

Intestinal cancer in inflammatory bowel disease: natural history and surveillance guidelines

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Abstract

Inflammatory bowel diseases (IBD) are associated to an increased risk of colorectal cancer, which is primarily related to long-standing chronic inflammation. Recognized risk factors are the duration and extent of the disease, severe endoscopic and histological inflammation, primary sclerosing cholangitis, family history of colorectal cancer and in some studies young age at diagnosis. Recent population-based studies have shown that the risk is lower than previously described or even similar to that of the general population, and this could be justified by methodological aspects (hospital-based vs. population-based studies) or by a true decrease in the risk related to a better control of the disease, the use of drugs with chemoprotective effect or the spread of endoscopic surveillance in high-risk patients. Apart from colorectal cancer, patients with IBD are prone to other intestinal neoplasms (lymphoma, small bowel adenocarcinoma, pouch neoplasia and perianal neoplasia). In this article, the magnitude of the risk of intestinal cancer, the risk factors, the natural history of dysplasia and the recommendations of screening and surveillance in IBD are reviewed.

Keywords Inflammatory bowel disease, colorectal cancer, risk factors, dysplasia, surveillance

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Introduction

Inflammatory bowel diseases (IBD) are associated to an increased risk of colorectal cancer (CRC), which is primarily related to long-standing chronic inflammation [1]. Recent population-based studies have shown that the risk is lower than previously described or even similar to that of the general population [2-7], and this could be justified by methodological aspects (hospital-based vs. population-based studies) or by a true decrease in the risk related to a better control of the disease, the use of drugs with chemoprotective effect or the spread of endoscopic surveillance in high-risk patients.

Apart from colorectal cancer, patients with IBD are also prone to other intestinal neoplasms (lymphoma, small bowel adenocarcinoma, pouch neoplasia and perianal neoplasia), but preventive measures are not properly established.

In this article, the magnitude of the risk of CRC, the risk factors for CRC and the recommendations of CRC screening and surveillance in IBD are reviewed, as well as the risk of other intestinal neoplasms and possible preventive options.

Risk of colorectal cancer in IBD

Since the first report by Crohn and Rosenberg [8], IBD is a recognized high-risk condition of CRC. However, the magnitude of the risk has been difficult to estimate, as many factors may bias the results of the studies: patient selection, number of patients included, prevalence and incidence, operation rate, completeness of case recruitment and ascertainment, duration and completeness of follow-up, differences in method of analysis and differences in endoscopic and other facilities [9]. Early studies reported a very high risk of CRC, but as they came from tertiary referral centers, where more severe cases were seen or patients were referred to because of cancer diagnosis, they tended to overestimate the risk. On the other hand, population-based studies, which covered defined geographical areas and were superior with respect to methodological standards, leaned towards more conservative risk or even a similar risk to that of the general population; but they probably included more patients with limited disease, and therefore the risk may have been underestimated. Moreover, geographical differences

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have been described: in a meta-analysis it was found that the incidence of CRC was higher in the USA and in the UK than in Scandinavia [2]; the 10-years follow-up of the European Collaborative IBD (EC-IBD) inception cohort showed that Northern European centers had a higher tendency to CRC compared with Southern centres (prevalence 0.9% vs. 0.25%, respectively, $p=0.17$) [10], but this North-South gradient was not apparent after 15 years of follow-up [11].

Epidemiology of colorectal cancer in ulcerative colitis (UC)

In 2001, Eaden et al published a meta-analysis of tertiary referral hospital-based, general hospital-based and population-based studies on CRC in UC [2]. They estimated an overall prevalence of CRC of 3.7% and 5.4% in patients with pancolitis, the incidence rate was 3/1000 person years of duration (pyd) (this means an annual risk of 0.3%), and they found a cumulative risk of 18.4% after 30 years of disease.

Population-based and cohort studies published after Eaden's meta-analysis suggest a lower incidence rate. Palli et al (Italy) found an annual incidence of 0.12% [3]; in the study by Bernstein et al (Canada) this figure was 0.16% for colon cancer and 0.06% for rectum cancer, which represents a relative risk (RR) of 2.75 and 1.9, respectively [4]; Winther et al (Denmark) found an annual incidence for CRC of 0.06%, and the risk was similar to that of the background population (standardized morbidity ratio 1.05; 95% CI, 0.56-1.79) [5]; Jess et al (USA) described an annual incidence of 0.10% and the risk was also similar to the general population (standardized incidence ratio, SIR 1.1; 95% CI, 0.4-2.4) [6]; finally, in the study by Lakatos et al (Hungary) the annual incidence was 0.15% [7].

