Journal of Crohn's and Colitis, 2015, 945–965
doi:10.1093/ecco-jcc/jjv141
Advance Access publication August 20, 2015
ECCO Guideline/Consensus Paper

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European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies

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1. Introduction

The global prevalence of cancer is increasing, largely as more patients are living into old age. Therefore, gastroenterologists caring for patients with inflammatory bowel disease [IBD] increasingly are managing patients with cancer, or a previous history of cancer. This often requires joint management with the patient's oncologist, enabling case-by-case decision-making based on the characteristics and expected evolution of the index cancer. Previously, no European guidelines existed describing the impact of IBD on malignancy. For this reason, the European Crohn's and Colitis Organisation [ECCO] Guidelines Committee [GuiCom] decided to elaborate a set of Consensus Statements on optimal risk/benefit strategies for treating IBD patients with cancer or a history of cancer. The development of clinical practice guidelines is expensive and time consuming, and it is the Committee's hope that these statements will facilitate and accelerate future efforts to elaborate formal guidelines, providing useful information on areas for which evidence is lacking and where controlled studies are needed. The strategy used to produce the Consensus Statements involved five steps:

1. Two members of Guicom [VA and RE] identified four main topics that needed to be addressed: a] IBD and solid tumours; b] IBD and skin and haematological malignancies; c] malignancy related to therapy: risk and prevention; and d] management of IBD patients with a history of malignancy. During 2014, calls for participation in the drafting of consensus statements were issued to ECCO members, and selected oncologists known for their expertise and active research in the field were invited to join the Consensus. Participants were selected by the Committee, and four working groups were created, each composed of a chairperson [LE, RE, LB, and VA], two ECCO members including young members [Y-ECCO], and one or two experienced oncologists. The chairmen and their groups

elaborated relevant questions on topics dealing with current practice and/or areas of controversy. Participants in the Consensus Process were asked to provide answers to the questions based on evidence from the literature and their own experience [Delphi procedure].[1]

2. Working in parallel, the four groups conducted a systematic review of the literature on their topic with the appropriate key words. The searches targeted Medline/PubMed and the Cochrane database, as well as other relevant sources.

3. Provisional statements on the group's topic were drafted by the chairmen. These statements were then reviewed and commented on by members of the working group. With the aid of a web-based platform [www.cpg-development-org], the review process was later extended to applicants not included in the working groups and the ECCO national representatives [see Acknowledgments].

4. In January 2015, a meeting [chaired by VA and RE] was held in Vienna to revise and approve the statements. Each statement was projected on a screen, discussed, and revised until a consensus was reached by > 80% of the participants at the meeting. The level of evidence supporting each statement was rated in accordance with the recommendations of the Oxford Centre for Evidence-based Medicine.[2] In some areas where the level of evidence is generally low, expert opinion was included as appropriate.

5. The final document on each topic was written by the chairperson in conjunction with the members of his working group. Consensus guideline statements in bold are followed by comments on the evidence and opinion. Statements are intended to be read not in isolation but together with the qualifying comments in the accompanying text. The final text was edited by VA and RE to ensure consistency of style and terminology and then submitted to the participants for final approval. In addition, ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI statement is not only stored at the ECCO Office and the editorial office of the *Journal of Crohn's and Colitis* [*JCC*] but also open to public scrutiny on the ECCO website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html], providing a comprehensive overview of potential conflicts of interest of the consensus participants and guideline authors.

