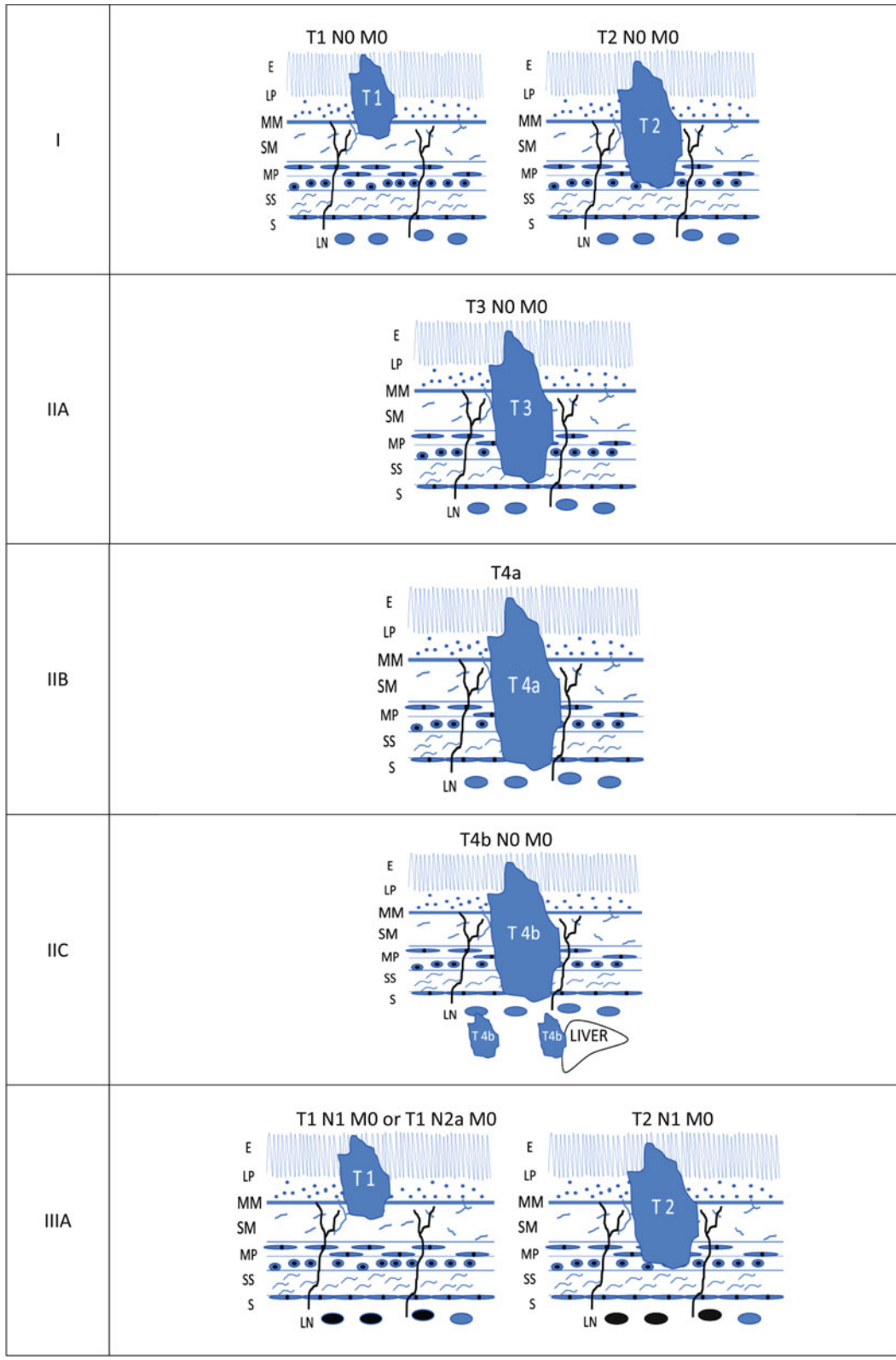

Fig. 1.2 (continued)