With respect to the long-term risk, Winther et al found a cumulative probability of 2.1% at 30 years [5], Jess et al a cumulative incidence of 2% at 25 years [6], and in the study by Lakatos et al 7.5% after 30 years [7].

Recently, a cohort study of patients with long-standing, extensive UC (the patients at higher risk) included in an endoscopic surveillance program described a cumulative incidence of CRC of 7.6% at 30 years and 13.5% at 45 years [12].

Epidemiology of colorectal cancer in Crohn's disease (CD)

The role of CD as a risk factor of CRC has been controversial. Early studies from referral centers reported high risks [13,14]. Subsequently, population-based studies offered different results; while some studies showed a moderately increased risk (2.5-3.4 fold in any patient with CD and 5.6-18 fold in patients with colonic CD) [4,15,16], others have found a risk similar to that of the background population [6,17-19].

Four meta-analyses have addressed this issue and, in summary, it could be stated that CD is a risk factor for CRC cancer, but compared with UC the risk is moderate. Jess et al, in a meta-analysis of population-based studies, described a pooled SIR of 1.9 (1.4-2.5) [20]. Canavan et al found an overall RR of 2.5 (1.3-4.7); in patients with CD-colitis the risk was 4.5

(1.3-14.9); finally, they found a cumulative risk of 2.9% at 10 years, 5.6% at 20 years and 8.3% at 30 years [21]. Von Roon et al estimated a RR of 2.44 (1.56-3.82) [22]. Laukoetter et al described an incidence of 0.5/1,000 pyd, which represents 2-3 fold the incidence of CRC in an age-matched background population [23].

A cohort study of patients with long-standing, extensive CD found that after a negative screening colonoscopy the probability of developing high-grade dysplasia (HGD) or cancer was 7% by the 10th surveillance examination [24].

Risk factors of CRC in patients with IBD

Currently accepted risk factors of CRC include longstanding extensive disease, young age at diagnosis, family history of sporadic CRC, co-existing primary sclerosing cholangitis (PSC) and persistent inflammation of the colon [25-27].

Duration, extension and inflammation

The disease duration is an important risk factor of CRC. In patients with UC it is well known that the cumulative risk of CRC increases with disease duration and, from the meta-analysis by Eaden [2], it is accepted that the risk becomes appreciable after 10 years of disease. In Crohn's colitis the risk of CRC is similar to that of UC if the extension and duration are comparable [28,29]. In Eaden's meta-analysis the disease incidence exponentially rose with disease duration: the incidence during the first decade was 2/1000 pyd, during the second decade 7/1000 pyd and for the third decade 12/1000 pyd. However, new population-based and surveillance cohort studies have found that the risk is stable over time. In a Swedish cohort of 7607 IBD patients followed from 1960 to 2004, the incidence of CRC (adjusted for type and extent of IBD, sex, age and time since diagnosis) did not show any statistically significant trend over successive calendar periods of follow-up evaluation [30]. In the surveillance program at St Mark's Hospital, the incidence of CRC was constant or even decreased with increasing disease duration [12].

The risk of CRC is higher in extensive UC (SIR 14.8) than in left-sided UC (SIR 2.8), while in proctitis it is similar to that of the general population (SIR 1.7) [31]. The extension of the disease should be determined by the maximum microscopic extension [32]. In CD patients, it is accepted that the risk is relevant if at least one third of the colon is involved [24].

The fact that long-standing, extensive disease is associated to an increased risk of CRC could be justified by a more severe inflammation in this context. The relationship between severity of the inflammation and risk of CRC is further strengthened by the finding that endoscopic features of previous or ongoing inflammation [33] or severe histological inflammation [34,35] are associated with an increased risk, while a macroscopically normal looking colonoscopy returns the cancer risk to that of the general population [33].

