

Colon Cancer: A Clinician's Perspective in 2019

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Abstract

Colon cancer is a common preventable cancer. With the adoption of widespread colon cancer screening in the developed countries, the incidence and mortality of colon cancer have decreased in the targeted population. But unfortunately, the incidence and mortality of colorectal cancer (CRC) have been increasing over the last 25 years in the young adults below the age of 50. There is disparity in benefit, i.e. reduction in risk of death between right-sided and left-sided colon cancer by screening colonoscopy. The reason could be multifactorial and various measures have been taken to decrease this disparity. Although most of the screened populations are average risk individuals, a minority of the population have various risk factors for developing colon cancer and need to follow specific colon cancer screening guidelines. Gene mutations (adenomatous polyposis coli (APC), deleted in colon cancer (DCC), K-ras, p53, B-Raf proto-oncogene serine/threonine kinase (BRAF), mismatch repair genes) and microsatellite instability lead to the development of colon cancer. Although various non-invasive methods of colon cancer screening are now available, colonoscopy remains the gold standard of colon cancer screening and adenoma detection rate is now being used as the quality metrics in screening colonoscopy. Although Multi-Society Task Force (MSTF) and American College of Physicians (ACP) recommend initiating screening colonoscopy at age 50 years in all individuals except African Americans who should begin screening colonoscopy at age 45 years, the American Cancer Society (ACS) recommends initiating screening colonoscopy at age 45 years in all individuals irrespective of race and ethnicity. Low-volume split-dose prep has been found to be as effective as high-volume split-dose prep and more tolerable to patients with increased compliance. Boston bowel preparation scale is recommended to measure the quality of colon cleansing. CRC is curative if it is diagnosed at an early stage but various palliative treatment options (endoscopic, oncologic and surgical) are available in advanced stages of this cancer. Adequate number of lymph node assessment during surgery is essential in accurate staging of CRC. Checkpoint inhibitors have been found to have dramatic response and durable clinical benefit in dMMR/MSI-H metastatic CRC. Different genetic and immune-oncologic research trials are ongoing for early detection and better management of CRC.

Keywords: Colon cancer; Colorectal cancer; Screening for colorec-

tal cancer; Management of colorectal cancer; Colon cancer in young adults

Introduction

When we think about common preventable cancers, first thing comes to our mind is colon cancer or CRC. In fact, CRC is now the third most common cancer diagnosis among men and women in the United States of America [1]. With the widespread availability of colonoscopy, CRC is increasingly being diagnosed now-a-days, sometimes at an early stage and sometimes at an advanced stage. According to the World Health Organization (WHO), in 2018, globally 1.80 million new cases of CRC were diagnosed and 862,000 patients died from CRC [2]. In USA, approximately, 145,600 cases of CRC are diagnosed annually. Out of them 1,014,200 cases are colon cancers and the rest are rectal cancers [3]. Generally, in CRC, 71% are in the colon and 29% in the rectum. About 50,000 patients die from CRC annually in USA. During the period of 2008 - 2014, the incidence of CRC decreased slightly in men (2.2% per year) but remained stable in women. The mortality rate from CRC also decreased by 1.8% per year among men and 1.4% per year among women from 1999 to 2015 [4]. There are various screening programs recommended by American Cancer Society (ACS), Multi-Society Task Force (MSTF) and American College of Physicians (ACP). Although most (about 70%) of the CRC occurs in the average risk individuals (sporadic), up to 25% of cases occur in patients with family history of CRC, and about 10% of cases occur in hereditary colorectal cancer syndromes [5]. Now we have much better understanding in the pathogenesis of sporadic and hereditary CRC on the basis of molecular research [6]. In metastatic CRC, targeted therapies and checkpoint inhibitors are chosen according to the status of K-ras mutations, mismatch repair (MMR) gene defect and microsatellite instability (MSI). In this review, risk factors for developing CRC, the screening recommendations of both average-risk and high-risk individuals, cancerogenesis, clinical manifestations and available treatments of CRC in 2019 will be discussed.