2. IBD and Solid Tumours

2.1. Colorectal cancer

ECCO Statement 2A

Patients with IBD are at increased risk of developing colorectal cancer [CRC] (evidence level [EL] 1) which, in the case of ulcerative colitis [UC], varies with the extent and duration of the disease [EL 1], family history of CRC, and the presence/absence of primary sclerosing cholangitis [PSC] [EL 1]. Over the past 35 years, the risk of CRC in patients with IBD has not declined significantly, but the risk of dying from CRC has decreased [EL 1]

Two recent meta-analyses of cohort studies have clarified the increased risk of CRC in patients with IBD. For those with Crohn's disease [CD],[3] the excess CRC risk has been estimated at 1.9, whereas the risk for small bowel cancer was 27.1. The excess CRC risk for patients with UC[4] has been estimated at a standardised incidence ratio [SIR] of 2.4. Male sex [SIR, 2.6], young age at UC diagnosis [SIR, 8.6], and extensive colitis [SIR, 4.8] were the major risk factors. Others[5] have shown that PSC is a major risk factor for CRC in IBD patients, particularly those with UC. The risk of CRC is not affected by prior liver transplantation. Time to CRC onset was similar in patients with PSC and UC and those with UC alone, but the former group was five times more likely to develop CRC. A recent meta-analysis of data from population-based studies[6] found a pooled SIR for CRC of 1.7 [95% confidence interval, 1.2–2.2] in all patients with IBD. These reports indicate that the risk of CRC is definitely increased in patients with IBD, but not to the extent previously reported and not in all patients.

ECCO Statement 2B

The risk of CRC is highest in UC patients with dysplasia detected on colonic biopsies, especially high grade dysplasia [EL 3]. Endoscopic surveillance and treatment tailored to the individual patient's risk factor profile are recommended [EL 1]. Proctocolectomy abolishes the risk of CRC, but not that of anal cancer or cancer of the rectal cuff or ileo-anal pouch in patients who have undergone ileal pouch-anal anastomosis

Several publications, including the most recent European[7] and US[8] guidelines, stress the importance of endoscopy for the surveillance and treatment of lesions in patients with IBD. Recommendations for cancer surveillance can be found in the 2013 European Evidence-based Consensus on Endoscopy in IBD.[7] Long-term follow-up data show that proctocolectomy with removal of the entire colon reduces the risk of CRC,[9] but other reports, including case series, suggest that cancer and/or de novo polyps can still develop in the anal transition zone [ATZ][10–12] [EL 3].

ECCO Statement 2C

On average, patients with IBD who are diagnosed with CRC are younger than non IBD-related CRC patients. Overall survival following CRC diagnosis in IBD patients is driven primarily by age, comorbidities, and cancer stage at diagnosis [EL 3]

A recent study in Japan showed that UC-related CRC patients were younger than those with CRC unrelated to UC. They were also more likely to have multiple neoplastic lesions and had higher proportions of superficial-type lesions and invasive-type lesions at histology, as well as mucinous or signet-ring cell histotypes. In patients with stage 3 CRC, UC-related disease was associated with poorer survival than sporadic CRC [43.3% vs 57.4%].[13] A case-control study found that, after adjustment for node and metastasis stage, the risk of death in CRC patients with IBD was roughly twice as high as that of patients whose cancers were sporadic (hazard ratio [HR] = 2.011). Stage 3 CRC patients with IBD also had significantly decreased survival [23.0 vs 133.9 months, $p = 0.008$].[14]

Similar findings emerged in a Danish cohort. CRC patients with IBD were younger at cancer diagnosis than their non-IBD counterparts. Those with CD had a lower frequency of Duke's A- and B-stage tumours [36% vs 42%] and a higher frequency of Duke's C- [31% vs 27%] and D-stage tumours [23% vs 21%], whereas the frequency of unknown-stage tumours [10%] resembled that of non IBD-related CRC patients. The 5-year adjusted mortality rate ratios for patients with UC or CD were 1.14 (95% confidence interval [CI], 1.03–1.27) and 1.26 [95% CI, 1.07–1.49], respectively, compared with patients without IBD.[15] In contrast, in an Irish population-based study, IBD-related CRC patients were about 7 years younger at cancer diagnosis

than non-IBD CRC patients, but they survived about 3 years longer. Older age, male sex, smoking, and advanced CRC grade and stage were independently associated with shorter survival times. When propensity score matching was used to analyse outcomes, the survival times of CRC patients with and without IBD were not significantly different.[16] Taken together, these results reveal that IBD patients tend to develop CRC at younger ages than non-IBD patients. However, no effect of IBD on patient survival has been consistently demonstrated.