Age at onset

In the meta-analysis by Eaden, young age at onset of IBD showed a trend to a slightly increased risk of CRC and the incidence rate in CRC in UC diagnosed in childhood was higher than the incidence in adults [2]. In CD, young age has been also associated with an increased risk of CRC [15]. In contrast, other studies could not confirm this finding, and it has even been reported that CRC develops earlier in patients diagnosed with UC after 40 years of age [36]. To summarize, young age at diagnosis has not been shown to be an independent risk factor, but as young patients will develop a long-standing disease, they may have a higher cumulative risk of CRC, and so surveillance recommendations are the same as in adults with the same duration of the disease.

Family history of CRC

Patients with a first-degree relative with a history of CRC have a more than 2-fold risk of CRC, and if the cancer was diagnosed in a first-degree relative before 50 years the risk was 9-fold [37].

PSC

PSC is a recognized risk factor of CRC in patients with UC, increasing the risk 4-fold compared to UC patients without PSC [38]. It is important to take into account that the risk of CRC remains high after liver transplantation [38]. PSC can also be associated with Crohn's colitis or undetermined colitis and it can also carry an increased risk of CRC, especially if the colitis is extensive [39].

CRC in patients with PSC-associated IBD have different clinical characteristics from CRC arising in IBD patients without PSC. CRC in PSC-IBD is diagnosed at a younger age, is more frequently located in the right colon (proximal to the splenic flexure), and it has been found that dysplasia or CRC appear soon after the diagnosis of the coexistence of both diseases (21.5 per 100 patients year of follow-up) [40].

Natural history of dysplasia

Dysplasia is defined as an unequivocal neoplastic transformation of the intestinal epithelium, and it is classified as low-grade dysplasia (LGD) or HGD; in cases in whom the pathologist cannot establish a positive or negative diagnosis of dysplasia it should be labeled as indefinite for dysplasia [41]. Dysplasia can arise from a normal-appearing mucosa (flat dysplasia) or from evident mucosal lesions, which can look like sporadic adenomas (adenoma-like mass) or appear as plaques, depressed or raised lesions (dysplasia-associated lesion or mass, DALM).

The diagnosis of dysplasia is not simple: on the one hand,

histological changes secondary to inflammation are sometimes indistinguishable from dysplasia, and on the other, there is a significant inter-observer variation in its diagnosis [42]. It is recommended that if dysplasia is diagnosed, the histological slides should be reviewed by a second expert gastrointestinal pathologist.

Dysplasia is associated to an increased risk of synchronous or metachronous CRC. In UC [12,43], synchronous CRC can be found in 10-20% patients with flat LGD, in 42-45.5% of patients with flat HGD, and in 33-43% of patients with DALM. The risk of developing metachronous CRC is high in patients with HGD (25-32%), while the risk reported in patients with LGD is extremely variable (from 0-3% over 10 years to 35-54% over 5 years) [44]. A meta-analysis estimated that the positive predictive value of LGD for progression to HGD or CRC was 14.6% [45]. In CD, the natural history of dysplasia can be assessed from the surveillance study by Friedman et al [24]: CRC was found in 25% of patients who underwent surgery because of recurrent or multifocal LGD, and in 50% of patients with flat HGD; none of the patients with unifocal LGD (not remitted for surgery) developed CRC during surveillance.

When indefinite dysplasia is detected on initial colonoscopy, progression to advanced neoplasia occurs in approximately 13% [12].

Surveillance guidelines

Prevention of CRC in IBD is based in three complementary approaches: appropriate control of the inflammatory activity of the disease, use of chemopreventive drugs and endoscopic surveillance.

Endoscopic surveillance is recommended in IBD patients in order to detect dysplasia or CRC in early stages so as to improve the survival of the disease [26,27,46], although the level of evidence of its effectiveness is low. A Cochrane meta-analysis did not find clear evidence that endoscopic surveillance prolongs survival in patients with extensive colitis, but it found that cancers tend to be detected at an earlier stage in patients undergoing surveillance [47]. In a more recent case-control study, patients who had undergone surveillance before CRC diagnosis were found to have earlier tumor stages, and moreover, overall and CRC-related mortality was reduced [48]. It is important to take into account that, despite these encouraging results, endoscopic surveillance is not perfect in preventing CRC: 15-22% of cases might be diagnosed before 8 or 15 years of disease duration [49] and around 50% of CRC found in a surveillance programs were interval cancers [12].

