Review Article

Narrative review of colorectal cancer risk in patients with inflammatory bowel disease

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Abstract: Inflammatory bowel disease (IBD) is a complex pathology that raises the risk of developing an oncological disease, mainly with the highest risk of developing dysplasia, colorectal cancer (CRC) in patients with Ulcerative Colitis (UC) and Small-Bowel Adenocarcinoma in patients with Crohn's disease (CD). The risk of developing these complications has decreased in recent years worldwide thanks to new treatments that achieve mucosal healing with long periods of remission and surveillance programs. The risk factors are different from those in patients with CRC in the general population. The main known factors in IBD are the extent and duration of the disease and the presence of primary sclerosing cholangitis (PSC) among others. There is evidence that genetic factor changes in the mucosa usually occur in less time than in the general population, that is why endoscopic surveillance programs have been implemented and are recommended depending on the risk factors of each patient, it is important to detect early precancerous lesions to perform timely treatment, it can be endoscopic with resection of the mucosa in early stages and visible lesions by the endoscopist, but in some cases where endoscopic treatment can't be performed or it is not recommended surgical treatment may be performed, to prevent the development of CRC, reduce mortality and improve survival rates.

Keywords: Cancer; Crohn's disease (CD); dysplasia; inflammatory bowel disease (IBD); ulcerative colitis (UC)

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Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are part of inflammatory bowel disease (IBD), these are chronic conditions, and they have an increased risk to develop colorectal cancer (CRC). This complication is one of the most frequent causes of death related to cancer around the world (1). The incidence of CD and UC in North America is estimated at 6.30–23.82 and 8.8–23.14, in Eastern Europe between 0.40–14.6 and 0.97–11.9, in Southern Europe between 0.95–15.4 and 3.3–11.47, in Western Europe between 1.85–10.5 and 1.9–17.2, Eastern Asia between 0.06–3.2 and 0.42–4.6, Western Asia between 0.94–8.4 and 0.77–6.5, Oceania between 12.96–29.3 and 7.33–11.4, in

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Africa 5.87 and 3.29 per 100,000 person-years respectively (2). CRC incidence in African Americans is 7.9, higher than in other ethnicities as non-Hispanic white patients that is of 6.7 person-years (3). African Americans a risk of death related to cancer of (1.35, 95% CI, 1.26–1.45) with a lower 5-year life survival of 54.9%, and in non-Hispanic Whites of 68.1% (4). The risk of IBD patients for developing CRC has been described in those patients with long-term disease evolution, family history of sporadic CRC, persistent colonic inflammation and coexistence of primary sclerosing cholangitis (PSC) (5). Mortality in patients with CCR and UC has decreased over the years, but mortality for CD remains stable, mortality can be up to double compared to the general population (6). Recent studies have demonstrated a slight decreased in the incidence of developing CRC, which might be due to an increased frequency of endoscopy surveillance programs and an impact on timely diagnosis and treatment (7). The endoscopic surveillance programs aim to detect lesions on time, to reduce mortality in the early stages, which improves short and long-term survival rates. It is important to raise awareness among physicians who see and follow patients with IBD to know the risk and importance of surveillance programs could reduce the frequency of development of CRC by less than 5% (8,9). The aim of this review was to show the evidence found in the literature on CRC, recommendations and their impact on IBD patients. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/dmr-20-111).

Research methods

A review of the literature was performed by searching for scientific articles in a database (PubMed) with the following keywords: “colorectal cancer”, “neoplasia”, “dysplasia”, “inflammatory bowel disease”, “ulcerative colitis”, “Crohn’s disease”, “epidemiology”, “treatment”, “endoscopy”, “guidelines”, “surveillance” of the articles published in during the period of 2000–2020.