2.2. Anal, fistula-related, and ileo-anal pouch cancers

ECCO Statement 2D

In patients with CD, adenocarcinoma complicating perianal or enterocutaneous fistula tracts can occur but is rare [EL 1]. Persistent chronic fistulas in long-standing CD, especially in young women, have been identified as potential risk factors for malignant transformation of fistulas [EL 2]

Anal adenocarcinomas arising from perianal fistulas are a rare complication in CD.[17,18,19] In a meta-analysis of 20 clinical studies [1965–2008] comprising a total of 40 547 patients with CD-associated cancer, the incidence of cancer related to CD-associated fistulas was 0.2/1000 patient-years.[20] In a 17-year follow-up study of 6058 CD patients with perianal and/or enterocutaneous fistulas, only 4 developed fistula-associated adenocarcinomas. These malignancies developed long after CD diagnosis and fistula detection (mean interquartile range [IQR]: 25 years [IQR 10–38] and 10 years [IQR 6–22], respectively), and the median age at cancer diagnosis was 48.3 years [IQR 43–58].[21] Fistula-related adenocarcinomas can arise in patients with long-standing perianal CD, and it may be associated with adenomatous transformation of the fistula tract epithelium.[22,23] Early disease onset, disease duration exceeding 10 years, chronic colitis with high inflammatory activity and persistence of chronic fistulas and stenosis seem to be associated with malignant transformation.[24] A systematic review of case series and reports published between 1950 and 2008 identified 61 cases of carcinomas arising in CD-related perineal fistulas, and well over half [61%] involved females. At cancer diagnosis, the women were significantly younger than their male counterparts [47 vs 53 years, $p < 0.032$] and had significantly shorter-duration CD [18 vs 24 years, $p = 0.005$]. Most of the tumours were adenocarcinomas [59%, $n = 36$] or squamous-cell carcinomas [31%, $n = 19$], and the involved fistulas usually originated in the rectum [59%, $n = 36$].[25]

ECCO Statement 2E

Chronic active perianal fistulising disease may be associated with advanced cancer stage at the time of diagnosis [EL 3]. Regular follow-up is recommended for CD patients with chronic persisting perianal fistulas, especially when symptoms change [eg new-onset pain] [EL5]. The optimum frequency and modalities of surveillance are not known [EL 5]

Fistula-related cancer is associated with non-specific signs and symptoms. This complicates and often delays diagnosis, thereby worsening the prognosis.[26] In a systematic review of 23 reports on fistula-related cancer [total *n* patients: 65], the average duration of the involved fistula was 14 years, and the mean delay of cancer diagnosis was 11 months.[27] In patients with long-standing perianal CD, a change in symptoms should always raise the suspicion of cancer.[28] Regular surveillance for ano-rectal carcinoma should be requested for all patients with perianal CD. It should include routine biopsy of any suspicious lesion[29] and a biopsy under anaesthesia or curettage of fistula tracts when needed.[30,31]

2.3. Pouch

ECCO Statement 2F

The risk for neoplasia in patients with UC and ileal pouch-anal anastomosis [IPAA] is low. A preoperative diagnosis of dysplasia or cancer of the colon or rectum is a risk factor for pouch dysplasia or adenocarcinoma [EL 1]