It used to be considered that conventional colonoscopy was not able to detect dysplastic lesions, so it was recommended to obtain at least 33 biopsies from various segments of the normal looking mucosa, as well as from any lesion found [27,46]. Nowadays, however, it is known that most dysplastic lesions are visible even with conventional endoscopy [50], and efforts

are made to improve dysplasia detection. Chromoendoscopy allows the detection of subtle lesions and, according to their chromoendoscopic appearance, can help in improving lesion characterization. It is considered a technique easily applicable to clinical practice and a meta-analysis has shown that it increases the detection yield of dysplasia up to 3-5 times that of conventional endoscopy [51]. Nevertheless, chromoendoscopy has some drawbacks. Firstly, it should be performed by skilled endoscopists, and it is not widely available. Secondly, the current knowledge of the natural history of dysplasia is based on findings from conventional endoscopy, and little is known about the meaning of some lesions found with chromoendoscopy. Taking into account these considerations, the latest UK guidelines consider chromoendoscopy and targeted biopsies as the preferred endoscopic method of surveillance, whenever available [26].

Main concepts in endoscopic surveillance guidelines

Currently accepted surveillance guidelines [26,27,46] can be summarized as follows:

Initial screening colonoscopy

Endoscopic surveillance is recommended in UC patients with extensive or left-sided colitis (patients with proctitis or proctosigmoiditis are not at increased risk of CRC), and in CD patients with colonic disease involving at least one third of the colon.

A screening colonoscopy should be offered 8 to 10 years after the onset of symptoms to reassess the maximum microscopic extension and other risk factors.

Screening should begin at 8-10 years from onset of symptoms for patients with extensive UC or Crohn's colitis involving more than 50% of the colon. For patients with left-sided UC or Crohn's colitis involving one third to one half of the colon, it should begin at 15 years.

Patients with PSC should begin surveillance as soon as IBD is diagnosed.

Surveillance colonoscopy

Surveillance should begin within 1 to 2 years after the initial screening colonoscopy. Interval surveillance is not clearly defined. While the ECCO consensus [27] recommends surveillance colonoscopies every 2-3 years with a decrease in the interval with increasing disease duration, the AGA position statement opens the possibility of a constant colonoscopy interval [46], and the current UK guidelines advocate a surveillance interval tailored according to endoscopic findings and other risk factors, and not influenced by disease duration [26].

Patients at higher risk of CRC should undergo yearly

surveillance. These are patients with extensive colitis with moderate-severe endoscopic or histological inflammation, patients with stricture in the previous 5 years, patients with dysplasia in the previous 5 years who declined surgery, patients with PSC or with liver transplantation for PSC, or patients with first-degree relatives with CRC before 50 years of age [26].

Colonoscopic procedure

Surveillance colonoscopy aims to detect dysplasia, so it should be performed when the disease is in remission, to reduce diagnosis bias related to inflammation. Chromoendoscopy with targeted biopsies is the preferred endoscopic method of surveillance, whenever available. If chromoendoscopy is not available, conventional endoscopy with multiple random biopsies (4 every 10 cm, a minimum of 33) and targeted biopsies of any visible lesion should be performed. It is recommended that high-risk patients should be offered chromoendoscopic surveillance and, if not available, one should consider referring them to a specialized center.

Management of dysplasia

Flat dysplasia

As commented previously, patients with flat HGD or multifocal LGD are at high risk of synchronous or metachronous CRC, and in such cases, colectomy is clearly indicated.

The management of unifocal LGD is more controversial. While some authors advise to perform a colectomy due to the high risk of synchronous CRC (around 20%) or of developing the disease if continue on surveillance (15-20%), others accept to repeat a surveillance colonoscopy at shorter intervals (3-6 months). The decision should be individualized, taking into account the patient's, gastroenterologist's and surgeon's opinion; additional risk factors should be considered (PSC, family history of CRC, endoscopic findings), as well as the moment of the detection of dysplasia (finding it at the first screening colonoscopy or recurrent dysplasia strengthen the option of colectomy).