Epidemiology

Epidemiological studies of CRC in patients with IBD have been focused on demonstrating the incidence and risk of developing CRC in various populations and looking for risk factors associated with the development of colon malignancies. In Hungary, the authors found a cumulative risk of 0.6% by 10 years of disease, 5.4% by 20 years of disease, 7.5% by 30 years of disease in the period of 1974–2004 (10). A meta-analysis that analyzed the period between 1972 and 2004 showed a cumulative risk of 2.9% by 10 years of disease evolution, 5.6% by 20 years of disease evolution, 8.3% by 30 years of disease evolution. A Korean study performed from 1970–2005 demonstrated a cumulative risk of 0.7%, 7.9% and 33.2% by 10, 20 and 30 years of disease duration, respectively. In a population-based cohort study in Denmark and Sweden, to report incidence and mortality conducted from 1969 to 2017, they observed an incidence in UC patients of 1.29 per 1,000 person-years and an incidence of CRC of 8.82 individuals (0.82 per 1,000 person-years; HR 1.66, 95% CI, 1.57–1.76) (11). In a retrospective study carried out in a tertiary center, 166 patients with PSC were included, of which 120 with a diagnosis of UC, 35 with CD and 11 with indeterminate colitis, with a mean follow-up period of 10 years. Of all the patients included, only 1 patient with CD developed dysplasia. In the patients included with UC, 2 cases of CRC and 8 with some degree of dysplasia developed in an average follow-up time of 11 years (12). In a follow-up study in Europe for 15 years, CRC was detected in 9 of 681 patients (1.3%) of whom 1 with a diagnosis of CD and 8 with a diagnosis of UC (13). China A total of 2,621 patients with IBD, 13 with UC and 6 with CD and CRC (14). In a study of veterans in the United States with cases and controls with incidence rates de 148/100,000 in IBD patients, 97/100,000 in controls; RR, 1.53; 95% CI, 0.86–2.69 (15). The overall risk of CRC is of 0.91 per 1,000 person-years in the first decade and of 4.07 per 1,000 person-years in the second decade of IBD diagnosis (16). In patients with IBD and PSC, the risk of development of CRC in 20 years from the onset of the disease is approximately 30% (17). The time of disease evolution considering from the beginning of the symptoms of IBD is very important to start endoscopic surveillance on time. Previous reports have shown the median duration of UC at the time of CRC diagnosis was 16 years (range, 0–64 years), and the median age at CRC diagnosis was between 46 years (range, 17–85 years) and 23.5 years (range, 11–48) (10). Gender bias is not clear, but some studies have found that it is more frequent in men, the increased risk of colon cancer was higher among men than women 3.2 versus 2.2, and two studies from the United States more than half of the patients were men as in patients without IBD (18). In the general population, small-bowel adenocarcinoma is rare. In patients with IBD, especially with CD, the risk of small-bowel adenocarcinoma is double than in patients without CD

and the risk increases with a longer time of disease evolution. Image studies can be useful for detecting advanced CD lesions, in a very few cases be an incidental finding during a surgical procedure for a symptom unrelated to neoplasia or spontaneous perforation (19).

Pathogenesis

In sporadic CRC, cancer typically has a specific process where the first change is the formation of an adenoma that progresses from indefinite dysplasia, low-grade dysplasia, high-grade dysplasia and finally carcinoma, while in the CRC associated with IBD this process is not carried out. The process of cancer development in IBD might be a short time. Several factors that contribute to the development of neoplasms in IBD include chronic inflammatory processes, the immunologic response to these processes, genetic alterations, microbiota, disease duration, the extent of disease, PSC, young age at diagnosis, anatomical abnormalities, family history of CRC (20).

Pro-inflammatory cytokines

Many cytokines, chemokines and the induction of cyclooxygenase (COX)-2 are responsible for the inflammatory processes in IBD that promote cell migration to these areas and may be responsible for neoplastic processes over time (21). There is evidence that nonsteroidal anti-inflammatory drugs decrease the risk of CRC in the general population up to 50% for their effects through their action on COX enzymes, by cytokine inhibition (22).

Genetics

Previous studies in animal models report that CRC onset is caused by prolonged inflammatory processes in the gastrointestinal tract that is characterized IBD patients with a constant inflammatory process, which causes high levels of oxidative stress of the gastrointestinal mucosal cells, with continuous DNA damage and activation of oncogenes (23). During the evolution of the disease, genetic alterations accumulate, leading to the expression of oncogenes such as the oncogenes K-ras, suppressor gene APC, mutations in the p53 and MYC gene (24). These mutations are detected in the same way in patients with CRC in the general population, with the difference that they occur at an earlier age in patients with IBD (25). Genetic alterations are characterized by three processes: chromosomal instability (CIN), which is the most frequent in sporadic CRC characterized by aneuploidies with preserved repair mechanisms. Microsatellite instability (MSI) with alterations in the insertion and deletion of specific DNA sequences and CpG island methylation that leads to hypermethylation in CpG islands represents a minority of tumors and is associated with a worse prognosis (26).

