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ECCO Guidelines on Inflammatory Bowel Disease and Malignancies

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1. Introduction

This guideline is the second European Crohn's and Colitis Organisation [ECCO] evidence-based consensus on inflammatory bowel disease [IBD] and malignancy and is an update to the guidance published in 2015.[1] This edition was designed to address key areas in which the management of IBD may be affected by either the risk of or the presence of malignancy. These include the risk of cancers associated with IBD, the risk of cancers from therapies used to treat IBD, and the management of IBD in a patient with active or recent cancer.

This guideline was created according to ECCO's standardized methodology. A panel of 27 experts was selected by the ECCO Guidelines Committee from a competitive pool of applicants. Two guidelines committee members, HG and TR, were selected as project coordinators. Participating experts were split into four working groups [WG] and a leader was selected for each WG. Topics were determined by the project coordinators and WG leaders and split between the four groups as follows: WG1, IBD and risk of malignancy; WG2, Small molecules and malignancy in IBD; WG3, Biologics and malignancy in IBD; and WG4, Managing IBD in patients with a history of cancer.

For each topic, a clinically relevant question was formulated and used to define a Population, Intervention, and Comparator[s] of interest. These informed a systematic literature search, performed by a professional librarian using PubMed/Medline, Embase, and the Cochrane Central databases. Abstracts from each literature search were screened by two participants. Full texts of potentially relevant abstracts were retrieved and evaluated in full by both authors, who reached agreement of which papers were most relevant to inform the answer to the clinical question. Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] diagrams detailing the literature screening are presented in the supplementary material.

A consensus statement and supporting text were drafted for each topic and posted on an online guidelines platform. Two rounds of online voting and revisions took place. During

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this process, each participant was asked to rank the statement from 'strongly agree' to 'disagree', with the option of abstaining. Authors were required to comment if a rank lower than 'strongly agree' was provided. During the second voting round, ECCO national representatives also participated, although consensus was calculated from votes cast by members of this project alone. The participants met over a web-based video conference in November 2021 to discuss and vote on the statements and recommendations. Consensus was defined as agreement by 80% or more participants. Resulting consensus statements [with percentage agreement] are presented in this manuscript. We would like to stress the importance of interpreting each statement within the context of the supporting text provided, which is designed to add context and is of particular relevance given the paucity of data available for some of these critically important topics. Indeed, expert opinion has been included where appropriate when data were considered sparse but the authors recognized that there was a clear need for clinical advice.

The level of evidence supporting all statements is defined using the Oxford methodology.[2] Throughout the text of this guideline, we cite original studies that use different epidemiological measures, such as hazard ratio [HR], odds ratio [OR], incidence ratio [IR], and relative risk [RR]. Where we refer to these measures, we have quoted the original values. There are some important differences between these terms and we encourage readers to familiarize themselves as necessary.[3] All figures were created with Biorender®.[4]

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2. IBD and Malignancy Risk

2.1 Colorectal cancer

2.1.1 Risk of colorectal cancer in IBD

Statement 1

Patients with IBD of the colon should be informed that they are at increased risk of developing colorectal cancer [CRC]. [EL 1]

The risk of colorectal cancer is highest in patients with ulcerative colitis [UC] with extensive disease and increases significantly 8–10 years after diagnosis or when dysplasia is detected on colonic biopsies [or both], especially high-grade dysplasia. [EL 1]

Risk factors include male sex, young age at UC diagnosis, family history of CRC, and the presence of colonic strictures and primary sclerosing cholangitis. [EL 1] **Consensus: 100%**

Defining colorectal cancer [CRC] risk in IBD raises methodological challenges, including clarification of terms, study endpoints, epidemiological descriptors, and variations between clinical practices within the populations upon which reference data are based.[5-8]

Recent studies consistently show a decline in rates of IBD-associated CRC over the past 20 years,[9-13] potentially as a result of improved therapies.[9, 14] However, there is still a greater than 2-fold RR of CRC in patients with ulcerative colitis [UC][15, 16] or with colonic Crohn's disease [CD] than the background population.[17, 18] IBD-related CRC is responsible for approximately 2% of the annual mortality from CRC overall, and 10–15% of the annual deaths in IBD patients. CRC in IBD is also associated with an

increased risk of death (HR: 1.45; 95% confidence interval [CI]: 1.29–1.63) and worse 5-year survival in individuals <50 years of age when compared with sporadic CRC.[19]

Nevertheless, the absolute risk of CRC in IBD remains relatively low, with best estimates of between 1.1–5.4% after 20 years of disease duration.[18] Hence, it is important to consider the risk specific to individual patients, which will be determined by several factors including disease extent, cumulative inflammatory burden, sex, and age of disease onset.

Colonic disease location and disease duration are significant risk factors for CRC in both UC and CD, with variable estimates between studies.[15, 20, 21] CRC risk increases with time from diagnosis, with CRC rarely encountered within the first 8 years after disease onset.[22-25] A 2007 meta-analysis of 60 122 patients with CD across 34 studies identified a RR of CRC of 2.4 [95% CI: 1.56–4.36], with a strong correlation between location of diseased colon segment and location of colon cancer.[26] Extensive colitis is a major risk factor for CRC in UC, whereas left-sided disease has a lower risk.[27] There is no increased risk of CRC in UC limited to the rectum.[15, 28] An increased risk of CRC is only present in CD patients with colonic involvement.[17]

High inflammatory burden[29, 30] and a stricturing phenotype[31, 32] are also risk factors for developing CRC. In a case-controlled study, mean histological and endoscopic activity over time were associated with future onset of CRC or dysplasia in univariate analysis. [29] In multivariate analysis, only histological activity was associated with risk of CRC [OR: 4.69; 95% CI: 2.10–10.48][30] Histological activity, even without endoscopically visible abnormalities, may itself be predictive of CRC.[10, 29, 33-35] The importance of cumulative inflammatory burden over time as a risk factor for CRC has been shown in a subsequent retrospective cohort study from the same centre.[36] In a retrospective study of patients with IBD undergoing surgery for colonic strictures, 3.5%

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were found to have dysplasia or cancer.[31] In another CD cohort, stenosing disease behaviour at diagnosis was identified as a risk factor for developing CRC.[32]

Untreated dysplasia is associated with a marked increase in subsequent risk of CRC in IBD. When low-grade dysplasia [LGD] is detected on surveillance, there is a 9-fold risk of developing cancer [OR: 9.0; 95% CI: 4.0–20.5] and a 12-fold risk of developing any advanced lesion [OR: 11.9; 95% CI: 5.2–27].[37] Dysplasia incidence rates were reported to have increased from 1993–2002 to 2003–2012 in a large UK surveillance cohort,[34] although the reason for this may in part be due to increased detection rates with improved high-definition imaging and chromoendoscopy.

Male sex appears to be another risk factor for CRC in IBD, with a meta-analysis of population studies suggesting the impact of UC on CRC risk to be numerically greater in men than in women, although both groups had higher rates of CRC than the age- and sex-matched non-IBD population.[15]

Young age at UC diagnosis is also a risk factor for CRC in population studies,[38] as is a family history of CRC,[39, 40] especially in the case of first-degree relatives diagnosed with CRC <50 years of age.[22-25]

PSC is a major risk factor for CRC in IBD patients, particularly those with UC [HR: 2.43; p<0.001].[41] The incidence rate of CRC since PSC diagnosis is 3.3 cases per 1000 patient-years [95% CI: 1.9–5.6].[42] CRC in PSC-IBD patients is predominantly in the right colon.[43] Having symptoms of PSC at PSC diagnosis is the only factor related to an increased risk of CRC after IBD diagnosis [HR: 3.3; 95% CI: 1.1–9.9].[42] Liver transplantation does not halt the development of CRC, although there is insufficient evidence to suggest that liver transplantation is associated with increased CRC incidence.[24, 44]

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Pseudopolyp formation, which indicates previous severe inflammation, is associated with an increased risk of neoplasia in previous studies[45-47] and is also associated with higher rates of colectomy.[48] However, the association with CRC has been challenged in recent large retrospective data sets,[49, 50] which showed no such association.

2.1.2: Screening and surveillance for CRC in IBD

Statement 2.1

Screening colonoscopy should be performed in all IBD patients 8 years after onset of first symptoms to assess disease extent and exclude dysplasia. [EL 4] **Consensus: 95%**

Statement 2.2

In IBD patients with disease limited to the rectum without evidence of previous or current endoscopic or microscopic inflammation proximal to the rectum or with isolated small-bowel disease, no subsequent additional screening program is needed and patients should be screened in accordance with national guidelines for CRC prevention. [EL2] **Consensus: 95.2%**

Statement 2.3

In IBD patients with concurrent PSC, an annual surveillance colonoscopy should be performed following the diagnosis of PSC, irrespective of disease activity, extent, and duration. [EL3] **Consensus: 96.3%**

Statement 2.4

Patients with high-risk features [family history of CRC in a first-degree relative ≤50 years of age, colonic stricture or dysplasia, PSC, extensive colitis with severe active inflammation] should have their next surveillance colonoscopy scheduled for 1 year. [EL4] Patients with intermediate risk factors should have their next surveillance colonoscopy scheduled for 2–3 years. Patients with neither intermediate nor high-risk

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features should have their next surveillance colonoscopy scheduled for 5 years. [EL5]

Consensus: 87.5%

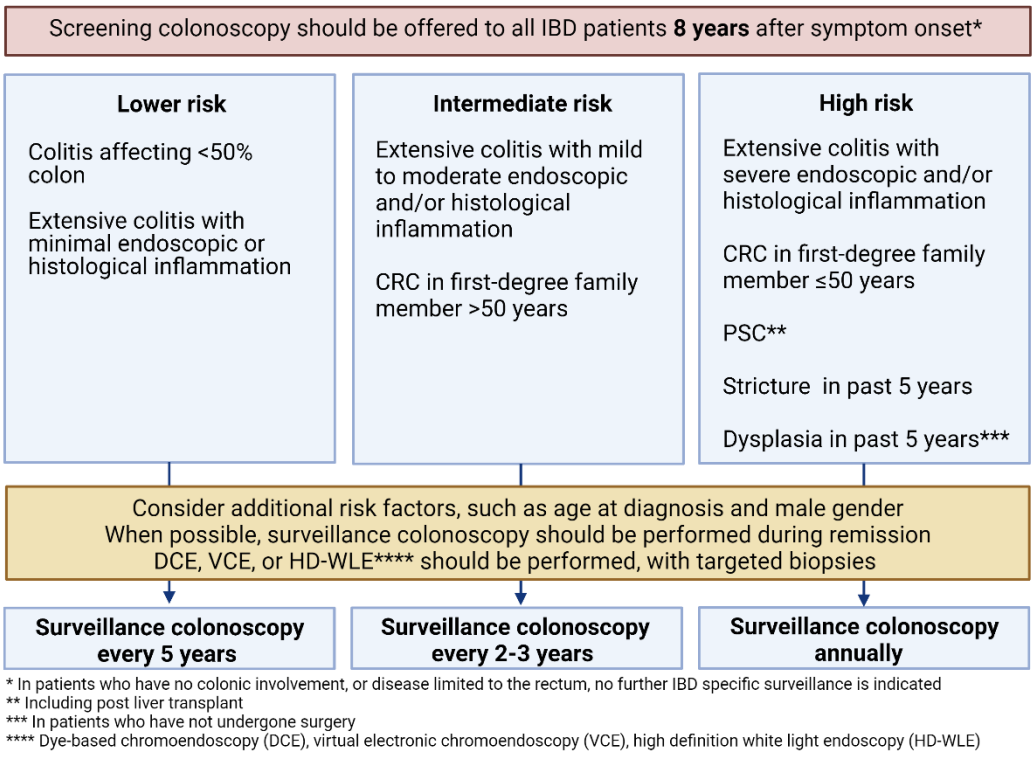
Statement 2.5

Colonoscopic surveillance is best performed when IBD is in remission, as it is otherwise difficult to discriminate between dysplasia and inflammation on mucosal biopsies. [EL5]

Consensus: 96.2%

Given that an increased risk of CRC is associated with dysplastic change in the colonic mucosa, surveillance colonoscopy programs have been developed to reduce CRC-associated morbidity and mortality.[51, 52] These surveillance programs involve not only systematic endoscopic and histological assessment, but also a review of the patient's symptoms, medications, and laboratory test results and an update of personal and family medical histories. A summary of the colorectal cancer screening and surveillance program endorsed by ECCO is presented in Figure 1.