Risk Factors for the CRC

The chance of developing CRC can be increased by environmental factors and/or genetic factors. The various risk factors for developing CRC include age above 50, low socioeconomic

Manuscript submitted November 3, 2019, accepted December 3, 2019

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doi: <https://doi.org/10.14740/gr1239>

Table 1. CRC Screening Recommendations by MSTF in 2017

Average-risk individuals	Family history of CRC
First tier tests: colonoscopy every 10 years or annual FIT. Colonoscopy should be offered first. If colonoscopy is refused, annual FIT.	Persons with one first-degree relative of CRC or documented advanced adenoma diagnosed < 60 years or two first-degree relatives with those findings at any age - screening colonoscopy every 5 years beginning 10 years before the age at diagnosis of youngest relative or age 40, whichever is earlier.
Second tier tests: CT colonography every 5 years or FIT-fecal DNA test every 3 years or flexible sigmoidoscopy every 5 to 10 years.	Persons with a single first-degree relative diagnosed at ≥ 60 years with CRC or an advanced adenoma - average risk screening options at age 40 years.
Third tier test: capsule colonoscopy every 5 years.	
Septin9 serum assay: not recommended for screening CRC.	

CRC: colorectal cancer; MSTF: Multi-Society Task Force; FIT: fecal immunochemical test; CT: computed tomography.

class, overweight and obesity, sedentary life style, tobacco smoking, heavy alcohol intake, low-fiber and high fat diet, consumption of red meat, processed meat and burnt or charred meat, diabetes mellitus and insulin resistance, acromegaly, renal transplantation with long-term immunosuppression, long-term androgen deprivation therapy, personal or family history of CRC or colorectal adenoma, long-standing inflammatory bowel disease (IBD), familial adenomatous polyposis (FAP), mutated MMR gene syndromes like hereditary non-polyposis colorectal cancer (HNPCC) or Lynch syndrome and Muir-Torre syndrome, hamartomatous polyposis syndromes like Peutz-Jeghers syndrome, Cowden syndrome and Juvenile polyposis syndrome, and non-inherited polyposis syndromes like serrated polyposis syndrome (SPS) and Cronkhite-Canada syndrome. We are also noticing that the incidence of CRC has been increasing in young adults (YA) in their 30s and 40s over the last 25 years in high income countries (United States, United Kingdom, Denmark, Norway, Canada, Australia and New Zealand), whereas it has been decreasing in adults after age 50. But the absolute incidence of CRC among YA remains much lower than among adults aged ≥ 50 [7]. YA generally present with late stage CRC (mainly left sided and rectal) as they ignore their symptoms most of the time. Smoking, alcohol intake, obesity, metabolic syndrome, male, black, Asians and family history of CRC have been found to be risk factors for early development of CRC. Thirty-five percent of YA with CRC have some sort of genetic mutation, whereas 3-5% of all CRC cases have genetic mutation. So genetic studies should be considered in YA with CRC even without any family history of colon cancer [8].

Screening Programs

MSTF which represents American College of Gastroenterology (ACG), American Gastroenterology Association (AGA) and American Society of Gastrointestinal Endoscopy updated the CRC screening in 2017 as shown in Table 1 [9]. In November 2019, ACP updated the CRC screening recommendation in average-risk individuals between the age of 50 and 75 years as shown in Table 2 [10].

ACS recommended last year that average-risk individuals

start regular CRC screening at age 45. AGA supported this new recommendation for earlier CRC screening. Tests recommended by ACS for CRC screening are two broad categories [11]: visual/structural tests and stool-based tests. Visual/structural tests include colonoscopy every 10 years, CT colonography every 5 years and flexible sigmoidoscopy every 5 years. Stool-based tests include fecal immunochemical test (FIT or iFOBT) every year, high-sensitivity guaiac-based fecal occult blood test (gFOBT) every year and multitarget stool DNA (MT-sDNA or FIT-DNA) test every 3 years. Cologuard is the only stool DNA test available approved by the United States Food and Drug Administration (FDA). It incorporates mutant KRAS, and β-actin, methylated BMP3 and NDRG4 gene promoter regions and fecal immunochemical test for human hemoglobin. iFOBT, gFOBT and FIT-DNA tests are home-based, and patients collect stool samples using a kit and mail the kit to a laboratory for testing. Colonoscopy is indicated if any of the stool-based tests or flexible sigmoidoscopy or CT colonography becomes positive [12]. Sometimes, patients present with FIT positivity after normal colonoscopy. In an observational population-based study, the incidence of developing CRC was 0.4% over a period of 4.7 years [13]. It is the author's opinion not to do FIT after a high quality normal colonoscopy as FIT can be positive due to other lesions in the gastrointestinal tract.