Risk factors

The risk factors for developing sporadic CRC are lifestyle factors as obesity, null or little physical activity, alcohol, tobacco use and a high-fat diet, but no relationship between these factors and patients with IBD has been found where the inflammatory process seems to be the most important. The risk factors associated with CRC in IBD patients are: coexisting PSC, the extent of disease, disease duration, histological activity, strictures, pseudopolyps, and previous dysplasia, the occurrence of CRC is rare in patients without these risk factors (25).

Patients risk factors for CRC development

Advanced current age

The risk of presenting CRC is increasing in elderly people, it is a risk in patients with IBD and without IBD. The increase in incidence occurs between the sixth and seventh decade of life with a higher risk of requiring surgeries and presenting complications (27). In recent years there has been an accelerated increase in CRC cases in patients under 50 years of age, where approximately 11% of CRC is in this age group (28). In patients with IBD, the development of neoplasms usually presents at younger age due to chronic inflammatory process that these patients present.

Family history of CRC

It is an important factor in the general population as in patients with IBD, due to the genetic predisposition to develop malignant lesions at the colon and the rectal level. Up to 10% of CRC patients have a history of at least one first-degree relative with this same type of cancer, and the risk increases even more when a family member presents it at an age under 50 years. Familial CRC is not associated with IBD patients (29).

Microbiota in CRC

Alterations in the microbiota are associated with different diseases, an example of this is the association between

Helicobacter pylori and gastric cancer. In cancerous tissue, lower diversity of bacteria has been shown in the mucosal with a predominance of *Bacteroides vulgatus*, *Bifidobacterium longum*, *Ruminococcus torques*, *Ruminococcus albus*, *Streptococcus hansenii*, *Fusobacterium prausnitzii*, have been associated with an increased risk of developing CRC (6). All this has been confirmed by whole genome sequencing and has been linked to MSI (30). As well as a protective effect of other bacteria such as *Lactobacillus rhamnosus*, *Peptostreptococcus*, *Roseburia*, *Bifidobacterium lactis* (31). There are several theories, the main one being the driver-passenger theory, where it is suggested that the predominant bacteria are pro-oncogenic and can cause remodeling in the tissue, as well as to recruit other bacterial groups to jointly promote the CRC (32).

IBD risk factors for CRC development

Disease duration

The most frequently associated risk factor is disease duration (25). It is important to know the time since the confirmed diagnosis was made, to start with the surveillance programs for the detection of CRC promptly. The time indicated for initiation of surveillance may vary depending on the risk factors of each patient. At a longer time of evolution, greater exposure to inflammatory processes, which increases the risk over the years of developing CRC and other neoplasias.

Extent of disease

CRC risk is the highest in patients with extensive colitis and minimal risk for left-sided colitis and proctitis, but a recent study showed the only risk for extensive colitis (11), the greater the affected area, the cellularity of the inflammatory process characteristic of IBD is greater. Despite having extensive colitis, if the patient presented a few relapses in the course of his illness, the risk may decrease (33). Microscopic inflammation is an independent risk factor for the development of CRC in patients with frequent relapses and long-standing disease. Histological remission is associated with a lower risk of developing CRC in patients with UC. Goals have changed, it is no longer enough to just achieve endoscopic remission (34). Histological remission has been proposed as a goal in the treatment of these patients, it is necessary to standardize the concept and scales for universal use, it will be a goal in the coming years (35).

PSC

The majority of patients with PSC have IBD (36) with an estimated prevalence of IBD in patients with PSC up to 50% (37). As extraintestinal manifestation of UC is characterized by an excess of bile acids, in patients with PSC, as the main mechanism since it affects cell proliferation. These patients are in the high-risk category of developing CRC in less time of disease evolution and with a worse prognosis. Malignancies cause around 40–50% of the mortality in PSC patients (38). These patients have a special phenotype that they usually have UC, pancolitis extension, increased frequency of right-sided cancers (39), younger age at IBD diagnosis and symptoms onset, with worse prognosis with a survival rate at 5 years of 40% (40).