Figure 1: Endoscopic screening and surveillance for colorectal cancer (CRC) in IBD



* In patients who have no colonic involvement, or disease limited to the rectum, no further IBD specific surveillance is indicated
** Including post liver transplant
*** In patients who have not undergone surgery
**** Dye-based chromoendoscopy (DCE), virtual electronic chromoendoscopy (VCE), high definition white light endoscopy (HD-WLE)

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As CRC is rarely encountered within the first 8 years of disease onset,[22-25] the initial screening colonoscopy should be performed 8 years after symptom onset. We recommend inviting all patients for colonoscopy at this point due to the potentially progressive nature of IBD in the years following diagnosis; isolated ileitis or proctitis may evolve into a disease phenotype with more extensive colonic involvement. An exception to beginning screening at 8 years should be made in patients with PSC; surveillance in adults should begin as soon as PSC is diagnosed.

After initial screening, the timing of subsequent surveillance colonoscopy is stratified according to patient risk. Patients with disease confirmed as limited to the small bowel or rectum at 8 years do not need to participate in an IBD-specific CRC surveillance program. These patients should follow bowel-cancer screening programs recommended for the general population and should be offered colonoscopy as appropriate in response to any potentially significant change in symptoms.

For patients with colonic disease extending beyond the rectum, the interval of surveillance colonoscopy is annual, every 2–3 years, or every 5 years depending on the presence of high-risk, intermediate-risk, or low-risk features [Figure 1]. Such features were determined by associations with CRC onset. Surveillance colonoscopy should ideally be performed when the patient is in remission. Good bowel preparation is essential for effective surveillance.

For patients with a history of colonic IBD who have undergone defunctioning ileostomy with residual colon left in situ, colonic surveillance should proceed according to the same principles and intervals. Bowel preparation and the development of stenotic lesions may be problematic; in patients for whom surveillance colonoscopy is not possible, consideration should be given to definitive surgical resection.

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A particular challenge is the risk of rectal cancer in IBD patients after subtotal colectomy. In these patients, episodes of rectal blood loss and discharge secondary to diversion proctitis are common. These symptoms can mimic or mask an underlying tumour, particularly at earlier, more treatable stages. Early studies revealed a high prevalence on the risk of rectal stump cancer following subtotal colectomy; a 1983 series of 273 patients with UC revealed that the cumulative probability of developing rectal cancer after subtotal colectomy reached 17% at 27 years after disease onset.[53] However, more recent studies have shown more favourable outcomes. A systematic review and meta-analysis published in 2016 of 1011 IBD patients with ileostomy and rectal stump revealed a rectal cancer prevalence of only 2.1% [95% CI: 1.3–3.0]. Follow up of the included studies ranged from 0.25–40 years and PSC and IBD duration were identified as specific risk factors.[54] A subsequent study of 250 IBD patients with a retained rectal stump revealed the incidence rate of rectal stump cancer to be 4.8 per 1000 patient years, with prior colorectal neoplasia identified as a risk factor [HR: 3.795; 95% CI: 1.065–13.53].[55]

Where possible, patients who have undergone subtotal colectomy should undergo either a completion proctectomy or the formation of an ileal pouch anal anastomosis [IPAA] according to their wishes. In patients who do not undergo further surgery, due to comorbidities that preclude surgery or patient preference, surveillance should continue, with proctoscopies undertaken at least every 5 years. As patients with disease duration ≥8 years, prior colorectal cancer, or concomitant PSC are at particular risk, these patients should undergo proctoscopy at a reduced surveillance interval of 2 years.

It is generally expected that the colonic IBD surveillance program will entail more careful monitoring than bowel-cancer screening programs offered to the general population. However, IBD patients who do not fulfil the criteria for IBD-specific CRC surveillance should participate in appropriate local screening and surveillance programs.

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2.1.3. Detection and management of dysplasia in IBD

Statement 3

Polypoid dysplastic lesions can be treated by endoscopic resection when the lesion can be excised entirely en-bloc, provided there is no evidence of multifocal or invisible dysplasia elsewhere in the colon. [EL 2]

Non-polypoid dysplastic lesions without stigmata of invasive cancer can be treated by endoscopic mucosal resection or submucosal dissection by trained endoscopists in selected cases, provided there is no evidence of multifocal or invisible dysplasia elsewhere in the colon. [EL3] Ideally, complete en-bloc resection should be achieved.

Surveillance colonoscopy with high-definition dye chromoendoscopy or virtual electronic chromoendoscopy should be performed after 3–6 months and then annually after endoscopic resection based on the grade of dysplasia detected. [EL 4]

Patients should be offered surgery when dysplastic lesions cannot be endoscopically resected. Factors that may render endoscopic resection impossible or unfavourable include indistinct borders, the dysplasia grade detected on biopsy analysis, and evidence of multifocal or invisible dysplasia elsewhere. [EL 2]

Polyps with dysplasia that arise in a 'non-colitic area' [with no involvement of the disease at the macroscopic or histological level] should be considered sporadic adenomas and should be endoscopically removed as appropriate. [EL2] **Consensus: 100%**

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2.1.3.1. Detection of dysplasia

Effective detection of dysplastic lesions is essential for surveillance to prevent CRC. New advanced endoscopic technologies that use high-resolution and optical-enhancement colonoscopes increase the visual definition of colonic dysplasia when compared with standard white light endoscopy [SD-WLE]. These offer early detection and characterization of the colonic lesions with a better demarcation of the border and reduce the number of unnecessary biopsies and guide endotherapy with organ sparing.[56-58]

Dye-based chromoendoscopy [DCE] using methylene blue or indigo carmine or virtual electronic chromoendoscopy [VCE; e.g., iSCAN, NBI, BLI] with targeted biopsies are considered modalities to increase the yield of colonic dysplasia in IBD patients. [56, 58, 59].

Optimal bowel preparation, absence of inflammation, and careful inspection of the colonic mucosa are important factors when optimizing detection of dysplasia.[60, 61] A meta-analysis of four randomized controlled trials [RCT] reported a 1.6-fold greater dysplasia yield with DCE than high-definition white-light endoscopy [HD-WLE].[62] However, several recently published studies and a meta-analysis of RCTs showed similar effectiveness of DCE to VCE and HD-WLE regarding dysplasia detection by experts.[63-65]

Using these techniques, targeted sampling biopsies of any suspicious lesions are adequate during surveillance colonoscopy. Two RCTs and a retrospective cohort study [66-68] revealed the same proportion of dysplasia with either random plus targeted biopsies or only targeted biopsies alone. However, in high-risk patients with a history of dysplasia and PSC, random biopsies [4 quadrants every 10 cm, starting from the caecum totally around 32] should be considered.[69] In a large prospective study of 1000 patients with IBD at risk of neoplasia undergoing DCE surveillance colonoscopy with targeted biopsies and quadrantic random biopsies, the proportion of patients with

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neoplasia detected only by random biopsies performed in unsuspicious appearing mucosa was approximately 15%.[69]

2.1.3.2. Classification of dysplasia

Consistent and accurate endoscopic and histologic classification of potentially dysplastic lesions is vital for optimal management. Adopting standard terminology is crucial to provide clarity in a multidisciplinary team discussion. A suitable systematic approach to the characterization of dysplasia in IBD is summarised in Figure 2.

Figure 2: Classification of dysplasia in IBD

Visible vs Invisible *	
Site	
Size	<2 cm favours endoscopic resection EMR or ESD can be considered for larger lesions
Shape	Polypoid (Modified Paris 1p or 1s) vs Non Polypoid (IIa, IIb, IIIc) Borders (distinct vs indistinct)
Surface	Kudo or FACILE (Frankfurt Advanced Chromoendoscopic IBD lesions)
Surroundings	Mucosal activity, other lesions in surrounding area, submucosal fibrosis
HGD	High-grade dysplasia
LGD	Low-grade dysplasia
Indefinite dysplasia	Unclassified atypia **

* When invisible dysplasia is detected from biopsies, the patient should be referred for a repeat colonoscopy with DCE or VCE with targeted and random biopsies, by an expert endoscopist, with the aim of unmasking dysplastic lesion
** consider referral to expert GI histopathologist

Endoscopic morphology of dysplasia in IBD can grossly be defined as polypoid, non-polypoid, or invisible.

When dysplasia is visible, the 'Five S' features can be used to describe colonic lesions by Site, Size, Shape, Surface, and Surroundings.[60]

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Size can be measured using biopsy forceps as a reference standard. The shape can be defined using the modified Paris classification, which classifies colonic lesions as polypoid [well-circumscribed pedunculated 1p and sessile 1s] when the lesion protrudes into the lumen ≥2.5 mm, and non-polypoid [flat elevated IIa, flat IIb, or flat depressed IIc].[70] Borders can be classified as distinct or indistinct.

Surface descriptions are enhanced using standardized classifications, such as the Kudo pit pattern and the more recent FACILE [Frankfurt Advanced Chromoendoscopic IBD lesions] classifications.[71, 72] Relevant descriptions of surroundings include comments on mucosal activity, surrounding lesions, or tethering to suggest submucosal fibrosis.

Histological classification of IBD-associated dysplastic lesions as LGD and high-grade dysplasia [HGD] is based on cytology and architecture, while unclassified atypia is termed indefinite dysplasia. Confirmation by a second expert histopathologist is required when there is uncertainty.

2.1.3.4. Management of dysplasia

The management of dysplastic lesions in colonic IBD is complex and depends upon whether the lesion is visible, the morphological classification at endoscopy [if visible], and the histological findings. Potential management options include endoscopic or surgical resection [including colectomy] and surveillance. The physician also plays a vital role in optimizing medical therapy such that lesions can be reliably classified. In complex cases, the approach is best determined within a multidisciplinary setting, involving an endoscopist, surgeon, and histopathologist. In addition to determining the best approach to the lesion itself, clear follow-up strategies must also be planned. A summary of the ECCO recommendations for management and follow up of dysplasia in IBD is outlined in Table 1.

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Table 1: Therapeutic management of dysplasia in IBD

Endoscopic features	Therapeutic management	Follow up
Polypoid lesion OR Non-polypoid lesion ≤2 cm without stigmata of invasive cancer or fibrosis and distinctive border	Endoscopic en-bloc resection (EMR, ESD, Hybrid ESD) Undertaken by expert endoscopist	Close surveillance with DCE or VCE + targeted biospies HGD: 3 months for the first year then annually Non-polypoid LGD: 6 months for the first year then annually Polypoid <1 cm or pedunculated LGD: 12 months
Non-polypoid large lesion >2 cm without stigmata of invasive cancer or fibrosis and distinctive border	Endoscopic en-bloc resection (ESD) by expert endoscopist Surgery as an alternative to endoscopic resection	Intense surveillance with DCE or VCE + targeted and random biopsies Every 3-6 months for the first year and then annually
Unresectable large lesion (indistinctive borders), invasive cancer	Surgery	
Invisible dysplasia on random biopsies	Confirmation by second pathologist Repeat surveillance colonoscopy with DCE +random and targeted biopsies by an expert endoscopist	Unmasked visible dysplasia: as above Persistent unifocal invisible LGD: consider intensive DCE surveillance follow up Persistent unifocal invisible HGD: consider colectomy
Indefinite dysplasia	Confirmation by second pathologist Optimise therapy and control inflammation Repeat surveillance colonoscopy with DCE or VCE +random and targeted biopsies in quiescent disease	Annual surveillance colonoscopy
Multifocal dysplasia LGD or HGD	Surgery In select cases of colonic lesions with discrete borders, en-block endoscopic resection can be considered following MDT discussion	Surgery should be performed in the majority of patients with multifocal LGD or HGD If endoscopic resection is undertaken, surveillance should be performed every 3 months for the first year then annually
Sporadic adenoma in IBD	Endoscopic en-bloc resection	Surveillance colonoscopy as per post-polypectomy guidelines

2.1.3.4.1. Management of visible dysplasia

Several studies and guidelines support endoscopic resection of visible dysplasia when the dysplastic lesions have a clearly demarcated border, especially if ≤2 cm in diameter and without invasive cancer or submucosal fibrosis. Simpler polypoid lesions can be resected with standard polypectomy technique, while large flat non-polypoid lesions may require advanced endoscopic resection techniques, such as endoscopic mucosal resection [EMR], endoscopic submucosal dissection [ESD], or hybrid techniques for en-bloc resection.[73, 74]

In a previous meta-analysis of 10 studies including 376 patients, the pooled incidence of CRC after endoscopic resection of polypoid dysplasia was 5.3 cases per 1000 patient-years [95% CI: 2.6–10.1] after an average follow-up period of 54 months.[75] A more recent meta-analysis of 18 studies [1037 patients, 1428 lesions] that detailed outcomes

following endoscopic resection of dysplastic lesions in IBD also showed favourable outcomes following endotherapy, with recurrence rates of any lesion of 43 per 1000 patient-years [95% CI: 30–57] and CRC rates of 2 per 1000 patient-years [95% CI: 1–3].[76] This supports endoscopic resection as an often preferable alternative to surgery, especially in cases with an absence of dysplasia in the margins, no evidence of multifocal dysplasia, and no adjacent dysplasia.