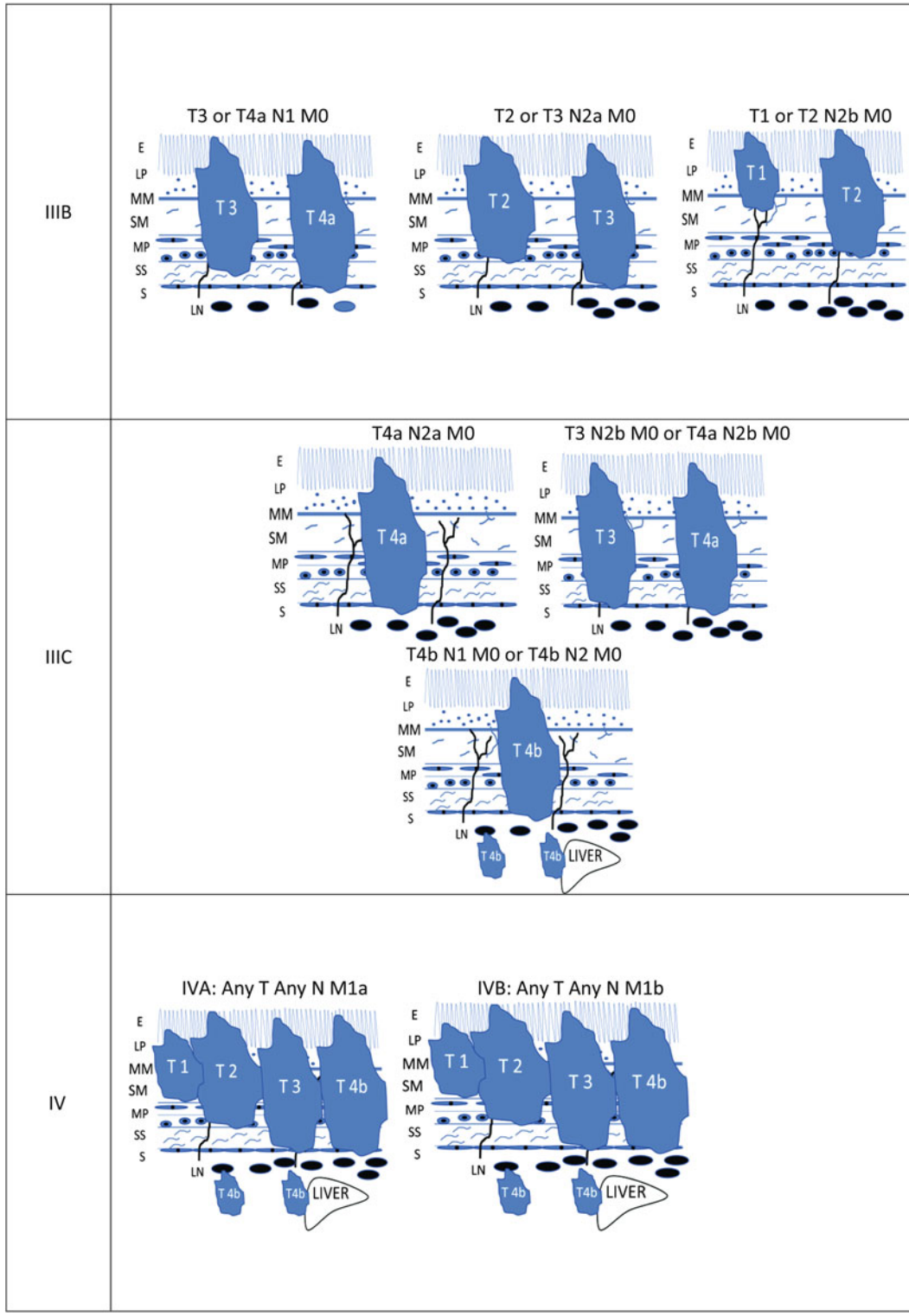

Fig. 1.2 (continued)

The stages of CRC (Figs. 1.1 and 1.2) according to the AJCC guidelines are the following:

- Stage 0: Tis, N0, M0
- Stage I: T1 or T2, N0, M0
- Stage IIA: T3, N0, M0
- Stage IIB: T4a, N0, M0
- Stage IIC: T4b, N0, M0
- Stage IIIA: T1 or T2, N1, M0
- Stage IIIB: T3 or T4a, N1, M0; T2 or T3, N2a, M0; T1 or T2, N2b, M0
- Stage IIIC: T4a, N2a, M0; T3 or T4a, N2b, M0; T1 or T4b, N1 or N2, M0
- Stage IVA: Any T, any N, M1a
- Stage IVB: Any T, any N, M1b

This is shown in Fig. 1.2.