In 2014, capsule colonoscopy was approved by the United States FDA to detect colon polyp only for patients with incomplete colonoscopy [14]. Methylated SEPT9 DNA is shed into the blood from colon cancer and it can be detected by polymerase chain reaction (PCR) in the blood. In a meta-analysis, methylated SEPT9 had a sensitivity of 71% and specificity of 92% in detecting CRC [15]. Methylated SEPT9 assay

Table 2. CRC Screening Recommendations by ACP in 2019

Average-risk individuals
FIT or gFOBT every 2 years.
Colonoscopy every 10 years.
Flexible sigmoidoscopy every 10 years plus FIT every 2 years.

CRC: colorectal cancer; ACP: American College of Physicians; FIT: fecal immunochemical test; gFOBT: guaiac-based fecal occult blood test.

(Epi proColon) is the first blood test approved by the FDA for CRC screening in April 2016. Although colonoscopy is the gold standard test for detecting colon polyps and cancer, it is not perfect. Interval cancer (CRC diagnosed after a screening or surveillance colonoscopy in which no CRC was found and before the date of next recommended colonoscopy) was found in 6% of all patients with CRC within 6 to 60 months of a colonoscopy in a population-based study. The interval cancers were more in the right colon, at an early stage with lower risk of death, and associated with higher rate of adenoma and family history of CRC [16, 17].

How much benefit can be gained by strictly following these tests? FOBT if performed annually can reduce the number of death due to CRC by 15-33% [18]. Stool DNA test is more sensitive than FOBT and can detect greater proportion of colorectal neoplasia [19]. Regular screening with flexible sigmoidoscopy can lower the mortality from distal CRC by 50% [20]. Screening colonoscopy may reduce the CRC mortality by 60-70% [21]. It is not yet known whether CT colonography can reduce CRC mortality.

Screening Colonoscopy

The decreased CRC incidence and mortality are probably due to the adoption of colon cancer screening, removal of adenomatous colon polyps, early detection of colon cancer and availability of better treatment. Doubeni et al conducted a nested case-control study and found that screening colonoscopy was associated with a 75% reduction in risk of death for left-sided colon/rectal cancer and a 65% reduction for right-sided colon cancer [22]. The disparity in benefit between the two sides is multifactorial. Missed polyp or lesion in the right colon is an important factor. This could be due to inadequate cleaning of right colon, incomplete colonoscopy or difficulty in visualizing polyps on the proximal aspect of colonic folds by standard colonoscopy. Biologic factor includes difficulty in visualizing right colonic flat serrated adenoma containing BRAF V600E that can develop microsatellite unstable right-sided colon cancer. Some studies showed that there could be an increased incidence of right-sided colon cancer in females [23] and elderly population [24]. Different measures have been taken to improve detection of right-sided colon polyp. These include use of split dose colon preparation, high definition colonoscopy (1,080 pixels), double-right colon examination (DRCE), retroflexion of colonoscope in right colon, Endo cuffs, transparent caps, Endo rings, G-Eye balloon endoscope and Third Eye panoramic device.

Adenoma detection rate (ADR) is now considered as the national benchmark on quality of screening colonoscopy and primary indicator for decreasing CRC through the use of screening colonoscopy. ADR is measured by dividing the number of screening colonoscopies in which one or more adenomas are detected by the total number of screening colonoscopies. ADR does not count the total number of adenomas detected [25]. High ADR percentages have been found to be associated with low colon cancer cases. If the ADR increases by 1%, a patient's risk of developing colon cancer over the

next year decreases by 3%. ADR is inversely associated with development of interval CRC, advanced stage interval cancer and fatal interval cancer [26]. The recommended ADR is 20% or more in females, 30% or more in males and 25% or more on an average [27].

Of the colon surface, 13.4% is not visualized during standard colonoscopy as suggested by a simulation study that used CT colonography. ADR is higher with high-definition colonoscopy compared with standard definition colonoscopy. Wide angle colonoscopes are also now being used for screening colonoscopy. A study done by Rex et al did not find any significant difference in missing polyp using standard colonoscope with 140° field of view and wide angle colonoscope with 170° field of view [28]. Different measures like split-dose preparation, retroflexion of the colonoscope in the right colon, DRCE and adjunctive accessories like Endo cuffs, transparent caps, Endo rings, G-Eye balloon and Third Eye panoramic device are being used to improve right-sided colon polyp detection rate [29].