In patients with biopsy specimens considered indefinite for dysplasia, guidelines suggest surveillance colonoscopy between 3 to 12 months.

An algorithm for the management of flat dysplasia is proposed in Figure 1.

Raised or macroscopically visible dysplasia

When raised or polypoid lesions are found it is important to define the location (inside or outside colitis area), the resectability, and the presence of dysplasia in the surrounding flat mucosa (Fig. 2).

A polypoid lesion outside the colitis area, with no dysplasia

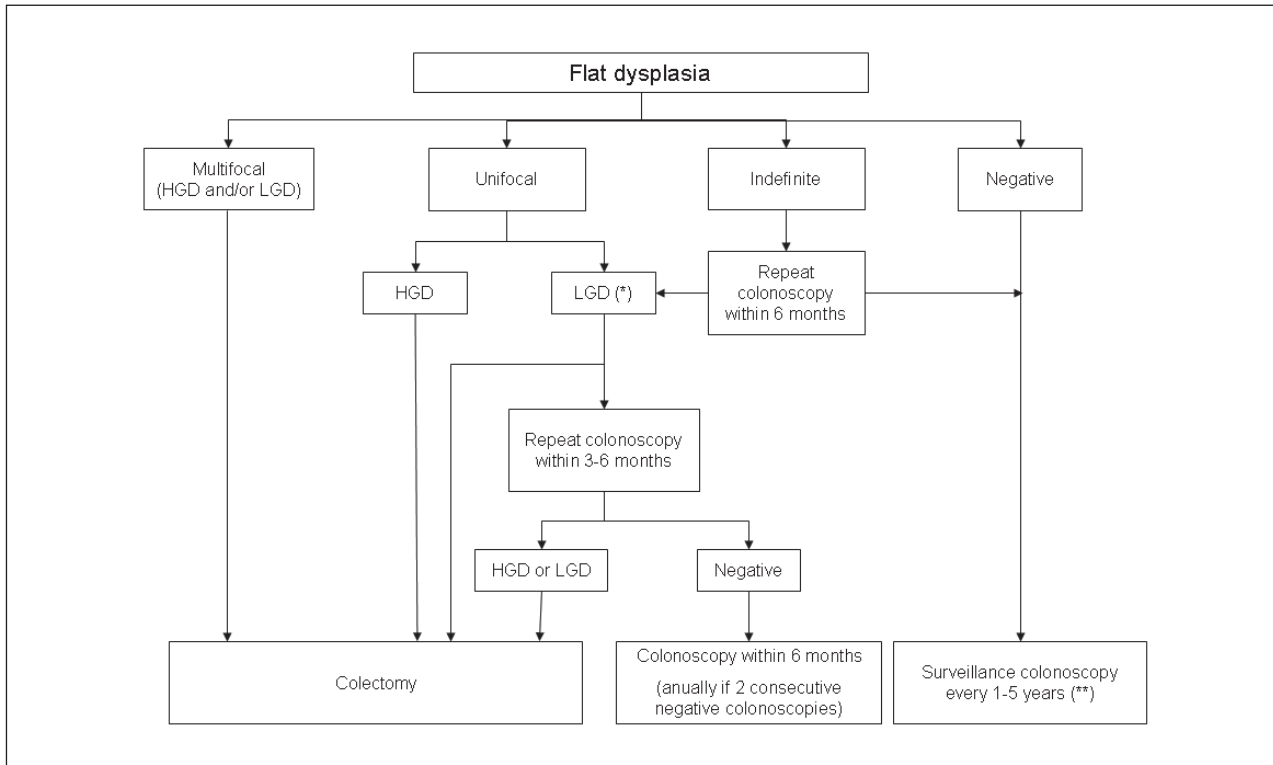


Figure 1 Management of flat dysplasia

(*) Consider colectomy in high risk patients (PSC, family history of CRC, extensive colitis with severe endoscopic or histological inflammation); (**) High-risk patient: yearly colonoscopy; (*) Low or moderate risk patient: colonoscopy every 2-3 years [40,41] or every 3-5 years [42] PSC, primary sclerosing cholangitis; CRC, colorectal cancer

in surrounding flat mucosa, can be considered and managed as a sporadic adenoma.