The cumulative analysis also revealed a decrease in surgical referral in recent years,[76] perhaps reflecting the increased uptake of endoscopic resection as an alternative. The rates of CRC following detection of dysplasia are much lower compared to previous meta-analyses. This may also be explained by the higher total number of studies included since the introduction of advanced endoscopic diagnostic and therapeutic technologies. Additionally, with better control of colonic inflammation in IBD with current therapeutic and management approaches, the risk of *de novo* CRC may have decreased, irrespective of how prior dysplasia has been managed.

EMR en-bloc is the preferred technique for lesions ≤2 cm in diameter since it is technically easier to complete and has a low rate of complications. However, piecemeal resection may be required in larger lesions, which may hinder histological evaluation and may be associated with increased rates of recurrence. ESD is a newer technique that can achieve complete en-bloc resection of a non-polypoid large lesion, with observational studies supporting complete resection rates between 70–79% of flat dysplastic lesions when performed by expert endoscopists. Reported local recurrence rates after ESD were 3–14%, with metachronous lesions found in 4–71% and the need for additional surgery in 2–57%.[76-81] However, this technique is associated with relatively higher risks of complications, such as perforation and bleeding, and may be complicated by fibrosis in IBD patients. It should therefore only be performed by expert endoscopists and in selected cases. Surgical alternatives to ESD include total colectomy, subtotal colectomy, or IPAA with a residual cuff or possible segmental resection in patients with CD.

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2.1.3.4.2. Management of invisible and multifocal dysplasia

Macroscopically invisible dysplasia is defined as dysplasia diagnosed from random biopsies in the absence of any corresponding endoscopically visible lesions during surveillance colonoscopy. Much of the data on invisible dysplasia come from older studies in the pre-high-definition endoscopic era. In 1994 a systematic review was performed to evaluate outcomes of surveillance colonoscopy in UC; 272/312 [87%] detected cases of dysplasia were invisible.[82] There is evidence that the new generation of endoscopes better unmasks dysplasia. Indeed, in more recent data from the St Mark's cohort study, only 16/172 [9%] of UC patients diagnosed with LGD had invisible dysplasia.[10]

Studies published before 2000 also revealed a significantly higher cancer rate associated with pre-operative LGD [33%; 95% CI: 20–50] than studies published after 2000 [11%; 95% CI: 4–29].[83] This can be explained by the wider adoption of advanced VCE or DCE, standardization of surveillance intervals, and endoscopic resection.

Therefore, when invisible dysplasia is identified in random biopsies, it is reasonable for the patient to undergo a repeat endoscopy with DCE or VCE with random biopsies performed by an expert endoscopist in IBD to unmask invisible lesions. Similarly, histological classification of invisible dysplasia [indefinite, low grade, or high grade] should also be reviewed by an expert histopathologist [see ECCO guidelines 2017].[84]

Recommendations regarding the optimal management of UC patients with endoscopically invisible LGD remain controversial with regards to whether colectomy or high-intensity surveillance colonoscopy should be recommended. Seven cohort studies and one case series reported advanced neoplasia progression rates after an initial diagnosis of invisible LGD of 2.3–13.0% at 1 year and 4.6–44.0% at 2 years. Cancer progression rates ranged from 0–28.0% at a median of 2 years.[85-93] However, a recent multicentre study that used DCE revealed an advanced neoplasia incidence rate of 2.29 cases per 100 patient-

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years, and only 3.8% developed cancer over a median of 5 years follow up. Interestingly, in this study, the incidence of detected invisible LGD decreased significantly from 88% before 2010 to 12% after 2010.[89]

When a visible lesion is confirmed by repeated DCE by an expert endoscopist and is found in the same region of the colon previously described as invisible dysplasia, patients should be managed appropriately with endoscopic resection if possible as described above. If no visible lesion is identified, management depends on the grade of initial dysplasia. However, the decision to offer colectomy versus continued surveillance in patients with invisible LGD should be individualized and discussed with the patient following a multidisciplinary discussion. It is generally recommended that patients with invisible HGD should be offered colectomy given the high risk of CRC, while a patient with confirmed LGD detected in mucosa without an associated endoscopically visible lesion should undergo repeat DCE colonoscopy with additional four random quadrantic biopsies every 10 cm within 3 months [reviewed in ECCO guidelines 2017].[84] Thereafter, in patients who do not undergo colectomy, surveillance every 3 months for HGD and every 6 months for LGD is recommended for the first year and annually thereafter, using DCE or VCE with targeted and random biopsies.[74, 94]

When a histologically indefinite lesion for dysplasia is detected, random biopsies [4 every 10 cm] should be repeated after adequate therapy, since inflammation can obscure and sometimes lead to misdiagnosis of reactive atypia as dysplasia.[95]

In addition to the visibility [and hence resectability] of dysplasia, the number of dysplastic lesions, both visible and invisible, are associated with a higher future incidence of CRC and transformation from LGD to HGD.[34, 83] Evaluation of the St Mark's cohort data revealed that both multifocal LGD [defined as LGD present in more than one location] and metachronous LGD [defined as more than one episode of

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dysplasia during surveillance] were both associated with progression to advanced lesions [HR: 3.9; 95% CI: 1.9–7.8 and HR: 3.6; 95% CI: 1.6–7.5, respectively]. Non-polypoid and invisible lesions were also risk factors in univariate analysis [HR: 16.5; 95% CI: 6.8–39.8 and HR: 6.2; 95% CI: 2.1–18.4, respectively] in comparison with polypoid lesions.[34] Given the high risk of progression to HGD or cancer, we recommended that surgery forms the mainstay of management for both visible and invisible multifocal dysplasia. In select cases where more than one polypoid lesion is entirely resected with clear margins, intense surveillance can be considered as an alternative, with surveillance colonoscopies every 3 months during the first year and annually thereafter. However, patients should be counselled very carefully.

2.1.3.4.3. Follow-up strategies after endoscopic resection of colonic dysplastic lesions

Since advanced endoscopy is increasingly performed for the management of dysplastic lesions, consideration of follow-up strategies is pertinent. A meta-analysis exploring incidental synchronous cancer rates in colectomy resection specimens in IBD patients in the era of VCE/DCE found synchronous cancer rates to be 13.7% in patients with prior detected HGD [visible] and 2.7% in patients with known LGD [visible].[83] Thus, when endoscopic resection is performed in lieu of surgery, surveillance is not only essential to detect local recurrence but also to assess for lesions potentially missed at the initial colonoscopy.

Whilst there is robust evidence to support the need for endoscopic follow up post-resection, no trials have established the risk-benefit profile of one surveillance interval over another. As such, recommendations for surveillance intervals [Table 1] are based on retrospective data inferring risk for different lesions. A recent study evaluated outcomes for patients with IBD in a Belgian national registry who had previously been diagnosed with dysplasia, with progression to colitis-associated cancer as the primary outcome.[96] In this cohort, 69% underwent endoscopic resection of the lesion at the

time of initial endoscopy, with 21% undergoing subsequent endoscopic resection or surgery, and only 10% undergoing no surveillance. The calculated 10-year cumulative incidence of colitis-associated cancer was 8.5% for LGD and 24.3% for HGD.[96] In the same study, the overall cumulative incidence of HGD or CRC 1 year after endoscopic resection of LGD was 1.9%.

Of note, the reported rates of CRC and HGD in the Belgian cohort were considerably lower than those reported for the St Mark's LGD cohort in 2015, where 19.1% of the cohort developed HGD or CRC during the study period.[34] However, the St Mark's cohort included patients with invisible, multifocal, and metachronous LGD, all of which are specific risk factors for future HGD or CRC, as discussed above. These differences highlight the uncertainties when determining surveillance intervals and counselling patients appropriately when deciding between endoscopic and surgical management of high-risk lesions.

Following resection of a visible lesion, subsequent colonoscopy with VCE or DCE is recommended at 3–6 months for the highest-risk lesions before reverting to annual surveillance. Particular care should be exercised with HGD or carcinoma-positive biopsy samples when the dysplasia cannot be managed endoscopically, in concomitant PSC, and in patients <50 years of age due to the potential risk of metachronous lesions.

2.1.3.4.4. Sporadic adenomas in IBD

If a polyp occurs in a 'non-colitic area' with both macroscopic and microscopic absence of disease, it can be regarded as a sporadic adenoma, treated endoscopically, and subsequent surveillance colonoscopy should be performed following post-polypectomy guidelines [Reviewed in ECCO guidelines 2017].[57, 70, 74, 84]

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2.2. Anal cancer in IBD

Statement 4

Patients with anal or perianal Crohn's disease [CD] or both are at increased risk for anal cancer, particularly fistula-related adenocarcinoma. [EL3] Chronic active perianal fistulizing disease may be associated with advanced cancer stage at the time of diagnosis. [EL 3] In case of any change in anal symptoms, patients with chronic perianal CD should be re-evaluated. [EL5] **Consensus: 100%**

Population-based data on the incidence of squamous cell cancer [SCC] in IBD patients are lacking, and there are also no specific data from IBD patients on the incidence of adenocarcinoma primarily arising from the epithelium of the anal canal.[97] The overall incidence of SCC in patients with CD and UC is similar to that of the general population.[98]

However, adenocarcinomas arising from perianal fistulas are a rare complication in CD.[99-102] In a meta-analysis of 20 clinical studies comprising a total of 40 547 patients with CD-associated cancer, the incidence of cancer related to CD-associated fistulae was 0.2 per 1000 patient-years.[103] In a 17-year follow-up study of 6058 CD patients with perianal or enterocutaneous fistulae [or both], only 4 patients developed fistula-associated adenocarcinomas. Onset of anal SCC in CD patients also seems to be closely related to perianal disease.[104] In a recent study, the incidence rates were 0.26 per 1000 patient-years for anal squamous cell carcinoma and 0.38 per 1000 patient-years for fistula-associated adenocarcinoma.[105]

Fistula-related malignancies typically develop about 25 years after CD diagnosis and about 10 years after fistula detection,[106] usually in patients with longstanding perianal disease. Such malignancies may be associated with adenomatous transformation of the fistula tract epithelium.[107, 108]

A systematic review of case series and reports published between 1950 and 2008 identified 61 cases of carcinomas arising in CD-related perianal fistulae. Most tumours were adenocarcinomas [59%] and typically involved fistulae originating in the rectum [59%], including recto-vaginal and recto-gluteal, with the remaining fistulae originating from the anus or perianal region.[37]

Fistula-related cancer may present with non-specific signs and symptoms. This complicates and often delays diagnosis, thereby worsening the prognosis.[109] In a systematic review of 23 reports on fistula-related cancer involving 65 patients, the average duration of the involved fistula was 14 years, and the mean delay of cancer diagnosis was 11 months.[110] In patients with long-standing perianal CD, a change in symptoms should always raise suspicion of cancer. In case of any change in anal symptoms, all patients with chronic perianal CD should be examined in depth, including biopsies under anaesthesia and fistula curettage when necessary.[111]