Early onset of IBD

It is a risk factor identified mainly in patients with disease onset at an early age, these patients tend to have longer periods of active disease, more aggressive clinical patterns and present complications at an early age. Contrary to what happens in patients diagnosed in the average age who may have mild clinical courses and fewer periods of inflammation in the colon (41).

Anatomical abnormalities

Pseudopolyps are developed during inflammatory processes that infiltrate the mucosa and submucosa, forming a granulation process in these areas, characterized by lymphocytes, plasma cells, neutrophils and eosinophils, during the healing process and form, post-inflammatory polyps. Studies have shown that 3.5% of strictures develop pre-malignant lesions and they have the highest rates of malignant transformation to CRC. Just as pseudopolyps are developed during inflammatory processes, stenoses can reflect disease activity and more aggressive clinical behavior (42).

Backwash ileitis

It is defined as the condition in which backwash of colonic contents into the terminal ileum where up to the third part of UC patients present this characteristic (43). It has been proposed as a risk factor for developing neoplasia in this area. A previous study showed the association of backwash ileitis and neoplasia, this may be because most of the patients with this feature have an extensive disease as risk factor for CRC.

Chemoprevention

IBD treatment is based on decreasing the inflammatory process on the intestine, these treatments can suppose that could decrease the incidence of CRC by reducing inflammation and relapse. The available treatments such as 5-aminosalicylates (5-ASA), thiopurines and biological agents are potential chemopreventive agents, which have been studied for their protective effect, the only one that is attributed to a possible preventive effect in molecular studies are 5-ASA. A dosage ≥1.2 gr per day of 5-ASA has an impact on reducing CRC risk in IBD patients (44). Treatment with ursodeoxycholic acid reduces the number of bile acids which is the main proposed cause for the development of malignancy and reduces the risk of CRC in IBD with PSC. The chemoprotective effect of ursodeoxycholic acid without PSC has not been studied, and is not widely recommended as chemopreventive treatment in the general population or IBD patients.

Diagnosis and surveillance strategies

Surveillance colonoscopy should be performed for the early detection of dysplasia and CRC in IBD with colonic involvement. There is a proven benefit of endoscopic surveillance estimated up to 5 years in IBD patients, which is up to ten times greater than in the rest of the population. Diagnosis of dysplasia is a challenge because is asymptomatic in most cases and its detection can be operator dependent, as well as the ability and expertise of the endoscopist. In most cases, regardless of the operator's ability, if the patient has activity at the time of the study, it may make difficult to detect dysplasia (3) so that's why a screening colonoscopy is recommended in clinical remission to detect dysplasia and not only see inflammatory changes in the mucosa. Intervals between surveillance colonoscopy should be according to CRC risk factors and the previous results of colonoscopy studies (45). A high detection rate of dysplasia or CRC lesions is due to a trained endoscopist, complete bowel preparation, high definition equipment and the use of techniques that improve the detection of lesions such as chromoendoscopy Compared to standard evaluation with a big number of colonic biopsies and finally a procedure with longer duration to increase dysplasia detection (46).

Target biopsy with chromoendoscopy detects a major number of dysplastic lesions is a technique more cost-effective compared to random biopsies (47) and has the benefit that found lesions that can be seen by conventional colonoscopy. It has been shown that in target biopsies dysplastic lesions are more frequently detected around 11.4% *vs.* 9.3% in random biopsies (47). A recent meta-analysis compared the efficacy of standard white-light endoscopy and high-definition white-light endoscopy where the superiority of one technique over the other could not be demonstrated only one benefit was shown of chromoendoscopy over standard with-light endoscopy (48). Disease extent is important due to several studies by radiological, endoscopic and histological methods that have demonstrated that pancolitis affection is involved in higher cancer risk over time (49). It has been demonstrated that the combined use of chromoendoscopy and endomicroscopy has detection rate of colonic lesions more than other colonoscopy techniques and half the number of biopsies is required for dysplasia detection. This approach has been associated with a significant reduction in the development of CRC and related mortality that's why is now considered the standard of care by several societies (50). When a biopsy of a dysplastic lesion is taken, it is pertinent that it be evaluated by a pathologist specialized in gastrointestinal lesions when it is available in the surveillance center (51).

