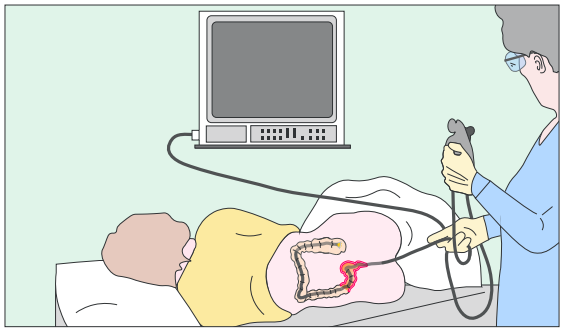
Mistakes in malignancy surveillance in IBD and how to avoid them

Edyta Tulewicz-Marti and Axel Dignass

Inflammatory bowel disease (IBD) comprises chronic, progressive, lifelong, and currently incurable disorders of the gastrointestinal tract, which may also be associated with the development of colorectal dysplasia and cancer. However, technological improvements in disease management and malignancy screening over recent decades have enabled earlier detection of precancerous lesions and timely resection of premalignant lesions or even localised malignant lesions, resulting in improved patient outcomes.

Here, we discuss mistakes encountered in the screening of dysplastic and malignant lesions when managing patients with IBD. Based on our clinical experience and an evidence-based approach, we present nine common mistakes and how to avoid them.



Mistake 1 Performing a screening or surveillance colonoscopy too late

One of the most severe complications in patients with IBD, both in ulcerative colitis (UC) and Crohn's disease (CD), is the development of colorectal cancer (CRC). Extensive colitis, especially in cases of chronic disease, is associated with a risk of dysplasia of the colonic mucosa and is a major risk factor for CRC. The increased risk of developing colorectal neoplasia is observed in both patients with UC and those with CD and colonic involvement, all of whom should undergo active surveillance. However, CRC is rarely encountered in the first 8 years of disease onset.[1] Therefore, active surveillance with colonoscopy is recommended 8–10 years after the appearance of clinical symptoms and diagnosis of colonic IBD in patients with extensive involvement and after 15 years in patients with left-sided UC or proctitis. See also Rutter MD. Mistakes in colonoscopic surveillance in IBD and how to avoid them (https://ueg.eu/a/279).

Mistake 2 Performing a screening or surveillance colonoscopy without sufficient bowel preparation

A high-quality endoscopy by experienced investigators, especially following suitable bowel preparation, is crucial for accurate evaluation of the colon and detection of dysplastic lesions. Recent observations revealed that IBD specialists are more likely to perform recommended dye chromoendoscopy compared with other endoscopists.[2] Examination by inadequately trained endoscopists, especially in the case of non-polypoid dysplastic lesions without stigmata of invasive cancer, increases the risk of missing the lesion or not achieving complete '*en-bloc*' resection. Therefore, adequate detection of dysplasia and its classification is essential for optimal patient management.

It is noteworthy to mention that the absence of active inflammation and an adequate colonoscopy withdrawal time (minimum 6 minutes), which permits the detection of visible dysplastic lesions, is essential.[3–5] A retrospective study by McMillan et al.[3] showed that a colonoscopy withdrawal time of ≥15 minutes was significantly associated with higher detection rates of visible dysplasia, suggesting that a longer withdrawal time may result in more detailed exams and better detection rates.

High-quality bowel preparation is crucial for accurate evaluation and should follow the European Society of Gastrointestinal Endoscopy (ESGE) guidelines [6] (high-volume or low-volume polyethylene glycol (PEG)-based bowel preparation). Even though colon preparation may cause a disease flare in some patients, one should strive for correct bowel preparation.[6]

Mistake 3 Performing a screening or surveillance colonoscopy too fast, carelessly or with insufficient exploration of segments of the bowel

When managing left-sided colitis, a full screening colonoscopy should be performed, not only a partial evaluation. It is of utmost importance that patients should have a full endoscopy with dye-based chromoendoscopy, virtual electronic chromoendoscopy, or high-definition white light endoscopy performed during remission.

On the other hand, neoplasia may appear as symptoms frequently related to a flare, such as changes in bowel movement, blood in the stool, or anaemia. Particularly in patients with active disease, neoplasia should be considered as an alternative diagnosis. In this case, evaluation of the colon ought to be performed promptly to exclude possible neoplastic lesions.

The most important aspects of performing a good-quality endoscopy are summarised in Figure 1.