As the absolute risk of anorectal cancer in IBD is low, there is no need for a formal surveillance program for all patients. However, clinicians must remain vigilant to changes in symptoms and encourage patients to report such changes accordingly. Thereafter, further evaluation for anorectal carcinoma should be considered, particularly for CD patients with chronic perianal disease. This should include biopsy of any suspicious lesion [112] and a biopsy under anaesthesia or curettage of fistula tracts when needed.[113, 114]

2.3. Ileo-anal pouch cancer

Statement 5

In patients with IBD and IPAA, a preoperative diagnosis of dysplasia or cancer of the colon or rectum is a risk factor for pouch dysplasia or adenocarcinoma. [EL 1] In these patients and in patients with PSC, annual pouch surveillance should be performed. [EL3]

Consensus: 100%

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Conservative proctocolectomy with IPAA represents an important treatment option for patients with severe refractory UC.[115, 116] Overall, the risk for neoplasia in patients with UC and IPAA is low. In a series of 3203 patients with preoperative diagnoses of IBD who underwent IPAA formation between 1984 and 2009, the cumulative incidences of pouch neoplasia at 5, 10, 15, 20, and 25 years were 0.9%, 1.3%, 1.9%, 4.2%, and 5.1%, respectively.[117] Of these patients, 38 [1%] had pouch neoplasia. In a systematic review of 23 observational studies and case series encompassing 2040 patients, the pooled prevalence of confirmed dysplasia involving the pouch, anal transition zone [ATZ], or rectal cuff after restorative proctocolectomy for UC was 1.13% [95% CI: 0–18.75].[118] A meta-analysis from 2016 that included 8403 patients with a variable duration of follow-up revealed that the pooled prevalence of carcinoma in the ileoanal pouch was 0.5% [95% CI: 0.3–0.6%].[54] Even studies that only included high-risk patients, such as patients with chronic pouchitis, prior CRC, long pouch duration [>8 years], or PSC showed relatively low pouch neoplasia prevalence [0.9–4.6%].

A systematic review revealed a low pooled cumulative incidence of SCC after IPAA [0.06%].[119] However, although rare, SCC is associated with extremely poor survival. [119] The pooled cumulative incidence of pouch-related adenocarcinoma is 0.33% [95% CI: 0.31–0.34] 50 years after diagnosis and 0.35% [95% CI: 0.34–0.36] 20 years after IPAA.[120]

There is a greater risk of anorectal cancer following stapled IPAA than with hand-sewn anastomosis with mucosectomy [OR: 8; 95% CI: 1.3–48.7].[120] However, the absolute risk is low, and other factors, such as lower rates of nocturnal incontinence with stapled IPAA, should also be considered when deciding between surgical approaches.[121] Prior colorectal neoplasia is associated with an increased risk of ileoanal pouch neoplasia in patients with IBD. A Dutch registry study identified 25 cases of pouch neoplasia [including 16 adenocarcinomas] in 1200 patients with IBD who had had IPAAs [1.83%]. The risk was increased approximately 4-fold in those with prior colorectal dysplasia and

25-fold in those with a history of CRC.[122] A 2014 meta-analysis also identified neoplasia in the colectomy specimen to be a significant risk factor for future pouch cancer [OR: 8.8; 95% CI: 4.61–16.88].[120] An association between pouchitis and pouch or ATZ cancer has not been clearly established,[123] with the exception of patients with 'type C' inflammation with aneuploidy on biopsy, which is associated with dysplasia.[124, 125]

A concurrent diagnosis of PSC is associated with histological changes within the pouch. In a histological evaluation of samples from 16 patients with PSC and IPAA, proportionately more atrophy was present in the PSC group with a tendency toward dysplasia when compared with non-PSC IBD IPAA controls.[126] However, a retrospective review of 21 patients with PSC and IPAA did not reveal an increased cancer risk compared with non-PSC UC IPAA.[127] Larger cohorts of PSC IPAA patients, including a 2021 meta-analysis of 11 studies, have not focused on pouch or anal anastomosis cancer as an outcome.[128] Accordingly, there are currently no studies with sufficient patient-years of follow up to assess the impact of PSC as an independent risk factor for pouch cancer, independent of dysplasia within the colon.

Due to the low absolute numbers of pouch and ATZ cancers, we do not routinely recommend surveillance for patients with who have undergone proctocolectomy with IPAA. However, in patients with prior dysplasia or cancer in the colectomy specimen, we recommend annual surveillance pouchoscopy, due to the associations with subsequent cancers of the pouch or rectal cuff described above. We also recommend annual surveillance in all PSC patients, including those without prior dysplasia, despite a more equivocal evidence base for this group. This is due to the overall high incidence of CRC in PSC and the higher rates of pouchitis in PSC patients, which may mask early cancer symptoms.[128] In all patients with pouchitis, histology should guide the need for future surveillance; patients with type C mucosa with aneuploidy may also be considered for annual pouchoscopy.

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Pouchoscopies should be performed by experienced IBD endoscopists. Each pouchoscopy report should clearly describe the pre-pouch ileum, the body of the pouch, and the ATZ [rectal cuff], with biopsies taken from each area.[129]

While IPAA in CD patients is rarely performed, annual surveillance should be performed in patients with the same risk factors as for surveillance in UC.

2.4. Cholangiocarcinoma in IBD

Statement 6

Patients with IBD are at higher risk for cholangiocarcinoma compared to the general population, particularly patients with UC and concomitant PSC. [EL3]

Surveillance for cholangiocarcinoma should be considered in all patients with IBD and PSC regardless of disease stage and is most relevant in the first year after diagnosis. [EL3]

Surveillance for cholangiocarcinoma should include appropriate imaging and should be performed every 6 to 12 months. [EL4] **Consensus: 100%**

Cholangiocarcinoma is a devastating disease and often presents in an advanced stage. There are very limited treatment options and consequently there is a very high mortality within 1 year of diagnosis.[130]

PSC is the most important risk factor for cholangiocarcinoma and confers an up to 400-fold increased risk when compared with the general population.[41, 131, 132] Factors associated with the risk of cholangiocarcinoma in PSC include older age, male sex, and the presence of IBD [which is the case in approximately two thirds of PSC patients].[133, 134]. Cholangiocarcinoma incidence rates for patients >60 years of age are 20-fold higher than in those <20 years of age. Rates of cholangiocarcinoma in PSC patients without IBD or with CD are lower than in patients with UC [1.02 and 1.11 vs 1.22 per 100 patient-years, respectively].[134] Population-based studies suggested that

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27–37% of incident cholangiocarcinomas are detected within 1 year of PSC diagnosis, while cholangiocarcinoma is diagnosed in up to 10% of PSC patients within the first 10 years of PSC diagnosis.[131, 134-136]

Due to the prognostic implications of cholangiocarcinoma, bi-annual or annual surveillance with imaging is generally advised. So far, there are no prospective studies on cancer surveillance in PSC patients. A 10-year nationwide UK registry-based study of 284 560 patients [2588 with PSC] revealed that the risk of hepatopancreatobiliary cancer-related death is lower among patients with PSC-IBD receiving surveillance by annual imaging evaluations than in those who did not [HR: 0.43; 95% CI: 0.23–0.8].[41] Another retrospective study revealed that a large PSC patient population receiving regular surveillance had significantly higher 5-year overall survival than the no-surveillance group [68% vs 20%; $p<0.001$] and significantly lower 5-year probability of experiencing an hepatobiliary carcinoma-related adverse event [32% vs 75%; $p<0.001$].[137]

The options for serologic screening are limited but usually rely on serum carbohydrate antigen [CA19-9], a glycolipid expressed by cancer cells and the most common serum marker associated with cholangiocarcinoma. Limitations of CA19-9 include wide variability in both sensitivity and specificity, resulting in frequent false positive and false negative testing. Therefore, it is challenging to provide clear counselling on the use of CA19-9 as part of cholangiocarcinoma surveillance.[135]

Currently, the only lifesaving treatment for cholangiocarcinoma is orthotopic liver transplantation. Unfortunately, PSC reoccurs in approximately 20–25% of patients within 10 years after transplantation. Colectomy prior to transplantation appears to be associated with a reduced risk of recurrent PSC.[138]

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2.5. Small-bowel cancer in patients with CD

Statement 7

Patients with CD, particularly those with small-bowel involvement, have an increased risk of small-bowel cancers. [EL1]

Small-bowel adenocarcinoma is the most common subtype and is found in areas of inflammation, predominantly the distal jejunum and ileum. [EL3] The diagnosis should be considered in patients with refractory, longstanding stricturing disease or relevant symptoms. [EL5]

At present, routine surveillance with imaging or endoscopy is not recommended for small-bowel cancers. [EL5] **Consensus: 95.0%**

Small-bowel cancers [SBC] are rare and account for <5% of GI malignancies,[139] with an incidence rate in the general population of 2.4 per 100 000 patient-years.[140] Histologically, approximately 40%[141] are adenocarcinoma, with the remainder being neuroendocrine neoplasms and sarcomas.[142]

Although patients with CD have an increased risk of SBC, the absolute risk remains low. A meta-analysis estimated the incidence of SBC in CD as 30 per 100 000 patient-years,[103] with a more recent Nordic cohort study yielding a similar rate of 24.4 per 100 000 patient-years.[142] According to a recent meta-analysis of 26 studies, there is a 10-fold increased risk of SBC in patients with CD [95% CI: 8.04–11.60].[143] The risk is greatest for those with small-bowel CD, although it is also increased in patients with purely colonic involvement [HR: 3.99; 95% CI: 2.31–6.88].[142]

Most SBCs in CD are small-bowel adenocarcinoma [SBA].[142, 144, 145] Due to the limited number of heterogenous studies, the reported standardized incidence ratio [SIR] varies greatly between studies, ranging from 14.4 [95% CI: 8.8–22.2][144] to 67.0 [95% CI: 18.1–170.7].[146]

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Unlike sporadic SBA, which typically occurs in the duodenum,[139, 147] CD-associated SBA has a predilection for the distal jejunum and ileum.[142, 146, 148-150] They also occur more frequently in men[143] and usually occur in inflamed segments.[139, 145, 146, 148, 151] They are strongly associated with a stricturing phenotype, fistulizing disease, and prior surgical resections.[103, 142, 144, 147, 149, 152, 153] Disease duration is also a likely risk factor.[103] A nationwide French cohort study revealed that patients with CD for <8 years had an SBA SIR of 17.8 [95% CI: 0.45–99.1], compared with 46.0 [95% CI: 12.5–117.8] in patients with CD for >8 years.[148]

The identified risk factors reflect the disease severity, and it is likely that SBA in CD follows an inflammatory-dysplasia-carcinoma pathway akin to colorectal cancer in colitis. Resected SBA specimens have identified adjacent dysplasia in 69–79% of cases.[144, 154] Despite this, endoscopic screening for SBA has a low sensitivity [33%], owing to the high prevalence of impassable strictures.[155] Early diagnosis is a challenge; most SBAs in CD are diagnosed either postoperatively [49.6%] or intraoperatively [35.6%].[156] CT and MR enterography can aid preoperative detection with characteristic findings such as presence of a heterogenous or obstructive stricture with abrupt margins or shouldering, irregular nodularity along the serosal margin, and small-bowel masses.[149, 157] Video-capsule endoscopy may also provide early tumour detection [sensitivity 83.3%, specificity 100%], although limitations include risk of retention and inability to acquire tissue.

Data on CD-associated SBA and sporadic SBA tumour staging at diagnosis are conflicting. [147, 150] This may explain why a clear difference in 5-year survival between the groups has not been established.[150, 158, 159] However, survival may be lower for patients with CD and stage III and IV disease.[150]

Two recent cohort studies revealed a 5–7 fold increased risk of neuroendocrine neoplasms [NEN] in patients with CD.[103, 142-144] The pathogenesis of these tumours

appears distinct from SBA, with only 22% of lesions found in inflamed segments.[144] There are currently no known clear risk factors and long-term survival is unknown.