Conservative proctocolectomy with IPAA has become the intervention of choice for severe UC requiring surgery.[32,33] In a series of 3203 patients with preoperative diagnoses of IBD who underwent restorative proctocolectomy with IPAA 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. Of these patients, 38 [1.19%] had pouch neoplasia (adenocarcinoma of the pouch and/or ATZ in 11 cases [0.36%], pouch lymphoma in 1 [0.03%], squamous cell cancer of the ATZ in 3, and dysplasia in 23 [0.72%]), and this risk for this outcome was observed even in patients who had undergone mucosectomy.[34] In a systematic review of 23 observational studies and case series [total *n* patients: 2040], the pooled prevalence of confirmed dysplasia involving the pouch, ATZ, or rectal cuff after restorative proctocolectomy for UC was 1.13% [range 0–18.75].[35] Branco *et al.* reported 1 case of rectal cancer in the 520 IPAAs performed for UC by their group between 1978 and February 2008. Based on their retrospective analysis of this case and 25 others reported in the literature, they concluded that post-IPAA cancer can occur: 1] after mucosectomy or stapled anastomosis; 2] after IPAAs performed for UC alone or for UC with neoplasia; and 3] regardless of whether the initial cancer or dysplasia involved the rectum.[36] 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 IBD patients 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.[37]

There is little evidence to support the need for routine surveillance of the pouch and ATZ mucosa in the absence of high-risk features [ie type C changes at histology, sclerosing cholangitis, unremitting pouchitis].[10,38] In patients with high-risk features or who have been operated on for dysplasia or cancer, pouch surveillance may be conducted. ECCO endoscopy guidelines suggest that annual surveillance in such patients with high risk of pouch neoplasia may be worthwhile, at clinician discretion.[7] If dysplasia is noted early after surgery, careful annual pouch surveillance is needed,[39] with multiple biopsies of the ileal reservoir and the anorectal mucosa below the ileo-anal anastomosis.[40] Finally, the risk of rectal cancer is relatively high in IBD patients after subtotal colectomy. In a series of 1439 patients with UC, the cumulative probability of developing rectal cancer after subtotal colectomy was 17%, 27 years after disease onset.[41]

2.4. Carcinoid tumours

Carcinoids are rare in IBD,[42,43,44,45] and there is no convincing evidence that the two conditions are associated. Thus far no risk factors

for the development of carcinoids in IBD patients have been identified. The tumours are generally asymptomatic, and almost all are discovered incidentally after surgery for IBD. No screening test of clear-cut diagnostic value is available.

2.5. Small bowel cancers

ECCO Statement 2G

Patients with CD involving the small bowel are at increased risk for small bowel neoplasia [EL 1]. Adenocarcinomas are the most frequent small-bowel neoplasm in CD patients [EL 3], and they usually arise in inflamed segments [EL5]

About 2% of all gastrointestinal cancers affect the small bowel,[46] and a high percentage of these are adenocarcinomas.[47] In a recent meta-analysis of 20 clinical studies, the estimated incidence of small-bowel carcinoma in CD patients—0.3/1000 patient=years [CI, 0.1–0.5]—was increased by a factor of 18.753 with respect to that found in an age-matched standard population.[20] More recently in France, a nationwide cohort study found incidence rates of small-bowel adenocarcinoma of 0.235 per 1000 patient-years among patients with small bowel CD, and 0.464 per 1000 patient-years among those whose small-bowel CD had been present for > 8 years. In these two populations, the SIRs for small-bowel adenocarcinoma were estimated at 34.9 [95% CI, 11.3–81.5] and 46.0 [95% CI, 12.5–117.8], respectively.[48] However, although the relative risk is high, the absolute risk of developing small-bowel cancer in CD remains low.[20,49]

ECCO Statement 2H

Prolonged duration of stricturing disease may be associated with the development of small-bowel cancer in patients with CD [EL4]