Mistake 4 Scheduling the next screening colonoscopy without considering high-risk factors

Ignoring risk factors for an increased incidence of CRC when analysing the history of patients with IBD may result in missing important data and developing inappropriate screening strategies. These factors include a family history of CRC in a first-degree relative ≤50 years of age, presence of a colonic stricture or dysplasia, primary sclerosing cholangitis (PSC), extensive colitis with severe or refractory active inflammation, but also patients with IBD after liver transplantation.[7] Patients affected by these high-risk factors should receive a screening colonoscopy every year. In the case of patients with intermediate risk factors, like extensive colitis or CRC in first-degree family members >50 years, colonoscopy should be scheduled every 2–3 years. Patients with IBD who are unaffected by these risk factors should have a colonoscopy scheduled every 4–5 years[1,8] (Figure 2). Colonic lesions should be described

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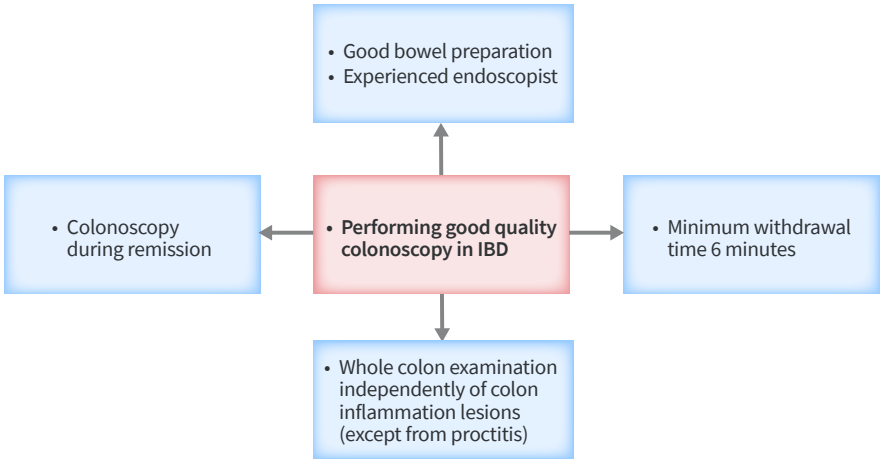

Figure 1 | How to avoid mistakes in surveillance colonoscopy in IBD.

by the five S's: site, size, shape, surface, and surroundings; this helps to standardise the endoscopic report and pathological evaluation.[9] Moreover, endoscopic treatment of the lesions should take place in specialised centres by experienced endoscopists performing complete '*en-bloc*' resections to ensure complete resection of the lesions (see also Mistake 2).[1]

Mistake 5 Ignoring re-evaluation of anal disease symptoms, especially in Crohn's disease or of pouches following ileoanal pouch anastomosis

Adenocarcinomas arising from perianal fistulas and neoplasia in patients with UC with ileoanal pouch anastomosis (IPAA) are rare. However, they should always be considered when malignancy screening is performed. The incidence of cancer-related CD-associated fistulas is around 0.2 per 1000 patient-years.[3] The formation of fistula-related malignancies usually occurs around 25 years after CD diagnosis and approximately 10 years after fistula detection, but may also occur earlier in the disease course.[10] Fistula-related cancer is challenging because its symptoms may not be specific; therefore, in patients with CD, any change in symptoms should always be a trigger for screening. The optimal approach is exploration and examination under anaesthesia and fistula curettage, if necessary. In certain situations, pelvic MRI or endoscopic ultrasonography may be useful to complement surveillance in patients with perianal fistulising disease.

Generally speaking, the risk of pouch neoplasia following IPAA is low. However, some factors that may increase the risk of neoplasia following IPAA should be considered. In the case of patients with IBD, IPAA and a history of preoperative dysplasia or cancer, missing important risk factors for dysplasia in the pouch may lead to a misdiagnosis. Other relevant factors are concomitant PSC, backwash ileitis, or CD, which should prompt the clinician to plan annual pouch screening. The pouchoscopy should be performed by an experienced endoscopist who should describe in detail the pre-rectum ileum, the body of the rectum, and the rectal cuff without omitting biopsies from each area; this is extremely important. It should also be remembered that some patients with CD (e.g., those initially diagnosed with UC who later underwent proctocolectomy) should also receive an annual colonoscopy.

Mistake 6 Considering colorectal cancer as the only possible tumour in IBD

Colorectal dysplasia and CRC detection is crucial in patients with IBD. However, it is vital to know that IBD also increases the risk for other types of cancer. Patients with UC and concomitant PSC are at a high risk of developing cholangiocarcinoma, as PSC has been identified as an important risk factor for hepatobiliary cancer.[1,11] Screening for cholangiocarcinoma in patients with IBD should include appropriate imaging and lab tests, for example, measurement of alkaline phosphatase and gamma-glutamyl transferase every 6–12 months, especially in older male patients with high-grade biliary stenosis.[12] Additionally, regular assessment of the tumour marker CA 19-9 is encouraged. The differential diagnosis between progressive PSC and early cholangiocarcinoma is still very difficult as currently available standard laboratory tests and imaging modalities do not discriminate between these two disorders. Nevertheless, once a patient with IBD is diagnosed with PSC, they should have a colonoscopy scheduled and, as was noted above, this should be performed annually, because subclinical colitis may be present years before diagnosis.[13,14]

Patients with CD, particularly those with lesions in the small bowel, are also at increased risk of non-gastrointestinal solid-organ tumours and the development of small bowel lymphoma compared with the general population. Even though small-bowel cancer incidence represents only <5% of gastrointestinal cancers,[15] patients with IBD should be encouraged to follow primary and secondary prevention programmes. In both cases, abdominal ultrasound and MR enterography with magnetic resonance cholangiopancreatography may initially be helpful to detect either solid lesions or control the progression of areas of biliary stenosis.