Penetrability of Colonoscopy in General Population

Screening colonoscopy is an effective means of detecting and removing pre-cancerous lesions in the colon. But acceptance of having this test done in the target population is not very high. Many individuals consider colonoscopy as a cumbersome test probably due to the hassle of going through colon cleansing, procedure related pain and complications. Cost is also an important factor. One in three target patients (age 50 to 75) who (about 38 million people) need screening colonoscopy are still not getting the procedure done. In 2012, 6.3 million screening colonoscopies were done in the United States. CRC screening in the target population increased from 58% in 2013 to 63% in 2015 [30]. Screening colonoscopy rate is increasing steadily because of different medical society guidelines, instructions by the primary care physicians, national media coverage, digital marketing and social media.

Many patients do not tolerate high-volume colon cleansing regimens. A systematic review of 17 randomized controlled trials showed that low-volume, split-dose regimens were as effective as high-volume, split-dose regimens in colon cleansing with better tolerance and superior compliance [31]. Patients should be given easy-to-understand colonoscopy prep instructions to improve compliance. Adequate cleansing of colon mucosa is essential for higher detection of colon polyps. Quality of colon cleansing is now-a-days measured by the Boston bowel preparation scale (BBPS) - a nine-point standardized and validated bowel cleanliness rating scale as shown in Table 3 [32]. The right colon, i.e. cecum plus ascending colon, the transverse colon including the hepatic and splenic flexures, and the left colon, i.e. descending colon, sigmoid colon and rectum are assessed for cleanliness. Each of them gets 0 to 3 points and as a result, total BBPS score can be 0 to 9. It is recommended to repeat colonoscopy within a year if BBPS score is < 5 and if the BBPS score is ≥ 7, repeat colonoscopy should be done at regular intervals [33].

Table 3. BBPS Scores

Score	Colon cleanliness
0	Unprepared colon segment with mucosa not seen due to solid stool that cannot be cleared.
1	Portion of mucosa of the colon segment seen, but other areas of the colon segment not well seen due to staining, residual stool and/or opaque liquid.
2	Minor amount of residual staining, small fragments of stool and/or opaque liquid, but mucosa of colon segment seen well.
3	Entire mucosa of colon segment seen well with no residual staining, small fragments of stool or opaque liquid.

BBPS: Boston bowel preparation scale.

High-Risk Individuals for CRC

Risk for the development of CRC can be average or high. Average-risk individuals are those who do not have any polyposis syndrome, hereditary colorectal cancer syndrome, long-standing IBD and personal or family history of CRC or advanced colorectal adenoma. Most of the average-risk individuals develop CRC after 50 years of age. Individuals with high risk of CRC develop CRC at an early age and as a result, it is essential for them to follow a specific screening and surveillance program. They are as follows: 1) Family history of CRC: Single first-degree relative with CRC or advanced adenoma (adenoma ≥ 1 cm in size, or with high-grade dysplasia or villous histology) diagnosed below the age of 60 years or two first-degree relatives with CRC or advanced adenomas at any age. ACG recommends screening colonoscopy every 5 years beginning at age 40 or 10 years earlier than the youngest index case in the family [34]. 2) Patients with classical (germline mutation of APC gene) should be screened for CRC by annual colonoscopy or flexible sigmoidoscopy until the time of colectomy. The average age of onset of polyposis is 16 years and the average age of development of CRC is 39 years [35]. The time of colectomy depends on patients' symptoms, size and number of adenomas, presence of cancer or high-grade dysplasia. Elective colectomy is generally done in late teens or early twenties if there is less number (< 10) of adenoma or small-sized (< 5 mm) adenomas. Early colectomy should be done if the patient is symptomatic with gastrointestinal bleeding, there are many 6 to 10 mm polyps which cannot be cleared by endoscopic polypectomy or there is marked increase in number of colon polyps in consecutive colonoscopies [36, 37]. Urgent colectomy should be considered if there is adenoma with high-grade dysplasia, or suspected or documented CRC. Following surgery, ongoing surveillance should be continued as there is a chance of developing adenoma or adenocarcinoma in the ileal pouch, rectal cuff or in the ileostomy site [38, 39]). 3) Patients with attenuated FAP (germline mutation of APC gene near its 3' end or 5' end) develop 100 or less adenomatous colon polyps (predominantly right-sided) at age 20 to 25 with a tendency to spare the rectum and the average age of development of CRC is 55 years. Colon cancer screening should start at age 20 to 25 and there is no upper limit of stopping the surveillance. Regular screening esophagogastroduodenoscopy (EGD) should also be done to look for gastric and duodenal adenoma [40]. 4) HNPCC: Patients who fulfill the Amsterdam or Bethesda criteria for HNPCC should have their CRC tested for