Risk factors reportedly associated with the development of small-bowel cancer in CD patients include distal jejunal/ileal CD localisation, strictures and chronic penetrating disease, long disease duration, young age at diagnosis, male sex, use of steroids and immunomodulators, small-bowel bypass loops, strictureplasties, and environmental factors.[50] However, other studies have failed to confirm some of these associations. In a 2008 case-control study, small-bowel resection and use of aminosalicylates for > 2 years were significantly associated with a lower incidence of small-bowel adenocarcinoma (odds ratios [OR] 0.07 and 0.29, respectively). Both associations remained significant in multivariate analysis [OR 0.04, $p = 0.001$; OR 0.16, $p = 0.02$, respectively].[51] No significant association with duration of CD, age at CD diagnosis, or anatomical area of CD involvement emerged from the meta-analysis by Laukoetter *et al*. cited in the previous section.[20] In almost all case series reported thus far,[46,48,50,52,53,54,55,56,57,58,59,60,61,62,63] small-bowel adenocarcinomas tended to develop in inflamed intestinal segments. On the whole, long-standing CD and stricturing disease seem to be the factors most strongly associated with elevated risk of small-bowel cancer.

ECCO Statement 2I

Symptomatic strictures developing after a prolonged remission and strictures that are refractory to medical therapy should be investigated for underlying small-bowel neoplasia [EL5]

There is not enough strong evidence to make clear recommendations on primary prevention of small-bowel neoplasia in CD patients. Advanced imaging and endoscopic techniques (eg capsule endoscopy, double-balloon endoscopy, magnetic resonance imaging [MRI], computed tomography [CT]) may allow earlier detection of small-bowel neoplasia, but they are too costly and complex to be used for routine surveillance of all CD patients with small-bowel involvement.

In patients with CD, adenocarcinoma may present on CT or MRI as a sacculated loop with asymmetrical thickening[57] or as a short segment of stenosis mimicking benign fibrostenosis.[64,65] Differentiating a benign inflammatory stricture from an early-stage small-bowel tumour can be difficult. Capsule endoscopy can be useful for detecting neoplastic lesions, but it does not allow biopsy collection. Capsule endoscopy has displayed 83.3% sensitivity for tumour detection, with a negative predictive value of 97.6%. The specificity and positive predictive value were both 100%.[63] Double-balloon enteroscopy or surgery may be indicated if small-bowel obstruction occurs during a long-standing remission or if non-responsive small-bowel strictures or fistulas are present, since either may be associated with small-bowel neoplasia.[64,66] The possibility of small-bowel cancer should be suspected and investigated if CD patients develop symptomatic strictures after a prolonged symptom-free period or strictures that are unresponsive to medical therapy.

2.6. Cholangiocarcinoma

ECCO Statement 2L

Patients with IBD, UC in particular, are at higher risk for cholangiocarcinoma than the general population [EL2], and the excess risk is caused mainly by the association between these cancers and PSC [EL2]

Data from the Swedish Hospital Discharge Register and the Swedish Cancer Registry indicate a strong association between UC and extrahepatic bile duct cancer [SIR 5.6].[67] Analysis of the U.S. Surveillance, Epidemiology, and End Results [SEER] Program registry shows that intrahepatic cholangiocarcinoma is increased in patients with UC, but not those with CD.[68] Danish population-based studies have revealed that extrahepatic cholangiocarcinoma is increased in patients with UC as well as those with CD.[69,70] However, in patients who do not have PSC, there is no evidence linking cholangiocarcinoma to IBD.[71] The effects of IBDs on the natural history of PSC and its complications [including cholangiocarcinoma] have not been well characterised. Clinical management of the biliary cancer risk is necessary in all patients with PSC, regardless of whether they have IBD.[72] Survival after a diagnosis of cholangiocarcinoma is poor, even in patients without IBD.

2.7. Gastrointestinal stromal tumours

Gastrointestinal stromal tumours [GIST] are stromal or mesenchymal neoplasms affecting the gastrointestinal tract, typically the subepithelial layers. They represent only 1% of primary gastrointestinal cancers.[73] A few cases of GIST have been reported in IBD patients: they include a solitary GIST of the omentum incidentally found during surgical exploration for fulminant UC,[74] a GIST of the rectum in a patient with UC in remission,[75] and a *DOG1*-expressing GIST found in a surgical specimen, 20 cm from the adenocarcinoma, from a patient with long-standing UC.[76] There is no convincing evidence of an association between IBD and GIST.