In a meta-analysis of 15 population-based studies, Lo et al.[16] showed a slightly higher risk of lung cancer in people with CD (incidence rate ratio: 1.53; 95% confidence interval: 1.23, 1.91), without corresponding elevated risk of lung cancer in people with UC. This relationship, however, is still unclear. There is insufficient data to suggest a benefit in performing lung cancer screening in patients with IBD.

In terms of haematological malignancies, chronic inflammation and immune dysregulation, which may occur in IBD, may lead to increased risk in patients with IBD, especially in the elderly.[17–19] However, most studies included mostly patients receiving immunosuppressive therapy, and the appearance of lymphoma may be related to immunosuppressive use.[20]

Mistake 7 Assuming that regular screening for skin cancer and cervical dysplasia in patients with IBD under advanced therapies is not important

Even though skin cancer is one of the most common types of neoplasia, affecting millions worldwide, the vast majority of patients with

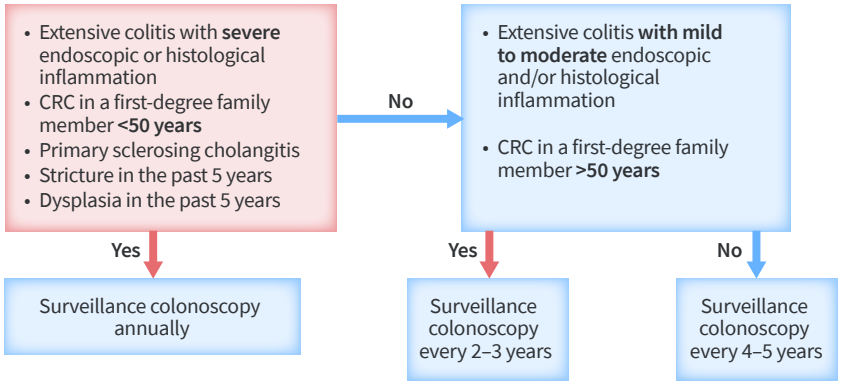

Figure 2 | Making decisions in Endoscopic screening and surveillance for CRC in IBD.

IBD forget about proper skin protection and dermatological screening, which is especially important when receiving immunosuppressive treatments.[21] Several meta-analyses[22,23] have shown that patients on thiopurines have an increased risk of non-melanoma skin cancer. Patients receiving thiopurines should undergo regular skin cancer screening, avoid sun exposure, and always use sun-protective measures. There is no evidence that tumour necrosis factor alpha (TNF-α) antagonists or small molecules in monotherapy increase the risk of skin cancer. However, patients in this group should remember to undergo more regular screening than the general population.[24]

By focusing on the primary IBD, clinicians tend to overlook female patients' concomitant health problems. There is little data so far regarding relationships between IBD, immunosuppressives or biologics, and breast lesions. Even though the risk of breast cancer seems to be similar to that in the general population,[25] in our opinion, patients should be reminded to perform regular self-examination and undergo ultrasound exams of the breast or mammography. Moreover, female patients should regularly undergo gynaecological control examinations and receive regular cervical cytology. Patients with IBD under therapy with thiopurines are at an increased risk of cervical dysplasia and cancer compared with healthy controls (odds ratio: 1.34, 95% CI: 1.23, 1.46),[25–27] which is why they should participate in surveillance programmes that are available to the general female population.[1] For some high-risk populations, e.g., those taking immunosuppressants or those with human papillomavirus (HPV) infection, gynaecological screening every year or every 3 years may be advised. As part of the primary prevention strategy, both female and male patients should be advised to receive HPV vaccinations.[28]

Mistake 8 Forgetting about the risk of lymphomas associated with monotherapy or combined TNF-α antagonist, thiopurine and JAK inhibitor therapy, particularly in elderly patients

High seropositivity of Epstein–Barr virus (EBV) in patients with IBD has been described in a few studies. In a single-centre study [29] of 1483 patients with IBD in Spain, the overall EBV seropositivity rate was 97.4%. However, according to a retrospective study by Al-Bawardy et al.,[30] up to 17% of patients may be EBV naïve (the authors highlighted that the vast majority of patients were less than 35 years old), which is important for the risk of thiopurine-induced lymphoma. The risk of this malignancy may be elevated, especially in patients who are seronegative for EBV, young people, and older men. Moreover, according to data from the Estudio Nacional en Enfermedad Inflamatoria intestinal sobre Determinantes genéticos y Ambientales (ENEIDA) registry, patients starting thiopurines after 60 years had higher rates of myelotoxicity, digestive intolerance, and hepatotoxicity.[31] Therefore, according to current guidelines,[32] the use of thiopurines should be reduced to a minimum in this group of patients.