The relationship between UC and SBC is less clear than in CD. A large Nordic cohort study identified an increased risk of SBA [HR 1.99] and NEN [HR 2.01] in UC, citing extensive colitis, family history, and PSC as possible risk factors.[142] However, this finding was not observed in a recent meta-analysis of 26 studies.[143]

2.6. Other solid-organ tumours in IBD

Statement 8

There is a small increased risk of non-gastrointestinal solid-organ tumours in IBD compared with the general population. [EL2] Since there is no evidence to recommend a different approach to prevention and early diagnoses of extraintestinal cancers, patients with IBD should be encouraged to follow the same primary and secondary prevention programs as the general population based on individual risks. [EL5] **Consensus: 100%**

Two meta-analyses and several large population-based studies have been published on the risk of extra-intestinal solid cancers [EIC] in IBD patients.[142, 160-180] The key studies are included in a systematic review and meta-analysis of population-based cohort studies published in 2021 that addressed the risk of EIC in IBD.[170] This study included 40 studies, encompassing 882 622 patients with IBD and contributing 5.1 million patient-years of follow up. There was an increased risk of EIC in both patients with CD (incidence rate ratio [IRR]: 1.43; 95% CI: 1.26–1.63) and UC [IRR: 1.15; 95% CI: 1.02–1.31]. Patients with CD and UC had an increased risk of non-melanoma skin cancer [CD, IRR: 2.22; 95% CI: 1.41–3.48 and UC, 1.38; 95% CI: 1.12–1.71] and hepatobiliary malignancies [CD, IRR: 2.31; 95% CI: 1.25–4.28 and UC, 2.05; 95% CI: 1.52–2.76]. Furthermore, patients with CD had an increased risk of haematologic [IRR: 2.40; 95% CI: 1.81–3.18] and lung [IRR: 1.53; 95% CI: 1.23–1.91] cancers. Other

studies reported an increased risk of cervical, prostate, renal, oral, and laryngeal cancer.[179]

Several meta-analyses and observational studies have investigated the role of IBD therapies on the risk of solid-organ EIC. Overall, no association was found between therapies and risk of EIC,[181-186] whereas any risk of EIC seems to be related to the concomitant IBD *per se*.

In case of symptoms and signs suggestive of EIC, patients should be referred for further investigations without delay. There is currently no evidence to support specific public-health strategies to mitigate risk within the IBD patient population. Therefore, patients with IBD should be encouraged to follow the screening programs recommended for the general population based on their individual risk.

2.7. Haematological malignancies in IBD

Statement 9

There is an increased risk of haematological malignancy in patients with IBD compared with the general population. However, there is insufficient evidence to determine whether the risk is independent of the effects of therapy or other risk factors. [EL3]

Consensus: 95.5%

An association between IBD and haematological malignancy has been observed.[170] A systematic review and meta-analysis of population-based cohort studies revealed an increased risk of haematological malignancy in patients with CD compared with the baseline population risk [IRR: 2.40; 95% CI: 1.81–3.18].[170] This systematic review also revealed that most of the included studies provided evidence for an increased incidence in UC. An earlier meta-analysis also revealed an increased incidence of leukaemia in UC, with pooled incidence estimate of 13.0/100 000 per year [95% CI:

5.8–20.3/100 000],[187] whereas the worldwide incidence at the time of analysis was 5.0/100 000 per year, increasing to 11.3/100 000 per year in developed regions.[187]

However, both meta-analyses included studies on patients who received immunosuppressive therapy. As such, it is difficult to ascertain whether the risk is due to an independent association with IBD *per se* or whether the risk is due to that posed by immunosuppressive therapy.

3. IBD therapy and risk of malignancy

Estimating the risk of cancer associated with IBD therapy is difficult as it can be challenging to separate the risk of the therapy from the disease itself. Furthermore, estimates are also confounded by exposure to different medications throughout the patient journey, thus making it difficult to be certain any association is due to one medication in isolation. Nevertheless, even considering these factors, there is evidence that some IBD therapies increase the risk of developing certain cancers. The available data are summarised in Table 2[4] and are discussed in this section.

Table 2: Cancer risk associated with conventional and advanced IBD therapies

Drug	Cancer	Evidence Level	Additional Considerations
Thiopurines	Lymphoproliferative Myeloproliferative NMSC Cervical	EL1 EL3 EL2 EL4	EBV exposure Age Gender Cervical Ca risk not replicated in all cohorts
TNF antagonist	Lymphoma Melanoma	EL2 EL2	Risk not replicated in other cohorts
TNF antagonist with thiopurines	Lymphoma	EL2	Risk increased compared with both unexposed populations and monotherapy
Vedolizumab	None	EL4	Limited duration of follow up
Ustekinumab	None	EL4	Limited duration of follow up in IBD; data from non-IBD indications with lower doses
JAK inhibitors	All except NMSC	EL4	In high-risk RA population only Not replicated in IBD
Methotrexate	NMSC	EL5	Risk not replicated in other cohorts

**Shading denotes that risk was not observed in all studies*

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3.1. Thiopurines and risk of haematological malignancy

Statement 10

Patients on thiopurine monotherapy are at increased risk for lymphoproliferative disorders [EL1] and myeloproliferative disorders. [EL3] The risk is increased for older patients.

Before starting therapy, screening for Epstein-Barr virus [EBV] infection should be considered in young adult male patients; [EL5] in patients negative for EBV IgG, medications other than thiopurines may be considered. [EL5] This should inform treatment selection, particularly in older patients or those with other risks for lymphoma. [EL5] **Consensus: 100%**

Evidence suggests that thiopurines play a role in lymphoma development in IBD patients[188-191] when taken as monotherapy or as part of combination therapy with TNFα antagonists.[192]

Most thiopurine-associated lymphomas are B-cell lymphomas associated with Epstein-Barr virus [EBV], occurring in patients seropositive for EBV. The association is consistent with a recent study showing that mercaptopurine propagated EBV-driven lymphomatoid transformation in an *in vitro* model of lymphoma.[193] Other rarer forms are represented by early post-mononucleosis lymphomas [mainly occurring in young male patients seronegative for EBV after acute viral infection][190] and non-EBV-related hepatosplenic T-cell lymphomas [mainly occurring in young men receiving combination therapy with thiopurines and TNFα antagonists for >2 years].[194, 195] For this reason, we recommend caution when considering thiopurines in young male patients [<35 years] who are EBV naïve.[196]

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A meta-analysis[197] revealed that the reported risk of lymphoma is higher in referral studies [SIR: 9.24; 95% CI: 4.69–18.2] than in population studies [SIR: 2.80; 95% CI: 1.82–4.32]. The increased risk was only found in IBD patients with current exposure of at least 1 year to thiopurines [SIR: 5.71; 95% CI: 3.22–10.1] and reverted back to baseline after thiopurine discontinuation [SIR: 1.42; 95% CI: 0.86–2.34 for prior use, SIR: 1.06; 95% CI: 0.81–1.40 for never use].

Patients <30 years of age, especially men, had the highest RR. The absolute risk was highest in patients >50 years of age. In a large prospective study, the highest incidence rates of lymphoproliferative disorders were observed in patients >65 years of age receiving thiopurines.[190]

A recently published meta-analysis of high-quality observational studies confirmed that IBD patients exposed to thiopurine monotherapy are at increased risk of lymphoma when compared with IBD patients unexposed to TNFα antagonists or thiopurines [IRR: 2.23; 95% CI: 1.79-2.79].[192] These findings are consistent with findings from an insurance database with coverage of approximately 88% of the French population, where the risk of lymphoma was higher in patients with IBD and a history of thiopurine exposure when compared with patients without a history of either thiopurine or TNFα antagonist exposure [adjusted HR: 2.41; 95% CI: 1.60–3.64].[198]

The use of thiopurines is also associated with an increased risk of acute myeloid leukaemia and myelodysplastic syndromes, theoretically explained by proliferation of blood cells with defective DNA-mismatch repair that escape the cytotoxic effect of drugs.[199] The evidence here is scarce, with some authors suggesting risk from previous exposure to thiopurines[200] and others suggesting an association only with current use of thiopurines.[201] In the latter study, the overwhelming majority of patients who developed acute myeloid leukaemia or myelodysplastic syndromes while on thiopurines were >60 years of age.

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3.2. Thiopurines and risk of solid-organ cancer

Statement 11

Thiopurines and overall cancer risk

There is insufficient evidence to conclude that there is an increased overall risk of solid-organ cancer or site-specific cancer other than skin cancer or cervical neoplasia in patients with IBD on thiopurine monotherapy. [EL3]

Thiopurines and skin cancer

Patients on thiopurine treatment have an increased risk of non-melanoma skin cancer and should undergo skin-cancer screening and take sun protective measures. [EL2] There is no increased risk of melanoma associated with thiopurine use. [EL2]

Thiopurines and cervical abnormalities

Patients on thiopurine treatment may have an increased risk of cervical high-grade dysplasia and cancer. [EL4] These women are therefore encouraged to participate in screening programs available for the general population. **Consensus: 100%**

3.2.1. Thiopurines and overall cancer risk

Contradictory results on the overall risk of solid cancers associated with thiopurine treatment have been reported. Several studies described an increased overall cancer risk in patients with IBD on thiopurine treatment,[202-207] whilst other studies found no increased risk.[208-216] However, several of these studies were underpowered. Four studies reported large population-based cohorts; two of these studies [n=17 047 and n=45 986][202, 203] identified thiopurines as a risk factor, whereas two studies [n=9100 and n=11 011][212, 216] did not report an increased overall cancer risk

among those on thiopurine treatment. This latter finding is consistent with two large nested case-control studies.[209, 212] There are no recent meta-analyses that have performed pooled analyses of these data.

3.2.2. Thiopurines and risk of non-melanoma skin cancers

Several systematic reviews and meta-analyses reported an increased non-melanoma skin cancer [NMSC] risk in patients with IBD exposed to thiopurines.[217-219] The largest and most recent pooled analysis of 13 studies including 149 198 patients suggested that thiopurine use in IBD significantly increased the risk of NMSC [RR: 1.88; 95% CI: 1.48–2.38].[217] The total cumulative thiopurine dose may affect the NMSC risk profile.[220-222] When compared with patients not exposed to thiopurines, IRRs rose from 1.6 during the first year of thiopurine use to 3.6 in the fifth year [p<0.00001].[218, 221] Contradictory results have been reported on the residual NMSC risk after thiopurine discontinuation. Whilst large population-based cohort studies [221, 222] indicated that the risk of NMSC returned to baseline after thiopurine discontinuation, a large French observational cohort reported an increased risk for NMSC for ongoing thiopurine therapy [HR 5.9; 95% CI: 2.1–16.4] that was numerically reduced but still above the background population after thiopurine discontinuation [HR: 3.9; 95% CI: 1.3–12.1].[223]

Data regarding NMSC-related mortality in IBD are scarce. One retrospective cohort study [n=467] reported an increased risk of SCC-associated mortality in thiopurine-exposed IBD patients [adjusted HR: 8.0; 95% CI: 2.0–32.8].[224]

3.2.3. Thiopurines and risk of melanoma

Two meta-analyses reported no increased melanoma risk in thiopurine-exposed patients with IBD.[177, 217] The most recent meta-analysis was based on two large nested case–control studies, and two cohort studies, and reported a non-significant RR of 1.22 [95% CI: 0.90–1.65].[217, 222, 225]

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3.2.4. Thiopurines and risk of colorectal neoplasia

Several systematic reviews and meta-analyses have been performed to assess the potential chemoprotective effect of thiopurines on colorectal neoplasia development in patients with IBD.[226-230] Although one previous meta-analysis[230] reported no reduction in colorectal neoplasia risk in patients treated with thiopurines, the two most recent meta-analyses, which included 24 studies [n=76 999][228] and 27 studies [n=95 397],[227] reported a protective effect for both advanced colorectal neoplasia [HGD and CRC combined] and CRC development. The reported OR for CRC development were 0.56 [95% CI: 0.34–0.93] based on 16 case-control studies[227], 0.96 [95% CI: 0.94–0.98] based on 11 cohort studies[227], and 0.65 [95% CI: 0.45–0.96] based on 24 observational studies.[228] However, any protective effect was more apparent in case-control and clinic-based studies than in cohort and population studies.[227, 228] Confounding factors such as disease duration, extent and severity of inflammation, cumulative thiopurine dose, and concomitant therapies were not well controlled in several of the included studies in the meta-analyses, which may impact the outcomes. In patients with IBD already diagnosed with LGD, no protective effect of thiopurines was found for the development of advanced colorectal neoplasia.[226]

3.2.5. Thiopurines and risk of cervical abnormalities

A meta-analysis on the available literature regarding the correlation of immunosuppressive medication in the development of cervical abnormalities in IBD revealed an increased risk of cervical HGD or cancer in patients with IBD on immunosuppression compared with population controls without IBD [OR: 1.34; 95% CI: 1.23–1.46].[231] However, a recent review highlighted variable adjustment for smoking or HPV status and variability of outcomes [cervical dysplasia, cervical carcinoma, or cervical abnormalities].[232] It remains unclear whether immunosuppressants are associated with a greater risk of cervical dysplasia in IBD than in patients with IBD not

receiving immunosuppression, a conclusion also previously reached during the 3rd ECCO scientific workshop.[232, 233]

Intensified cervical screening strategies have been proposed with cytological screening yearly or every 3 years, but evidence for such a strategy is currently lacking.[231, 233] Therefore, women treated with thiopurines should be strongly encouraged to engage with any available general population cervical screening programs.