Thus, when a tumor is resected, the following factors need to be reported for staging:

- Grade of the cancer
- Depth of penetration (T)
- Number of lymph nodes evaluated and number that are positive (N)
- Status of proximal, distal, and radial margins
- Presence of lymphovascular invasion
- Presence of perineural invasion
- Presence of extranodal tumor deposits

Treatment of CRC

The treatment of CRC depends on the stage of disease, with colon and rectal cancers having different recommendations from the National Comprehensive Cancer Network (NCCN). The recommendations are usually surgery with or without adjuvant therapy in the form of chemotherapy or radiation. With regard to colon cancer, Stage I can be treated with surgery and does not require adjuvant therapy. Stage II can be treated with surgery, and adjuvant therapy may be used for patients with risk factors that indicate a high rate of recurrence. These factors include tumor grade of 3 or 4, the presence of lymphatic/vascular invasion, bowel obstruction or perforation, or close/indeterminate surgical margins. Adjuvant therapy can be in the form of chemotherapy with 5-FU/leucovorin/oxaliplatin or other chemotherapy agents such as capecitabine. Stage III colon cancer can be treated with surgery and chemotherapy in the form of one of several agents. The treatment of Stage IV colon cancer is dependent on whether the metastases are resectable. For example, if there is a single liver metastasis, then treatment is the surgical removal of both the primary tumor and liver lesion and chemotherapy.

The major difference between rectal and colon cancer is that the former has a higher rate of recurrence partly due to anatomic difficulty of resection in the pelvis [226]. Therefore, Stage II and III rectal cancers require adjuvant therapy in the form of chemoradiation therapy after curative resection. Neoadjuvant preoperative chemoradiation may improve outcomes by shrinking the tumor and increasing the success rate of surgery [227, 228].

Surgical Resection of CRC

Surgical resection of CRC is the cornerstone of treatment in this cancer. For colon cancer, a preoperative CT scan of the abdomen and pelvis as well as data from the colonoscopy provides the information that dictates the extent of the surgery. In rectal cancer, an endoscopic ultrasound and or pelvic MRI can aid in the staging of the cancer [229]. Currently, carcinoembryonic antigen (CEA) and histology or grade of the tumor do not play a role in determining the resection approach. Lymphatic drainage and blood supply are the main factors that dictate the extent of resection. In addition, the AJCC recommends the removal of at least 12 lymph nodes that drain the region of the cancer [225]. When the cancer is located above the peritoneal reflection, the main factor for the amount of colon resected is the mesenteric vasculature [229]. For right-sided cancer, a right hemicolectomy is performed which includes the appendix, cecum, ileocecal valve, ascending colon, hepatic flexure, and a portion of the proximal transverse colon. The resection line distally is the main trunk of the middle colic artery, which is left intact to preserve the blood supply to the remaining transverse colon. With regard to left-sided lesions, the colon is resected from the splenic flexure to just above the peritoneal reflection.

Rectal cancer differs from colon cancer because resection is technically more difficult. One of the main concerns in resecting rectal

cancer is the preservation of a functional anal sphincter. The original approach to rectal cancer was a radical resection of the distal rectum and perineum. This method resulted in a permanent colostomy and had a high perineal wound complication rate [230]. The use of the low anterior approach has resulted in better sphincter preservation, but a technique known as total mesorectal excision (TME) has resulted in low recurrence rates [231]. TME involves the total surgical removal of the pelvic nodal tissue with the rectal tumor through sharp dissection. One of main factors that will help a surgeon decide between a sphincter-preserving approach and a more radical resection is the rectal examination. If there is sufficient length between the anal verge and the tumor, then a surgical approach with a colon-anal anastomosis will be considered.

Surveillance for Resected CRC

The recommendations by the NCCN for surveillance after resection of CRC include office visits, periodic CEA, chest/abdomen/pelvic CT, and colonoscopy. The intervals for these examinations are dependent on the stage of the tumor. With regard to colonoscopy, the multi-society task force recommends that a repeat exam be performed in 1 year if the initial colonoscopy was considered a complete evaluation [232]. If there was an obstructing mass or any other reason for incomplete visualization of the colon, then a complete colonoscopy 3–6 months after the surgery is recommended. On the surveillance examination, if there is an advanced lesion, then a repeat colonoscopy is recommended in 1 year. If that second exam is normal, then another colonoscopy should be performed in 3 years. If that exam is normal, then a repeat is recommended in 5 years.

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