MSI, i.e. variability in number of nucleotides in repeat DNA sequences within the tumor cells and MMR proteins by immunohistochemical staining. If the tests become positive, patients should get genetic testing for HNPCC. All the family members with positive genetic testing should get screening colonoscopy every 2 years starting age 20 to 25 until age 40, then annually [41]. 5) SPS: It is the most common polyposis syndrome. The prevalence is 0.033%, i.e. 1 in 3,000. According to WHO, clinical criteria for SPS include: 1) at least five serrated polyps proximal to the sigmoid colon, with two or more of those being ≥ 1 cm; 2) any number of serrated polyp proximal to the sigmoid colon in a person who has a first-degree relative with SPS; or 3) ≥ 20 serrated polyps of any size distributed throughout the colon [42]. In SPS, the cumulative incidence of CRC is 7% in 5 years under endoscopic surveillance [43]. The US MSTF on CRC recommends surveillance colonoscopy annually in all patients with SPS [44]. 6) Long-standing IBD: The incidence of CRC is six times more in IBD patients than that in general population. CRC is responsible for 10-15% of death in patients with IBD [45]. The risk factors for developing CRC in IBD include disease duration, extent of colitis, severity of colitis, presence of primary sclerosing colitis (PSC), orthotopic liver transplantation for PSC and family history of IBD [46]. The risk of developing CRC in ulcerative colitis (UC) and Crohn's disease (CD) is equivalent [47]. In case of UC, screening colonoscopy is recommended 8 to 10 years after the diagnosis of pancolitis, extensive colitis and left-sided colitis. The follow-up surveillance colonoscopy should be done every 1 to 2 years depending on the presence or absence of dysplasia. Proctitis and proctosigmoiditis do not pose increased risk of developing CRC [48]. Patients with personal diagnosis of PSC and family history of CRC should undergo screening colonoscopy at the time of diagnosis and then every year. In patients with Crohn's colitis involving at least one-third of the colon, the screening colonoscopy and surveillance colonoscopy protocol are same as in patients with UC. As the presence of active colitis has substantial impact on the diagnosis of dysplasia, screening colonoscopy and surveillance colonoscopy should be done when the disease is on remission [49]. Traditionally, white light colonoscopy with four quadrant random biopsies are taken every 10 cm starting from the cecum to the rectum as well as targeted biopsies are taken if there is any mucosal abnormalities. Recently chromoendoscopy or high definition colonoscopy is advocated to detect dysplasia in patients with IBD [50]. Chromoendoscopy using methylene blue or indigo carmine spray on the colon mucosa can detect fine mucosal changes and dysplasia 2 - 3 times more than conventional

Table 4. Screening for CRC in High-Risk Individuals

High-risk individuals for CRC	Recommendations
1. Family history: single first-degree relative with CRC or advanced adenoma diagnosed below the age of 60 years or two first-degree relatives with CRC or advanced adenomas at any age.	Screening colonoscopy every 5 years beginning at age 40 or 10 years earlier than the youngest index case in the family.
2. Classical FAP	Annual colonoscopy or flexible sigmoidoscopy starting at age 12 to 14 years until the time of colectomy.
3. Attenuated FAP	Colon cancer screening should start at age 20 to 25 and there is no upper limit of stopping the surveillance.
4. HNPCC	All the family members with positive genetic testing should get screening colonoscopy every 2 years starting age 20 to 25 until age 40, then annually.
5. SPS	Surveillance colonoscopy annually.
6. IBD	Screening colonoscopy is recommended 8 to 10 years after the diagnosis of pan-ulcerative colitis, extensive ulcerative colitis and left-sided ulcerative colitis as well as Crohn's colitis involving at least one third of the colon.

CRC: colorectal cancer; FAP: familial adenomatous polyposis; HNPCC: hereditary non-polyposis colorectal cancer; SPS: serrated polyposis syndrome; IBD: inflammatory bowel disease.

white light colonoscopy [51, 52].

The high-risk individuals for CRC with current recommendations for screening and surveillance are summarized in Table 4.