3.2.6. Thiopurines and risk of other site-specific solid cancers

Two population-based studies reported an increased risk of urinary-tract cancer in IBD patients treated with thiopurines,[202, 234] whereas another population-based study did not report an increased risk.[235] Other retrospective case-control studies did not identify thiopurine exposure as a risk factor for other site-specific cancers, including renal-cell carcinoma,[236] gastric cancer,[237] breast cancer,[238] and cholangiocarcinoma.[239]

3.3. TNFα antagonists and risk of malignancy

Statement 12

There is no evidence of an overall increase in the risk of cancer in IBD patients treated with TNFα-antagonist monotherapy, although the risk of lymphoma and melanoma may be increased. [EL2] Skin-cancer surveillance and sun protection measures tailored to individual risk should be encouraged. [EL5] However, there are insufficient data to recommend additional screening measures beyond those recommended for the general population. **Consensus: 100%**

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3.3.1. Overall risk of cancer associated with TNFα antagonists

Given the widespread use of TNFα antagonists in the treatment of IBD, several studies have assessed the potential cancer risk associated with these therapies. The evidence shows that the overall risk of malignancies in IBD is not increased. Nevertheless, the frequent concomitant use of thiopurines and difficulties in controlling for confounding factors, such as disease severity or patient demographics, leaves some open questions, particularly around risks of specific subtypes of cancer.

A systematic review and meta-analysis published in 2016 of 49 randomized placebo-controlled studies that included 14 590 patients found no increased malignancy risk associated with biological therapy in IBD [OR: 0.90; 95% CI: 0.54–1.50].[240] A similar result was observed when the different TNFα antagonists were considered separately. Indirect comparisons between TNFα antagonists and anti-integrins [natalizumab, vedolizumab] regarding malignancy risk did not reveal significant differences. Duration of follow up was limited to 2 years. These findings are consistent with earlier meta-analyses,[241, 242] which also showed no associations to overall risk of malignancy and were also limited by a relatively short follow-up duration.

A pooled analysis published in 2014 of clinical trials reported no increased overall cancer risk of adalimumab monotherapy in IBD. However, an increased risk with combined adalimumab and immunomodulators was observed.[243] The risks of combination therapy are discussed further below.

Real-world data, where follow-up duration is greater and patient risk profiles are more diverse than within a clinical-trial setting, also suggest that TNFα antagonist therapy does not increase the overall risk of cancer in IBD. A recent systematic review of 28 observational IBD cohort studies including 298 717 patients revealed that the overall risk of cancer in patients with IBD who received TNFα antagonists was comparable to that of patients with IBD who never received TNFα antagonists.[244]

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Several additional independent cohort and case-control studies support these findings.[152, 204, 245-249] A multicentre matched-control study published in 2006 that included 404 patients with CD treated with infliximab and 404 matched-control CD patients not receiving TNFα antagonists reported no overall difference in cancer risk [OR 1.33; 95% CI: 0.46–3.84].[246] A subsequent nationwide Danish registry study that included data on 4553 IBD patients exposed to TNFα antagonists and 51 593 IBD patients without such exposure revealed no difference in rates of cancer development [adjusted RR: 1.07; 95% CI: 0.85–1.36] over 48 943 person-years of follow up.[250]

For patients with IBD >65 years of age, there is also no evidence of increased cancer risk associated with TNFα antagonists. A multicentre study of 3079 patients compared the risk of malignancy in those with IBD >65 years of age treated with TNFα antagonists [n=95] with those not treated with TNFα antagonists [n=190]. No significant difference in cancer incidence was observed between these groups during follow up [3% vs 2%, respectively].[251] This is further supported by a recent systematic review and meta-analysis[181] including 14 studies [6 IBD, 1 psoriasis, 7 rheumatoid arthritis]. The malignancy risk was similar between older patients treated with [n=3760] or not treated with biologics [n=3907] [OR: 0.54; 95% CI: 0.28–1.05]. This finding remained consistent when analysis was restricted to data from IBD patients using TNFα antagonists. A more recent systematic review and meta-analysis[186] that included 15 studies also showed that the overall cancer risk in IBD patients >60 years of age was not increased by the use of TNFα antagonists [OR: 0.90; 95% CI: 0.64–1.26].

3.3.2. TNFα antagonists and risk of solid-organ cancer, including skin cancer

In patients with IBD without a personal history of cancer there is currently no evidence that suggests an increased risk of developing other solid tumours when using TNFα antagonists.[152, 181, 186, 222, 240, 244-247, 249, 252-254]

In particular, the role of TNFα antagonists in the risk of squamous-cell skin cancer, basal-cell carcinoma [BCC], and melanoma in patients with IBD has been

examined.[175] Studies have tended to suffer from confounding by prior or concomitant thiopurine exposure and lack of power; larger studies are still required.

A health insurance claims database study published in 2012 used data from 108 579 IBD patients each matched with 4 controls without IBD. This study suggested that therapy with biologics [TNFα antagonists and natalizumab] was associated with a significant increase in the risk of melanoma in the IBD population [OR 1.88; 95% CI: 1.08–3.29], particularly in CD [OR: 1.94; 95% CI: 1.03–3.68] but not in UC [OR: 1.73; 95% CI: 0.53–5.63].[225]

However, this finding has not been replicated in other studies. A Danish population registry study found no association between exposure to TNFα antagonists and melanoma [RR 1.31; 95% CI: 0.63–2.74].[250] A systematic review and meta-analysis published in 2020 that included 7901 patients with IBD exposed to TNFα antagonists and 135 370 biologic-naive patients did not reveal a statistically significant association between treatment with TNFα antagonists and melanoma in patients with IBD [pRR: 1.20; 95% CI: 0.60–2.40].[255] Similar findings were observed in the same meta-analysis for patients with rheumatoid arthritis [RA] exposed to biologics [pRR: 1.20; 95% CI: 0.83–1.74] or for patients with psoriasis [HR: 1.57; 95% CI: 0.61–4.09] when compared with those treated with conventional therapy.[255]

Several studies reported no association between NMSC and TNFα antagonist use in IBD. A large retrospective US claims database study found no association between NMSC and TNFα antagonist therapy in IBD patients [OR: 1.14; 95% CI: 0.95–1.36]. This finding was unchanged when the analysis was restricted to patients with CD [OR: 1.16; 95% CI: 0.95–1.41] or UC [OR: 1.06; 95% CI: 0.69–1.64].[225] A pooled analysis of clinical trials published in 2014 of adalimumab in CD [3050 patient-years of exposure] also did not show any association between adalimumab monotherapy and NMSC [SIR: 1.20; 95% CI: 0.39–2.80].[243] A recent systematic review that included 28 studies and 298 717 IBD patients reported 692 [1%] malignancies in patients with IBD exposed to TNFα

antagonists. NMSCs were the most frequently observed malignancies [123/692; 17.8%][244] and were reported at the same rates as expected in the general non-IBD population.[250]

3.3.3. TNFα antagonists and risk of haematological malignancy

More than a decade ago, an analysis of the first 500 IBD patients treated with infliximab at the Mayo Clinic revealed that 1% developed a haematological malignancy.[256] In 2020, a meta-analysis comprising four observational studies including 261 689 IBD patients revealed that treatment with TNFα antagonists was associated with a greater rate of lymphoma than that in patients with IBD unexposed to TNFα antagonists [pooled IRR: 1.52 per 1000 patient-years; 95% CI: 1.06–2.19].[192] A comparison of patients exposed to TNFα antagonists as monotherapy [without thiopurine exposure] with those exposed to thiopurine monotherapy [without TNFα antagonists] showed similar rates of lymphoma [IRR: 0.72; 95% CI 0.48–1.07].[192] Consistently, another meta-analysis of 26 studies including 8905 patients [21 178 patient-years of follow up] revealed an increased risk for non-Hodgkin lymphoma [SIR: 3.23; 95% CI: 1.5-6.9].[189] However, 66% of these patients received combination therapy with a thiopurine or methotrexate. Moreover, increased lymphoma risk could only be shown for male patients between 20–54 years of age. A recent analysis of the Swiss IBD cohort including 3119 patients revealed increased lymphoma rates with TNFα antagonists in both CD [HR: 3.26; 95% CI: 1.31–8.10] and UC patients [HR: 25.25; 95% CI 2.94–217.26].[207] Additionally, a nationwide cohort study using the French National Health Insurance database found an increased risk of lymphoma amongst patients exposed to TNFα antagonist monotherapy when compared with patients without a history of either TNFα antagonist or thiopurine exposure [adjusted HR: 2.41; 95% CI: 1.60–3.64].[198] This difference was not significant when the analysis was restricted to patients with a new IBD diagnosis during the time course of the database [and hence where prior exposure to thiopurine or other medical therapy could be excluded].

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The finding of increased lymphoproliferative disorders in association with TNFα antagonist therapy has not been replicated in all studies. A meta-analysis of 74 RCTs conducted in IBD and non-IBD patients including 22 904 patients revealed only 12 lymphoma cases, with numbers too low to allow calculation of HRs.[257] Similarly, RCTs of adalimumab in UC revealed only three lymphoma cases among 1010 patients [2338 patient-years of follow up], all of them with previous or current azathioprine exposure.[258] RCTs of adalimumab in CD did not reveal any haematological malignancies associated with use of TNFα antagonist monotherapy, based on 1594 patients with 3050 patient-years of follow up.[243]

Findings from RCTs may reflect a different risk profile in clinical-trial participants than in the general population and shorter durations of follow up. At the same time, RCTs are less prone to problems of confounding by disease severity or other patient factors that may affect prescribing decisions in cohort studies. Other population studies have also shown reassuring safety data. An analysis of the Quebec Claims database including 19 582 patients showed an increased risk for lymphoma only in patients with combination treatment [OR: 8.64; 95% CI: 1.33–56.06], although exposure to TNFα antagonists in this cohort was very low.[222] The PYRAMID registry was explicitly designed to investigate lymphoma risk in patients with CD exposed to adalimumab [5025 patients, 16 689 patient-years of follow up] and revealed a lymphoma rate [10 cases] that was actually lower than that estimated in the background population.[259] Congruently, there was no association seen between infliximab and lymphoproliferative disorders or malignancies in 1541 patients with CD treated with infliximab and included in the ENCORE registry.[254] Finally, the REFURBISH study analysed reports to the FDA adverse event reporting system and showed no increased risk for T-cell non-Hodgkin lymphoma with TNFα antagonist monotherapy when compared with combination treatment or thiopurine monotherapy.[260]

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Several studies compared TNFα antagonists with conventional therapy [including azathioprine] and did not reveal significant differences in lymphoma development [OPUS registry with 2239 patients; TREAT registry with 3340 treated patients].[248, 261] Moreover, a comprehensive Cochrane network meta-analysis that included 21 260 patients from 52 studies found no statistically significant difference in lymphoma incidence with TNFα antagonists compared with other treatments [OR: 0.53; 95% CI: 0.17–1.66].[262]