A raised lesion inside the colitis area, that can be entirely removed, with no dysplasia in surrounding flat mucosa, can be managed endoscopically and it is not necessary to recommend colectomy. However, if the lesion cannot be completely removed (irrespective of the grade of dysplasia), or if dysplasia is found in flat mucosa colectomy is recommended.

Other intestinal cancers

Lymphoma

Immunosuppression is associated with an increased risk of cancer. With the increasing use of thiopurines (TP) and biological agents for the treatment of IBD patients, concern arises about the risk of lymphomas. Population-based studies have generally failed to show an overall association between IBD and lymphoma [52]. However, a meta-analysis [53] and the prospective cohort study CESAME [54] have found a 4-to-5-fold risk of lymphoma in IBD patients on TP, and the risk seems to be higher in older patients. Intestinal lymphomas are associated to longstanding, active disease and with Epstein-Barr virus

infection [55], suggesting that besides TP treatment, chronic inflammation of the intestinal mucosa might also be a risk factor of lymphoproliferative disorders. In daily practice, the benefit of immunosuppressant therapy usually outweighs the risk of lymphoma, as the absolute risk is low (1 case/4357 patient-year in young people and 1/355 patient-year in patients aged over 70 years) [53]; however, the risk-benefit should be cautiously considered before long-term use of TP in older patients.

Anti-TNF agents are also associated to an increased risk of lymphoma [56], having a higher risk when used in combined therapy with TP [57]. Hepatosplenic lymphoma is a rare and usually fatal lymphoma that affects young men, and has been associated to anti-TNF and TP use. A recent systematic review describes that no cases were found in patients with anti-TNF alone, and the risk was higher in patients with combined treatment compared with those treated with TP alone [58]. Therefore, physicians should consider giving TP and anti-TNF agents to young male patients with IBD only in cases in which a clear benefit is expected, such as in early stage disease in untreated patients or possibly in very severe cases [58].