Development of CRC

There are sequential multistep mutational processes in the development of CRC. Seventy percent of CRC arises from adenoma-carcinoma sequence seen in sporadic adenoma and FAP [53] and 30% arises from other pathways which include MMR gene defect seen in Lynch syndrome, BRAF mutation seen in sessile serrated polyps and base-excision repair (BER) gene defect seen in MYH-associated polyposis syndrome [54]. In adenoma-carcinoma sequence, loss of function of tumor suppressor genes: adenomatous polyposis coli (APC) gene on chromosome 5q, deleted in colon cancer (DCC) gene on chromosome 18q and p53 gene on chromosome 17p and activation of oncogene KRAS on chromosome 12p lead to the formation of CRC. Loss of function of APC gene is considered to be the critical first step in the adenoma-carcinoma sequence. Loss of function of DCC gene leads to late stage of adenoma progression, whereas loss of p53 gene occurs at the terminal stage of adenoma-carcinoma sequence. KRAS oncogene activation occurs in 35-45% of CRC. It is associated with increased aggressiveness of CRC, decreased responsiveness to select chemotherapeutic agents particularly anti-EGFR (epidermal growth factor) agents in metastatic colon cancer, and poor survival [55]. MMR genes are involved in correcting the mistakes made during DNA replication. MMR-deficient cells have many DNA mutations which may lead to MSI and cancer. Sporadic CRC with somatic MMR gene mutations and MSI constitutes 12-15% of total CRC in USA. They occur mostly in Caucasians, middle-aged to older population without any family history of CRC, almost always in the right colon and

carry a relatively good prognosis. Aberrant DNA methylation of CpG islands, i.e. CpG island methylator phenotype (CIMP), is widely distributed in CRC. CIMP-associated methylation of MLH1 leads to sporadic cases of MMR deficiency. Germline mutations in the MMR genes (hMSH2, hMLH1, hPMS1 and hPMS2) occur in HNPCC and they account for 3-6% of total CRC in USA [56]. BRAF (B-Raf proto-oncogene serine/threonine kinase) gene mutation (valine-to-glutamate change at the residue 600 - V600E) is found in 10% of CRC. Sessile serrated adenoma (SSA) and traditional serrated adenoma (TSA) are developed due to BRAF mutation. CRC due to BRAF mutation are generally right-sided, occurring in old age, more recurrent in females and associated with MSI. BRAF-mutated CRC with MSI is generally associated with a better prognosis but proximal right-sided CRC carries a bad prognosis [57]. Almost all cases of BRAF-mutated CRC are CIMP-positive [58]. So CIMP-positive tumors are characteristic of tumors arising from serrated adenoma. About 50% of CIMP-positive tumors are microsatellite unstable. Twenty percent to 30% of all CRC are CIMP-positive and 10-12% of all CRC are CIMP-positive and microsatellite unstable.

Treatment of CRC

CRC is not only preventable but it is also one of the most treatable cancers if it can be diagnosed early. Treatment depends on the stage of the disease. TNM staging system and Dukes Class for CRC with 5-year survival are shown in Table 5.

Stage I CRC is treated by surgical resection of the tumor and the local lymph nodes. During surgery, examination of adequate number of lymph nodes is essential for correct staging of CRC. According to American Joint Commission on Cancer and the National Quality Forum, harvesting of at least 12 lymph nodes is considered as a quality indicator of CRC resection [59].

Table 5. TNM Staging System and Dukes Class for CRC With 5-Year Survival

Stage	Code	5-year survival	Dukes class
0	TisN0M0	100	
I	T1N0M0	100	A
	T2N0M0	90	B1
II	T3N0M0	75	B2
	T4N0M0	30	
III	Any TN1M0	60	C
	Any TN2M	30	
IV	Any T, any N, M1	3	D

Primary tumor (T): Tis - carcinoma in situ; T1 - tumor invades submucosa; T3 - tumor invades through muscularis propria into subserosal; T4 - tumor directly invades other organs or structures, and/or perforates visceral peritoneum. Regional lymph nodes (N): N0 - no regional lymph node metastasis; N1 - metastasis in one to three regional lymph nodes; N2 - metastasis in four or more regional lymph nodes. Distant metastasis (M): M0 - no metastasis; M1 - distant metastasis. CRC: colorectal cancer.