Risk stratification

Patients are typically classified based on their risk of developing CRC (52), the high-risk group includes patients with PSC, severe endoscopic or histological activity, previous dysplasia, family history of first-degree CRC. In the intermediate-risk group: after two negative colonoscopies, moderate endoscopic or histological activity and the presence of post-inflammatory polyps, and the group of low risk factors. The general recommendation is to start surveillance at an average of 8-10 years from the diagnosis of the disease in people without any risk (5,46,49,51-53). Different societies make their recommendations on surveillance as shown in *Table 1*.

Pouch neoplasia

Patients with proctocolectomy with ileal pouch anal anastomosis (IPAA) have a higher risk of pouch neoplasia when patients have previous dysplasia or cancer, PSC and persistent atrophy and refractory pouchitis (45). The incidence of neoplasia pouch in patients with IPAA is reported between 4.2–6.9% at 20 years (54-56). The suspicion of neoplasia in patients with IPAA can be little suspected due to the alterations in defecation that present,

Table 1 Surveillance recommendations based on risk factors for Colorectal cancer

Risk group	Time of surveillance
High risk	• 1 year ECCO (5), AGA (51), ACG (49), BSG (46), ASGE (53), PANCCO (52)
Intermediate risk	• 2–3 years ECCO (5) • 1–2 years AGA (51) • 3 years BSG (46), PANCCO (52), ASGE (53)
Low risk	• 5 years ECCO (5), BSG (46), PANCCO (52) • 8 years AGA (51) • 1–3 years ACG (49) • Beyond 3 years ASGE (53)

ECCO, European Crohn's and Colitis Organization; AGA, American Gastroenterological Association; ACG, American College of Gastroenterology; BSG, British Society of Gastroenterology; ASGE, American Society for Gastrointestinal Endoscopy; PANCCO, Pan American Crohn's and Colitis Organisation.

some guidelines recommend annual surveillance in high-risk groups and with a history of CRC and refractory pouchitis (5,46,53). Every 5 years in low-risk patients (46), while others propose in absence of risk factors is insufficient evidence for close monitoring (5,51)

Endoscopic and surgical treatment

Various strategies are available depending on the degree of dysplasia, it is important to know the type of lesions like undetectable lesions known as "flat" and detectable lesions known as "elevated" (57), therapeutic strategies are shown in *Figure 1*.

Endoscopic resection

After a dysplastic lesion is found, they need to be completely resected endoscopically by an experienced endoscopist, regardless of the degree of dysplasia (53). Patients with dysplastic polypoid lesions that have been completely resected should undergo close endoscopic surveillance, should be repeated in 6 months for any relapse or new lesion (58). In low-grade dysplasia, the presence of multifocal dysplasia justifies the indication for colectomy in these patients (59), while low-grade unifocal lesions may have a less aggressive treatment (45,53). The diagnosis of indefinite dysplasia is given by the pathologist when characteristics that correspond to low-grade dysplasia are found, but in addition to that there are characteristics of an active inflammatory process, so it cannot be distinguished if the changes in architecture are due to dysplasia or the inflammatory process itself. The progression to advanced neoplasia in indefinite dysplasia occurs in approximately 18–28% (57). Guidelines suggest surveillance colonoscopy between 3 to 12 months preferably with chromoendoscopy (45,57).

Colectomy

If resection is not possible in multifocal LGD or HGD colectomy should be considered (46), due to the high risk of CRC development. Colectomy is indicated in cases of carcinoma and high-grade dysplasia due to the risk of an