In children, an analysis of 5528 patients with a total of 9516 patient-years of follow up did not reveal an increased lymphoma risk associated with TNFα antagonists. Only 2 patients were identified that developed lymphoma [SIR: 3.5; 95% CI: 0.35–19.6].[263] In a second paediatric study including 24 543 patient-years of follow up, infliximab was not associated with an increased risk of malignancy or hemophagocytic lymphohistiocytosis. [264]

For patients with IBD who do develop lymphoma whilst on TNFα antagonists, limited data suggest that the oncological prognosis does not appear to be different than that in patients with lymphoma and IBD without a history of TNFα antagonist exposure.[265]

3.3.4. TNFα antagonists and immunomodulator [thiopurine and methotrexate] combination therapy and risk of solid-organ cancer

Statement 13

There is no evidence of an additional increase in risk of solid-organ or skin cancer in patients with IBD treated with combination therapy with an TNFα antagonist and a thiopurine or methotrexate [EL3] compared with the risks associated with monotherapy with either of these agents. Surveillance measures in addition to those recommended for monotherapy are not required. [EL5] **Consensus: 90.0%**

An initial analysis of data pooled from clinical trials of adalimumab in CD suggested that patients receiving combination therapy with a thiopurine or methotrexate had a greater

risk of both NMSC [RR: 3.46; 95% CI: 1.08–11.06] and all other cancers [RR: 2.82; 95% CI: 1.07–7.44] than that of patients with CD treated with adalimumab monotherapy.[243] However, this observation was not confirmed in the subsequent PYRAMID and TREAT post-marketing registries [for adalimumab and infliximab, respectively], where exposure-adjusted rates of malignancies except lymphoma were not statistically different between patients with CD receiving TNFα antagonists with or without concomitant thiopurine therapy at baseline.[249] Concomitant immunosuppressive medication was not identified as a risk factor for the development of any malignancy in case-control studies, in which the control group included IBD patients that had never been treated with TNFα antagonists or thiopurines or methotrexate.[245, 249, 250, 253]

3.3.5. TNFα antagonists and immunomodulator [thiopurine and methotrexate] combination therapy and risk of haematological malignancy

Statement 14

The risk of lymphoma associated with combined TNFα antagonist and thiopurine therapy is greater than that of thiopurine or TNFα antagonist monotherapy. [EL2] This should inform treatment selection, particularly in older patients or those with other risks for lymphoma. [EL5]

Combined TNFα antagonist and thiopurine therapy significantly increases the risk of a rare hepatosplenic T-cell lymphoma, particularly in male patients <30 years of age with CD. [EL4]

Insufficient data exist on the risk of lymphoma in IBD patients exposed to TNFα antagonists in combination with methotrexate. **Consensus: 100%**

An early meta-analysis of 26 studies including 8905 patients and 21 178 patient-years of follow up revealed that combined use of TNFα antagonists with immunomodulators is associated with an increased risk of non-Hodgkin lymphoma in adult patients with CD.

However, the absolute rate of these events was low.[189] In a French nationwide insurance database study, the risk of lymphoma was higher amongst patients exposed to thiopurine monotherapy (adjusted hazard ratio [aHR]: 2.60; 95% CI: 1.96–3.44), TNFα antagonist monotherapy [aHR: 2.41; 95% CI: 1.60–3.64], or combination therapy [aHR: 6.11; 95% CI: 3.46–10.8]. The risk was higher in patients exposed to combination therapy than in those exposed to thiopurine monotherapy [aHR: 2.35; 95% CI: 1.31–4.22] or TNFα antagonist monotherapy [aHR: 2.53; 95% CI: 1.35–4.77].[198]

A meta-analysis of four observational studies, including 261 689 patients with IBD, assessed the risk of lymphoma in four comparator groups (combination therapy [TNFα antagonist plus thiopurine], TNFα antagonist monotherapy, thiopurine monotherapy, and control [unexposed to TNFα antagonist or to thiopurines]). Patients exposed to TNFα antagonist monotherapy, thiopurine monotherapy, or combination therapy all had a significantly higher pooled IRR of lymphoma than that of the control group. The risk of lymphoma associated with combination therapy was higher than that with thiopurines or TNFα antagonists alone [pooled IRR vs thiopurines: 1.70; 95% CI: 1.03–2.81, pooled IRR vs TNFα antagonist monotherapy: 2.49; 95% CI: 1.39–4.47].[192]

Hepatosplenic T-cell lymphoma [HSTCL] has been observed in patients on combination therapy,[194] although it is not certain that the risk is increased when compared with thiopurine monotherapy. A systematic review published in 2020 identified 62 cases of HSTCL; all but 5 reported thiopurine exposure, suggesting this to be the strongest association.[266]

Decisions around whether to combine TNFα antagonists with thiopurines should thus consider the absolute risk of lymphoma in the patient group under treatment [highest in the elderly], the relative risk of lymphoma with thiopurine treatment [greatest in younger and EBV-naïve patients], and the risks of rare but often fatal malignancies [HSCTL risk greatest in younger males]. Conversations around risks should be individualized and consider patient preferences and attitudes to risk. These risks should

be considered in light of the improved response rates observed with combination therapy in infliximab[267, 268] and the improved treatment persistence for patients receiving combination therapy.[269, 270] Recent RCT evidence suggests that immunomodulator cessation and use of TNFα antagonist monotherapy may be a valid risk-reduction strategy for patients in remission on combination therapy. [271]

3.4. Methotrexate and risk of malignancy

Statement 15

Patients treated with methotrexate may be at increased risk of NMSC. [EL5] There is insufficient evidence to support additional screening for skin cancer beyond that recommended for the general population. [EL5] **Consensus: 100%**

Evidence for methotrexate exposure as a risk factor for cancer in IBD patients is scarce. There are no relevant meta-analyses or RCTs and evidence is based only on observational studies. Single-centre case-control studies,[236, 272-274] large population case-control studies,[173, 275-277] and a large cohort study based on data from the Spanish ENEIDA registry[216] have not shown an increased risk of extracolonic cancer or a site-specific risk of cancer in patients with IBD treated only with methotrexate, including lymphoma, melanoma, NMSC, renal-cell carcinoma, cervical cancer, and small-bowel carcinoma. [216] However, all studies included small numbers of exposed patients and very small numbers of events, which precludes solid conclusions.

The only study that reported a positive association was a large, nested case-control study including more than 800 patients exposed to methotrexate, which found a significant increase in NMSC [OR: 8.55].[222] Nonetheless, the number of events was very small [n=5], thus resulting in wide CIs [95% CI: 2.55–31.8]. The association was found only in patients receiving methotrexate for <1 year. The other two studies

exploring NMSC in patients with IBD failed to show such an association in those treated with methotrexate.[276, 277]

Although data from other diseases cannot be directly extrapolated to the IBD population, the rheumatology and dermatology literature also report a possible link between methotrexate use and NMSC, including in a large RCT.[278, 279]

3.5. JAK inhibitors and risk of malignancy

Statement 16

There is no evidence that the overall risk of cancer is increased in patients with IBD treated with JAK inhibitors. [EL4] However, long-term data are lacking in patients with IBD. **Consensus: 100%**

The only evidence currently available on the risk of malignancy associated with JAK inhibitors in patients with IBD is based on data from RCTs. A meta-analysis of RCTs did not report differences in the risk of NSMC associated with JAK inhibitors compared with placebo or active comparator [RR: 1.21; 95% CI: 0.19–7.65].[280] Incidence rates of any malignancies excluding NMSC in the tofacitinib phase 3 UC clinical development program were consistent with those reported for biologics in UC RCTs.[183]

Tofacitinib was first approved in 2012 by the FDA for the treatment of RA. Data from post-marketing studies assessing the risk of cancer in patients with RA treated with JAK inhibitors are conflicting. A pooled analysis of phase 2–3 and long-term extension studies involving tofacitinib revealed standardized incidence ratios for all malignancies [excluding NMSC] and selected malignancies [lung, breast, lymphoma, NMSC] within the expected range for patients with moderate-to-severe RA.[281] Conversely, a safety clinical trial comparing tofacitinib and TNFα antagonists in patients with RA >50 years of age and with at least one additional cardiovascular risk factor reported a greater risk incidence of any malignancy [excluding NMSC] with tofacitinib than with TNFα

antagonists [HR: 1.48; 95% CI: 1.04-2.09], particularly lung cancer and lymphoma.[282]

3.6. Anti-integrins and risk of malignancy

Statement 17

Current evidence does not show an increased risk of malignancy in patients with IBD treated with vedolizumab. [EL4] However, long-term data are lacking. **Consensus: 100%**

Post-marketing surveillance data from the Vedolizumab Global Safety Database has been reported with over 4 years of follow up for patients with CD or UC on vedolizumab treatment. These medium-term safety data encompassing 208 050 patient-years of vedolizumab exposure did not reveal overall increased signals for malignancy in either CD or UC.[283] Vedolizumab exposure was calculated assuming that 8-weekly dosing intervals were used. Development of malignancy was reported in 140 patients with CD and 123 patients with UC whilst on vedolizumab therapy, with the most common malignancy being lower gastrointestinal malignancy [16% in CD and 27% in UC]. Although limited by the lack of a direct comparator group, these malignancy rates were not clearly increased from the expected population rates, suggesting that no readily apparent malignancy risk was associated with vedolizumab therapy in the population studied.

3.7. Anti IL-12/23 agents and risk of malignancy

Statement 18

Current evidence does not show an increased overall risk of cancer in IBD patients treated with anti IL-12/23 agents. [EL4] However, long-term data are lacking in IBD. **Consensus: 100%**

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Data up to 5 years of follow up from the IM-UNITI program showed no apparent safety signal for malignancies in patients with CD treated with ustekinumab.[284] In particular, up to week 44, there were eight cases of NMSC in the entire study population, with no differences between patients receiving ustekinumab or placebo. Between weeks 44 and 96,[285, 286] the number of treatment-emergent malignancies per 100 patient-years of follow up was 2.60 for placebo and 0.37 for ustekinumab. Interpretation is limited by the lack of an adequate reference group [only 61 patients continued placebo in the long-term extension study beyond week 44].

For UC, data from 3 years of follow up in the UNIFI program showed an overall incidence of malignancy per 100 years of follow-up of 0.72 [95% CI: 0.33–1.36] for ustekinumab and 0.66 [95% CI: 0.08–2.38] for placebo.[287] Again, the placebo reference group during the long-term extension was small and not necessarily representative [115 patients who remained stable whilst receiving placebo were included].

Data from observational studies are consistent with these results, with malignancies appearing rare.[288, 289] In a multicentre cohort including 142 CD patients, ustekinumab dose escalation up to every 4 weeks did not result in an increased risk of adverse events, including malignancies. Up to 52 weeks, only one cervical intraepithelial neoplasia and one NMSC were reported.[290] More prospective data are needed in this context.

There were similar findings from the Psoriasis Longitudinal Assessment and Registry [PSOLAR] registry, a long-term registry of more than 12 000 patients with psoriasis [including about 200 patients with concomitant CD] treated with different biologics, in which the rates of malignancies other than NMSC in long-term ustekinumab users were comparable with those expected in the general population.[291, 292] However, results from this registry should be interpreted with caution since the risk in patients with psoriasis may differ from the risk in patients with IBD, and the licensed dose of ustekinumab in IBD is higher.

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4. Treating IBD in patients with a history of recent or active cancer

4.1. Natural history of IBD in patients undergoing treatment for cancer

Statement 19

There is limited evidence to suggest that hormone therapy increases the risk of relapse in patients with IBD in remission at treatment initiation, whereas radiation and chemotherapy do not. [EL3] Data on the use of checkpoint inhibitors in patients with IBD are limited but indicate higher rates of IBD reactivation. [EL4] Patients with IBD being treated for cancer should be monitored closely for potential flares. [EL5] **Consensus: 100%**

Clinical data on the natural course of IBD during cancer treatment are sparse, and the available studies are limited by small sample size, heterogeneity in cancer type, short follow-up times, and lack of data on medication or disease activity prior to initiation of cancer treatment. This underlines the importance of a multidisciplinary approach, including close collaboration between IBD-dedicated gastroenterologists and oncologists to provide appropriate advice to patients with IBD and active cancer.