Malignant polyps are T1 lesions in which cancer cells have invaded the muscularis mucosae into the submucosa. They account for 12% of polyps in polypectomy series [60]. They may appear benign looking endoscopically. When the histology comes back as a malignant polyp, we need to make a decision whether endoscopic resection is adequate or patient needs endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD) or segmental colonic resection. Pedunculated (Ip in Paris classification) malignant polyp is considered cured with snare polypectomy if the resection margin is 2 mm or more, the histology is not poorly differentiated and there is no lymphovascular involvement [61]. Segmental resection of colon is recommended if the resection margin is less than 2 mm, the histology is poorly differentiated and there is lymphovascular involvement. But sessile (Is in Paris classification) malignant polyp is not cured with snare polypectomy and segmental resection of colon is recommended. But if the patient is a poor surgical candidate, EMR (for 2 cm or smaller lesion with superficial submucosal invasion) or ESD (for > 2 cm lesion with superficial submucosal invasion or < 2 cm lesion with significant submucosal fibrosis making EMR impossible) should be considered. Depth of invasion of cancer cells into the colon polyp is associated with lymph node metastasis. In case of pedunculated malignant polyp, level 4 invasion (i.e. cancer cells invading the submucosa of colon wall below the level of stalk as per Haggitt classification) is associated with lymph node metastasis up to 27% [62]. In case of sessile polyp, cancer cells invasion into the lower third of submucosa is associated with lymph node metastasis up to 23% [63]. So ESD is contraindicated in deep submucosal invasion of cancer cells. Stage II CRC is treated by surgery alone and routine use of adjuvant chemotherapy is not recommended. The European Society of Medical Oncology (ESMO) (last updated in 2013) recommended adjuvant chemotherapy in the presence of any of the high risk features which included poorly differentiated cancer, lymphovascular invasion, perineural invasion, report

of < 12 lymph nodes, bowel obstruction, localized perforation and positive margins [64]. The adjuvant chemotherapy should include 6 months course of one of the following chemotherapy regimens: 5-fluorouracil (FU) with leucovorin (LV), capecitabine, or combination of 5-FU with LV and oxaliplatin (FOLFOX) or capecitabine and oxaliplatin (Capeox). Stage III CRC is treated by curative surgical resection of the tumor followed by adjuvant chemotherapy which includes six cycles of FOLFOX or Capex [65]. In USA, stage II and stage III rectal cancers are treated by neoadjuvant chemoradiation (infusion of 5-FU with LV plus 4,500 to 5,040 cGy of radiation therapy) over a period of 5 to 6 weeks followed by surgery (low anterior resection or abdominal perineal resection) 6 to 10 weeks after completion of chemoradiation [66]. Stage IV colon cancer can be managed by monotherapy or a combination of chemotherapy, biologic targeted therapy, immunotherapy/checkpoint inhibitor therapy, palliative surgery, radiotherapy and radiofrequency ablation. Before planning the treatment modality, the location of primary CRC and extent of the disease, tumor MSI, KRAS/NRAS and BRAF mutation status, patient's comorbidities, prior treatment history, goals of treatment and patient's preferences should be considered [67]. The treatment is palliative for most patients and the main aim is to maintain quality of life and prolong overall survival. Some of the common chemotherapeutic agents used in stage IV CRC are FOLFIRI (5-FU, LV and irinotecan), FOLFOX (5-FU, LV and oxaliplatin), CAPIRI (capecitabine and irinotecan), CAPOX (capecitabine and oxaliplatin), 5-FU with LV, irinotecan, capecitabine and trifluridine plus tipiracil (Lonsurf). Targeted therapy is generally given in combination with chemotherapy. The type of targeted therapy depends on whether the CRC is KRAS mutation-positive or is KRAS mutation-negative (wild-type). The targeted therapy includes: 1) bevacizumab (monoclonal antibodies against vascular endothelial growth factor (VEGF)); 2) ramucirumab (monoclonal antibody against vascular endothelial growth factor receptor (VEGFR)); 3) cetuximab and panitumumab (monoclonal antibody against epidermal growth factor receptor (EGFR)); 4) regorafenib (angiogenic, stromal and oncogenic kinase inhibitor) and 5) aflibercept (VEGF A inhibitor and placental growth factor inhibitor). Bevacizumab, ramucirumab, regorafenib and aflibercept are angiogenesis inhibitors [68]. They inhibit tumor angiogenesis and normalize tumor blood vessels [69]. Thus they increase the efficacy of chemotherapy agents by ensuring their delivery to the CRC. In AVF2107g trial, bevacizumab plus FOLFIRI showed improvement in overall survival (20.3 vs. 15.6 months) when given to patients with metastatic CRC [70]. The anti-EGFR agents showed improved survival in stage IV CRC and this benefit was seen only in KRAS wild type CRC [71]. Fifteen percent to 20% of stage II and stage III CRC are MMR-deficient (dMMR) or microsatellite instability-high (MSI-H) and carry a better prognosis than proficient mismatch repair (pMMR) or microsatellite stable (MSS) CRC, whereas 3.5% of stage IV CRC are dMMR or MSI-H and are associated with a bad prognosis [72, 73]. In dMMR or MSI-H CRC, there is an upregulation of checkpoint inhibitory proteins: PD1 (programmed cell death protein 1), PDL1 (programmed cell death protein ligand 1), CTLA-4 (cytotoxic T lymphocyte-associated antigen 4), LAG3 (lymphocyte activation gene-3 protein) and