There is an increased risk of lymphomas, particularly in elderly patients, associated with monotherapy using anti-TNF agents. However, recent studies have not found this risk to be significant. Some research indicates a slight increase in relative risk, suggesting that the use of anti-TNF agents in this population should be cautious, with long-term monitoring recommended.[33,34] In patients receiving JAK inhibitors (JAKi), a higher risk of lymphoma and other malignancies was observed compared with anti-TNFs.[34] Regular medical control with blood tests, thorough assessment of the medical history, e.g., fever, night sweats, weight loss and physical examination, and lymph node imaging like ultrasonography where warranted, should be performed in these patients.

Mistake 9 Not knowing about the different neoplasia risks of biologics and small molecules in patients with IBD and a history of prior malignancy

There is still little data on the long-term safety of biologics, especially anti-TNFα inhibitors, in patients with a history of prior malignancy. Nevertheless, they may be used in patients with current or past cancer. According to recent studies, not only in patients with IBD but also those with other autoimmune diseases and a history of malignancy, similar rates of cancer recurrence were observed in those without immunosuppression compared to those under different immunosuppressive treatments.[35] Data from vedolizumab, ustekinumab, IL-23 inhibitors, S1P modulators, and JAK inhibitors in patients with active malignant disease is insufficient to draw final conclusions. However, a post-marketing study[36] with the JAKi tofacitinib has raised concerns that increased cancer risk may be observed in elderly patients with rheumatoid arthritis and additional risk factors. In that study of patients with rheumatoid arthritis with existing cardiovascular risk, tofacitinib failed to meet non-inferiority thresholds when compared with TNF inhibitors for incident cancer. Notably, however, such a risk has largely not been demonstrated in patients outside the specific clinical situation examined in this trial. Nevertheless, this signal has practically re-aligned approaches to both tofacitinib and other JAKis to varying extents in other patient populations and contexts: within rheumatoid arthritis, but also IBD.

In terms of the risk of thiopurines in patients with past malignancy and IBD, according to the recent data, there is no additional risk of incident cancer, except from the class-associated risk. There is insufficient data on recommending methotrexate in patients with IBD and past or current malignancy. In the case of active cancer, thiopurines should be immediately withdrawn, aside from preneoplastic lesions of the cervix and non-aggressive basal-cell carcinoma, where this treatment may be continued.

Therefore, treatment recommendations for this group should be considered on an individual basis and screening examinations should be performed according to guidelines as those for the general non-IBD populations. Therefore, treatment recommendations for this group should be considered on an individual basis.[37]

To sum up, malignancy screening in patients with IBD may seem complex, but it is essential and focused on detecting precancerous lesions. In those cases, checklists may be helpful, as shown in Figure 3.

Malignancy screening in patients with IBD checklist

- ☑ Regular blood tests especially in patients receiving immunosuppressive treatment
- ☑ Regular skin-cancer screening (in case of immunosuppressive treatment, anti-TNFα inhibitors, JAK inhibitors)
- ☑ Regular colonoscopy screening even in patients following bowel surgeries depending on the risk factors (see Mistake 4)
- ☑ Imaging screening in patients with PSC every 6-12 months
- ☑ In female patients, regular breast self-examination (monthly), breast ultrasound (according to local guidelines), and cervical cytology (every 3 years or yearly in the case of immunosuppressive treatment)

Figure 3 | Checklist for malignancy screening in IBD.

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Your malignancy surveillance in IBD briefing

UEG Week

- IBD and colorectal cancer: Is there an increased risk and how to deal with it? Presentation at the UEG Week 2023 [https://ueg.eu/library/ibd-and-colorectal-cancer-is-there-an-increased-risk-and-how-to-deal-with-it/77ac004c-74da-11ee-8483-0242ac140004]

Mistakes in

- Mistakes in colonoscopic surveillance in IBD and how to avoid them [https://ueg.eu/a/279]
- Management of early-invasive (T1) colorectal cancer [https://ueg.eu/p/198]

Standards and Guidelines

- Clinical practice guideline. Diagnosis and prevention of colorectal cancer. 2018 Update. [https://ueg.eu/library/clinical-practice-guideline-diagnosis-and-prevention-of-colorectal-cancer-2018-update/e6c910f2-9360-11ed-82af-0242ac140004]