Pouch neoplasia

In UC patients who undergo restorative proctocolectomy

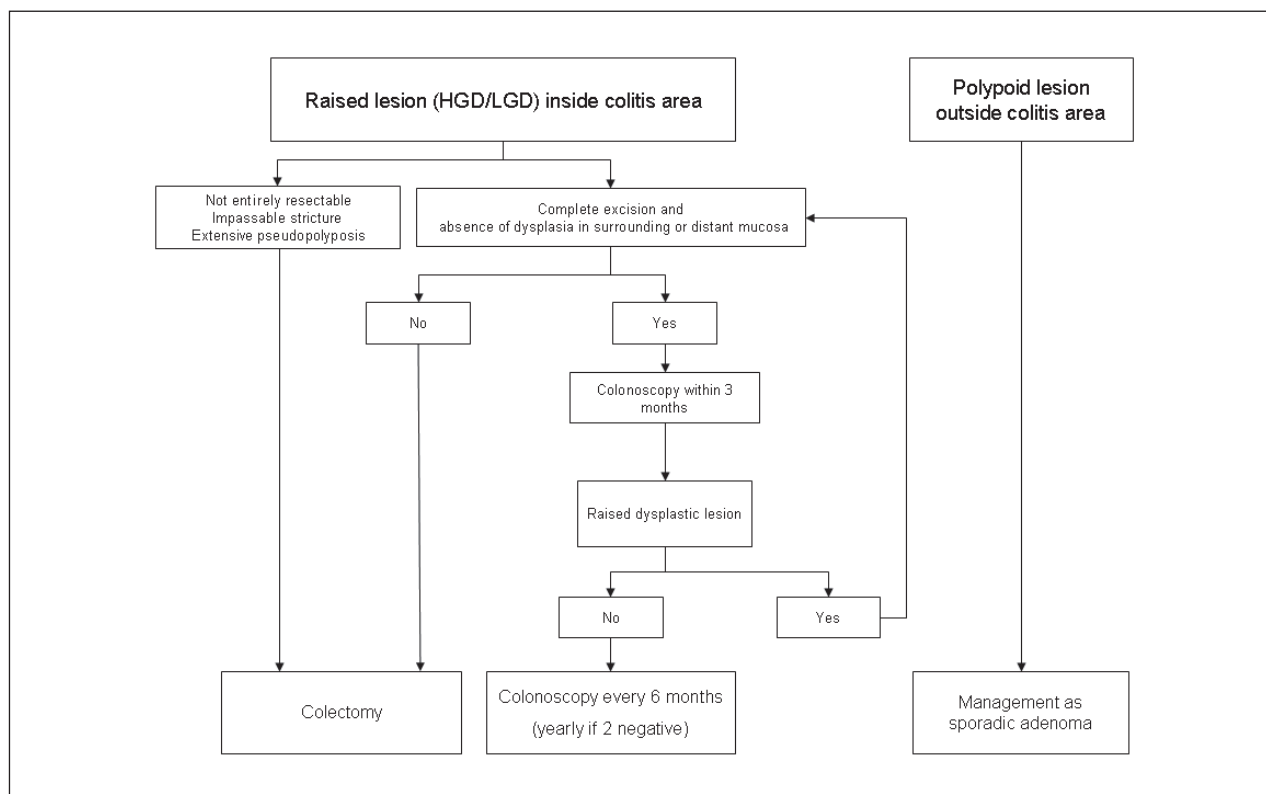


Figure 2 Management of raised dysplastic lesions

with ileal pouch-anal anastomosis, long-term complications include chronic pouchitis, cuffitis and CD of the pouch. Recently cases of pouch dysplasia and cancer have been described; with a cumulative incidence that has been estimated in 5.1% at 25 years [59]. The risk factors associated to pouch neoplasia are: a preoperative diagnosis of dysplasia or CRC [59], histological type C changes, PSC and unremitting pouchitis [60].

Surveillance in such patients is controversial as data supporting it are scarce; however, current UK guidelines consider it reasonable to perform yearly surveillance in patients with high-risk factors and every 5 years in patients without those factors [26].

Small bowel adenocarcinoma

Patients with CD have an increased risk of small bowel adenocarcinoma (SBAC) that ranges between 18.75 to 33.2 times the risk of background population [20-23]. However, it is important to take into account that SBAC has a low prevalence in the general population, so the absolute risk of SBAC in CD is low (0.3/1000 pyd) [23]. SBAC arises from chronically inflamed intestinal segments and it has been described that surgical resection and treatment with salicylates over 2 years are associated with a lower risk [61]. This suggests that the inflammation-dysplasia-cancer sequence plays an important role in its pathogenesis, and therefore, a thorough control of the

disease (pharmacological or surgical) could be an efficacious preventive measure.

Anal and rectum adenocarcinoma in perianal fistulizing disease

Malignant transformation in perianal disease is a rare event, but it is a challenging condition due to the difficulty in establishing a proper diagnosis. It should be suspected if the patient refers changes in perianal symptoms, and in such cases an exploration under anesthesia is warranted [62].

Conclusions

IBD is a recognized high risk condition to develop colorectal and other intestinal cancers. From recent population-based studies the risk of CRC seems to be lower than previously reported. The annual incidence of CRC in UC patients ranges from 0.06% to 0.16%, and in CD patients is estimated in 0.05%; the RR of CRC is 1.05-2.75 in UC and in 1.9-2.44 in CD. Several risk factors have been described, allowing preventive strategies to focus on these patients: extensive long-standing disease, severity of inflammation, family history of CRC and PSC. Endoscopic surveillance, aiming to detect dysplasia or

early CRC, is recommended to prevent CRC and improve its prognostic (although a high level of evidence is lacking). The better knowledge of the natural history of dysplasia, the improved yield of colonoscopy by targeted biopsies and new endoscopic procedures, and the increasing reports on surveillance outcomes have led to relevant changes in current guidelines, in which surveillance intervals take into account the recognized risk factors and a non-surgical management of dysplasia is recommended in some cases. Lymphoma development is associated to TP use, and the risk-benefit should be considered before advising these drugs, especially in old people and in young people treated with biological agents. Malignant transformation in ileal pouch-anal anastomosis has been described, and endoscopic surveillance should be considered in patients with high risk factors (preoperative diagnosis of dysplasia or CRC, histological type C changes, PSC and unremitting pouchitis). Although patients with CD are at a high risk of SBAC, endoscopic or radiological surveillance is not currently recommended, and thorough control of the disease is the only accepted preventive measure.

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