Table 6. Treatment of Different Stages of CRC

Stages of CRC	Treatment modalities
Stage 1	Endoscopic resection of pedunculated malignant polyp or surgical resection of tumor and local lymph nodes.
Stage 2	Surgery alone. Adjuvant chemotherapy only in presence of high risk features.
Stage 3	Surgery plus adjuvant chemotherapy.
Stage 4	Chemotherapy, biologic targeted therapy, immunotherapy, palliative surgery, radiotherapy, radiofrequency ablation and colonic stenting.

CRC: colorectal cancer.

IDO (indoleamine 2,3-dioxygenase) [74]. Recently checkpoint inhibitors have been found to be helpful in patients with dMMR or MSI-H CRC. Overman et al found a durable clinical benefit in patients with dMMR or MSI-H metastatic CRC when they were treated with nivolumab plus ipilimumab [75]. PD1 inhibitors pembrolizumab and nivolumab are approved by the FDA for the treatment of dMMR or MSI-H metastatic CRC.

Palliative surgery is generally offered in the setting of colorectal obstruction and bleeding [76]. Colonic stent is also placed in the palliative setting of colonic obstruction. It has more than 90% technical success of deployment and relief of obstruction. Palliative stenting can avoid major surgery and shorten hospital stay [77]. In a subset of patients with CRC and isolated liver metastasis, if surgical resection is possible before or after chemotherapy, patient's longevity can be prolonged. Positron emission tomography (PET)/CT imaging can detect small intrahepatic and extrahepatic metastasis. In a study done by Fernandez et al, fluoro-2-deoxy-D-glucose-PET (FDG-PET) was done prior to surgical resection of isolated hepatic metastasis, and the 5-year survival rate of patients was 58% [78]. Other methods of treatment of liver metastasis include radiofrequency ablation, transarterial chemoembolization (TACE), hepatic intra-arterial chemotherapy infusion, radioembolization, external beam radiation and stereotactic radiation [79]. But surgery is the best treatment modality and relapse-free survival is much prolonged after surgery. The treatments of different stages of CRC are outlined in Table 6.

Ongoing Research

In the National Cancer Institute (NCI), many clinical trials are on-going for early detection, prevention and management of CRC. These include blood DNA test to detect CRC, immunotherapy in Lynch syndrome and MSI-H metastatic CRC, cancer vaccines to stimulate patient's immune system, hyperthermic intraperitoneal chemotherapy for better contact of cancer cells to chemotherapy [80].

Conclusion

Although the incidence and mortality of CRC have decreased by adopting the screening colonoscopy program, CRC is still the second most common cause of cancer-related death among all cancers affecting men and women in USA [81]. To

reach the target of screening 80% of the eligible US population by 2024, 11 to 13 million colonoscopies would need to be performed annually. Appropriate measures should be taken to improve the ADR. The screening protocols recommended for average-risk and high-risk individuals for CRC should be followed. Malignant polyps should be managed appropriately by endoscopic treatment or segmental resection. Among all patients with CRC, 20-25% of patients have metastatic disease. Treatment should be chosen according to the extent of metastasis, KRAS mutation and microsatellite stability status of CRC. CRC should be managed by a multidisciplinary team which includes primary care physicians, gastroenterologists, surgeons, medical oncologists, interventional radiologists, radiation oncologists and palliative care team.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

None to declare.

Author Contributions

Monjur Ahmed solely contributed to this article.

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