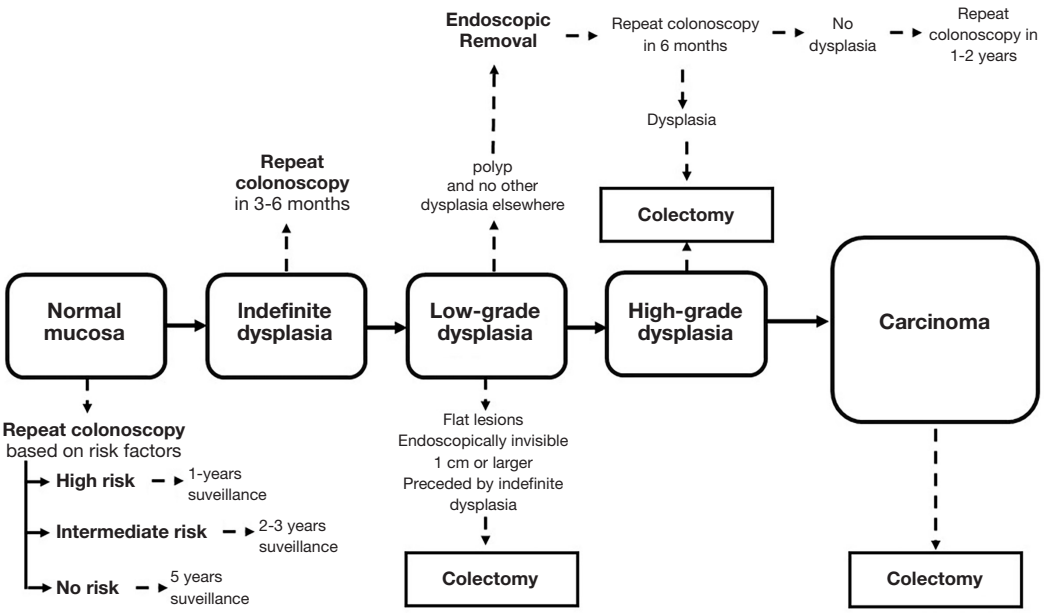

Figure 1 Colorectal cancer progression in inflammatory bowel disease and therapeutic strategies

invasive malignancy is higher than 40%, should also be considered for patients with strictures, or with a history of an injury previously resected by endoscopy. A previous meta-analysis demonstrates that after endoscopic removal of polypoid dysplasia, the risk of subsequent CRC is low, but the risk of persistent dysplasia that why some societies recommend colectomy with that type of lesion and dysplasia. Adenocarcinoma or high-grade dysplasia in CD without an associated endoscopically visible lesion are indications for surgery (45) and need colectomy. About 40% of CD patients with a segmental resection or subtotal colectomy have the possibility of having metachronous cancers, with high mortality (60).

Prognosis

Survival depend on the stage of the lesion found and if it is timely detected and treated by complete endoscopic resection technique, the survival can be more than 98% for a 5-year survival rate, proctocolectomy has the same percentage of survival in early stages. The history of a malignant lesion, the patient is considered in the high-risk group with annual surveillance for close follow-up. Recurrences can be high as 35% of IBD patients (61).

Future research in CRC and IBD

The microbiota plays an important role in the development of CRC, in recent years oncogenic gut microbiota biomarkers have been developed for screening, so far with promising results and is expected to be a less invasive diagnostic auxiliary tool (62-65). In addition to markers through bacteria, oncogenic markers have been analyzed in blood and fecal samples such as miRNA, tumor-associated antigens, the tumor specific M2 isoform of pyruvate kinase, tissue inhibitor of matrix metalloproteinase 1, which are molecules created by oncologic processes with a sensitivity greater than 90% (66). New endoscopic technologies have increased in recent years, confocal laser endomicroscopy (CLE) is a new technique that allows live visualization during the endoscopic study of the gastrointestinal mucosa. With this new technique, details about the microscopic architecture can be obtained in real time, being able to detect microscopic inflammation and the presence of dysplasia (67). Therapies for the treatment of CRC through chemotherapy can trigger exacerbations and IBD activity in these patients, so new therapies such as organometallic compounds and metal complexes are being sought for their anti-inflammatory effect in other pathologies (68).

Conclusions

The incidence of CRC in IBD patients is very low. The risk factors associated with the development of dysplasia and CRC are: extent of disease, disease duration, PSC and persistent mucosal inflammation. The surveillance should be stratified depending on the risk group divided in high that includes patients with PSC, severe endoscopic or histological activity, previous dysplasia, family history of first-degree CRC; the intermediate-risk group: after two negative colonoscopies, moderate endoscopic or histological activity and the presence of post-inflammatory polyps, and the group low risk factors. The European Crohn's and Colitis Organization (ECCO) and American College of Gastroenterology (ACG) guidelines are similar except in the risk stratification where ECCO considered three different groups (high, intermediate and low) and ACG take into account two groups as high and low risk.

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Footnote

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