A systematic review of 19 studies found that radiation therapy appears to be safe with acceptable toxicity profiles in patients with IBD.[293] In the largest study available of 240 patients with IBD and prostate cancer, 18% of patients experienced a flare following treatment for cancer. However, this rate did not differ between patients receiving radiation therapy or undergoing surgery.[294, 295] This was also true for IBD-related hospitalizations and surgery. Disease activity in the year preceding therapy was the best predictor of disease activity after therapy.[294]

In a cohort study of 447 patients with IBD and breast or prostate cancer, 28% of patients in remission at the start of cancer therapy had a flare following cancer treatment [surgery or radio-, chemo-, or hormone therapy]. Hormone therapy with or

without chemotherapy was associated with an approximately 2-fold increase in the risk of a flare.[296]

In a systematic review of adverse events in patients with autoimmune diseases treated with immune checkpoint inhibitors, 13/123 patients had IBD.[297] Of these, 5 [39%] patients had a flare of their IBD requiring treatment intensification. In a more recent study, 4/21 IBD patients flared a median of 7 weeks [range 4–40] after initiation of treatment with immune checkpoint inhibitors.[298] All patients received steroids and only 1 patient could not continue with checkpoint inhibitor therapy. Two small studies did not reveal an IBD flare during checkpoint inhibitor therapy.[299, 300]

4.2. Thiopurines in patients with past or current malignancy

4.2.1. Risk of thiopurines in patients with past malignancy

Statement 20

Current evidence suggests that there is no additional risk of incident cancer with thiopurine use in patients with IBD and a past history of malignancy beyond the known risk associated with this class. However, most observational data are from patients starting treatment with thiopurines more than 5 years after cancer resolution, and in patients with a low risk of cancer recurrence. [EL4] **Consensus: 100%**

Patients with IBD and a past history of malignancy have an increased risk of incident cancer when compared with the general population.[203] Due to the relatively small numbers of cases recorded in patients with IBD, it is not possible to provide precise, tumour-specific assessments of risk. Data from the transplantation literature suggests that cancer type is an important determinant of recurrence risk, with lung, gastrointestinal, and cervical malignancies generally considered as being higher risk and

prostate, testicular, and haematologic malignancies at lower risk, although there is likely further heterogeneity within these groups.[301]

A meta-analysis including data from 11 702 patients with an immune-mediated inflammatory disease and a past history of malignancy revealed that the risk of incident cancer was not greater in patients receiving immunomodulator therapy than that in patients without immunomodulator exposure or receiving TNFα antagonists.[302] Rates of new or recurrent cancer were similar in patients receiving thiopurine or methotrexate therapy. These findings were consistent in a subgroup analysis restricted to data from the 3706 patients with IBD. A separate subgroup analysis restricted to patients with a history of skin malignancy found a greater risk of new or recurrent skin cancer in patients exposed to immunomodulator therapy than that of patients who did not receive immunosuppression. A cohort study in patients with a history of immune-mediated inflammatory disease and breast cancer did not find evidence of a significantly increased risk of recurrent breast cancer in patients exposed to thiopurines, methotrexate, or TNFα antagonists. However, the confidence interval around the estimate of risk associated with thiopurine exposure was large.[238]

In summary, observational data in patients with IBD and a past cancer treated with thiopurines are limited and may be skewed by data from patients with cancers at overall low risk of recurrence, who initiated treatment >5 years since cancer resolution, or both. These data, and those drawn from patients with a history of other immune-mediated inflammatory diseases, do not show a clear signal of increased risk but should be interpreted with caution. On this basis, therapy may be initiated with caution and after appropriate consideration of risks. Screening examinations in patients using thiopurines after cancer should follow the same guidelines as applied to general non-IBD populations.

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4.2.2. Risk of thiopurines in patients with current malignancy

Statement 21

Thiopurines should preferably be withdrawn in patients with an active cancer diagnosis. [EL5] Patients with non-aggressive BCC or preneoplastic lesions of the cervix may continue thiopurine therapy with close monitoring. [EL5] **Consensus: 100%**

Due to their immunosuppressive properties and as suggested for transplant patients, thiopurines should preferably be withdrawn in IBD patients with a diagnosis of cancer until the cancer is controlled.[301, 303-305] A multidisciplinary approach to decision making that involves oncologists and careful patient counselling should be implemented.

For patients with cancers or pre-neoplastic lesions deemed to be at low risk of recurrence and that have been successfully removed endoscopically or surgically [e.g., non-aggressive BCC, pre-neoplastic lesions of the cervix, or sporadic colonic polyps], thiopurines may be continued.[306] These patients should be closely monitored according to the appropriate recommendations.

4.3. Risk of methotrexate in patients with past or current malignancy

Statement 22

There are insufficient data to make recommendations regarding the safety of methotrexate use in patients with prior malignancies. [EL5] **Consensus: 100%**

There are insufficient data available on the risk of recurrence of malignancies in patients with IBD that were treated with methotrexate following the diagnosis of malignancy. A recent retrospective cohort study found similar rates of new or recurrent cancer in patients with IBD and a prior history of malignancy exposed to methotrexate compared to similar groups treated with thiopurines, TNFα antagonists, or vedolizumab.[307] Due to patient heterogeneity, it was not possible to include the 64 patients exposed to

methotrexate in a comparison of incidence rates after adjustment for age- and cancer-specific variables.

Some indirect evidence may be gained from studies including both IBD and non-IBD populations with immune-mediated inflammatory disease, as discussed above. In a large meta-analysis, rates of recurrent or new cancers were similar in patients receiving thiopurine or methotrexate therapy.[302] Likewise, a cohort study of patients with a history of immune-mediated inflammatory disease and breast cancer found no evidence of increased risk of recurrent breast cancer in patients exposed to methotrexate, with narrower confidence intervals than those for the estimated risk associated with thiopurine exposure.[238] Nevertheless, since these studies address different patient populations and do not allow for stratification by specific malignancy types, it remains challenging to generate specific recommendations beyond stressing the importance of individualizing risk based upon consideration of oncological and patient factors and the possibility of alternative treatment options.

4.4. Risk of TNFα antagonists in patients with past or current malignancy

Statement 23

TNFα antagonists may be used in patients with IBD and current or previous cancer. However, data on individual cancer types and timing of treatment with TNFα antagonists are lacking. [EL4] Decisions should be made on a case-by-case basis in a multidisciplinary setting involving oncologists and should consider factors including current and recent IBD activity and alternative treatment options. [EL5] **Consensus: 100%**

In multiple population-based observational studies of patients with IBD and a history of cancer, exposure to TNFα antagonists was not associated with an increased risk of new or recurrent cancer when compared with patients exposed to other immunosuppressive agents, nonbiological disease-modifying therapies, or both. [185, 212, 214, 301, 306] A

meta-analysis published in 2019 evaluated 11 679 patients with a history of cancer, 3707 of whom were exposed to TNFα antagonists following cancer diagnosis.[185] The pooled IRR of those exposed to TNFα antagonists was similar to those within the unexposed cohort [IRR: 0.90; 95% CI: 0.59–1.37]. When analysis was restricted to patients with a diagnosis of IBD, new or recurrent cancer incidence also did not differ significantly in those exposed to TNFα antagonists [IRR: 1.06; 95% CI: 0.59–1.37].[185] Most recently, a retrospective cohort study of IBD patients exposed to TNFα antagonists after a prior cancer diagnosis [N=184] did not reveal an increase in new or recurrent cancer when compared with IBD patients unexposed to immunosuppressive therapy following cancer diagnosis [N=183] [HR: 1.03; 95% CI: 0.65–1.64].[308] Similar findings were observed in studies in mixed populations of patients with a history of immune-mediated inflammatory disease and prior malignancy. [185, 302]

In some small and generally underpowered studies, TNFα antagonists were not related to worse tumour evolution, recurrence, or survival in various malignancies. Specifically, TNFα antagonist use was not associated with poorer survival in melanoma or an increased risk for recurrent NMSC or breast cancer.[238, 309-311] However, the heterogeneity of study populations, cancer types, and the observational nature of these data limit the emphasis that can be placed upon individual study results.

4.5. Risk of ustekinumab, vedolizumab, and JAK inhibitors in patients with past or current malignancy

Statement 24

IBD patients with a history of prior malignancy do not appear to have an increased risk of cancer recurrence or new cancer when treated with vedolizumab [EL3] or ustekinumab. [EL4] There is insufficient evidence to make recommendations on the use of JAK inhibitors for patients with current or prior malignancy. [EL5]

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There are insufficient data regarding the safety of vedolizumab, ustekinumab, or JAK inhibitors in patients with active malignancy. Decisions should be made on a case-by-case basis in a multidisciplinary setting involving oncologists and should consider factors including current and recent IBD activity and alternative treatment options. [EL5]

Consensus: 100%

There is no evidence that vedolizumab increases the risk of new or recurrent cancer in IBD patients with a prior history of cancer. The largest study to have evaluated this is a retrospective cohort study that compared IBD patients exposed to vedolizumab after a prior cancer diagnosis [N=96] with IBD patients not exposed to immunosuppressive therapies following cancer diagnosis [N=183].[308] No association was found between vedolizumab use and subsequent cancer [HR: 1.30; 95% CI: 0.38–1.36]. These findings are supported by smaller cohort studies that have reached similar conclusions.[307, 312]

Due to the effects of vedolizumab on mucosal immune responses within the GI tract, there may be concern regarding the risk of digestive-tract cancers. Results from the GEMINI long-term safety studies and post-marketing data suggest no difference in rates of *de novo* lower gastrointestinal and hepatic malignancies in vedolizumab-exposed patients compared to age- and sex-adjusted estimates.[313] However, patients with a diagnosis of prior malignancy were excluded from analysis.

A retrospective cohort study that evaluated new or recurrent cancer in IBD patients treated with ustekinumab following a prior cancer [N=14] did not reveal an increased cancer risk compared with patients who did not receive immunosuppressive therapy [N=267] [HR: 0.96; 95% CI: 0.17–5.41].[312] Whilst safety signals are thus far reassuring, the numbers and duration of follow up are too limited to draw firm conclusions.

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There are no safety data on the use of JAK inhibitors in patients with prior malignancies beyond case reports. The tofacitinib UC clinical program found 19 patients who developed NMSC over 2576 patient-years of tofacitinib exposure; 7/19 patients had a prior history of NMSC.[314]

Outside of the IBD literature, there are again minimal data to support the use of ustekinumab or JAK inhibitors in dermatology or rheumatology patients with prior malignancy. From the PSOLAR database, a single abstract reported that 3.8% of psoriasis patients had a history of systemic malignancy, and that malignancy recurrence rates were comparable in patients treated with biologic therapies [including ustekinumab] and non-biologic therapies.[315]

Data on the use of vedolizumab, ustekinumab, or JAK inhibitors in patients with an active malignancy are inadequate to draw any conclusions. The general principle for treating such patients is to develop a treatment recommendation that incorporates oncological and patient factors and considers the range of possible treatment options.

Conclusion

Treatment of patients with IBD involves management of risk and assessment of data that are often partial or do not apply directly to the individual patient. This is particularly true in the areas covered by this guideline. In particular, whilst we can generate increasingly precise estimates of malignancy risk associated with well-established therapies based on large cohort studies and population databases, it is not always possible to uncouple observed risk from differences in underlying disease activity that may drive treatment decisions. Furthermore, data from RCTs for new drugs may be insufficient to build a complete picture of risks of rare events such as malignancy; post-

marketing data takes time to assemble and may be drawn from different patient risk groups.

Perhaps the most challenging but increasingly common area of decision making involves the patient with a recent or active malignancy. For these patients, it is important to distinguish between the decision to start a new therapy for active IBD in patients with a known malignancy and the decision whether to continue an existing treatment for a patient with IBD who receives a cancer diagnosis. In the former, it will generally be appropriate to select the treatment with the most favourable safety profile, including indirect data from non-IBD populations where appropriate. In the latter, it is important to consider the prior history of IBD activity while considering the likely consequences for the patient of interrupting IBD therapy, the chance of disease flare, and the chance of recapturing disease control using alternative, remaining lines of IBD therapy. In these discussions, it is vital to acknowledge uncertainty, obtain input from the treating oncologist, and involve the patient in decision making.

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