2.8. Extra-intestinal cancers

ECCO Statement 2M

The overall risk of extra-intestinal cancer in patients with IBD is not increased relative to the general population [EL 1]. However, analysis by individual cancer sites shows that CD patients are more likely to develop cancers of the upper gastrointestinal tract, lung, urinary bladder, and non-melanoma skin cancers [EL1], and UC is associated with an increased risk of liver-biliary tract cancers and leukaemia [EL1]

A meta-analysis of population-based cohort studies comprising a total of 17 052 patients with IBD revealed no increased risk of cancer at any site in the IBD population [SIR, 1.10].[77] However, when data have been analysed by specific cancer type and IBD type, CD patients have exhibited increased risk for cancer of the upper gastrointestinal tract [SIR 2.87] [particularly the stomach], the lungs [SIR 1.82], and the urinary bladder [SIR 2.03], as well as for squamous-cell skin cancer [SIR 2.35]. Fistulising forms of CD also seem to be associated with an increased risk of extra-intestinal cancer.[78] The meta-analysis also found patients with UC to be significantly more likely to develop liver–biliary cancer [SIR 2.58] and leukaemia [SIR 2.00], although their risk of developing lung cancer is reduced [SIR 0.39, 95 % CI, 0.20–0.74]. Possible risk factors for these tumours were suggested [smoking for the lung and bladder cancers, extra-intestinal manifestations of IBD for liver-biliary cancer, and disease location for upper GI tract cancer], although no clear evidence is available to support these conclusions.[77] Tumours of the cervix, ovary, pancreas, breast, kidney, and brain have not been found to be associated with IBD.[77,79]

3. IBD AND HAEMATOLOGICAL MALIGNANCIES

Patients with IBD are at increased risk for intestinal cancers.[50,80] Recent data suggest that IBD is also associated with excess risk for extra-intestinal malignancies, as a result of the state of immune activation it causes, but conflicting results have been reported on this issue.[55,77,81]

3.1. Epidemiology

ECCO Statement 3A

IBD patients show a trend toward higher risks of developing haematological malignancies. Compared with the general population, UC patients are significantly more likely to develop leukaemia, whereas those with CD are at higher risk for lymphoma, especially non-Hodgkin lymphoma [EL1]

According to the 2013 SEER database, the current lifelong risk of Hodgkin lymphoma is 0.2%, and the 5-year survival rate is 85.3%. Corresponding figures for other haematological malignancies are as follows: non-Hodgkin lymphoma [NHL]: 2.1% and 69.3%; leukaemia: 1.4% and 57.2%; myeloma: 0.7% and 44.9%.[82] Studies of small patient samples and single-centre series suggest that the risk for haematological malignancies is increased in IBD patients, but increases have been limited or not been observed in most population-based studies.[81] Jess *et al.*, however, analysed a population-based cohort of 2325 IBD patients and found that CD patients, but not those with UC, were at higher risk for lymphoma [SIR 3.01, 95% CI, 1.21–6.19], particularly the non-Hodgkin forms [SIR 3.43, 95% CI, 1.38–7.07], and this effect was independent of thiopurine exposure. The authors suggested that the apparent lack of excess risk reported by other groups might stem from the fact that all UC and CD patients were combined and analysed as a single group, whereas IBD subgroups might differ in terms of their risks for developing specific haematological malignancies. Heterogeneity in patient populations and differences in disease presentation may also have contributed to the discrepancies.[55] Moreover, most of the smaller studies are retrospective and often include primary intestinal lymphoproliferative disorders, the incidence of which is known to be increased in CD patients.[83]

Differences between IBD patients and the general population, as well as between CD and UC patients, also emerged from a meta-analysis of eight population-based cohort studies comprising nearly 17 000 patients. A trend toward higher risk for lymphoma [SIR 1.42, 95% CI, 0.95–2.12] was noted in CD patients, whereas those with UC were twice as likely as members of the general population to develop leukaemia [SIR 2.00, 95% CI, 1.31–3.06]. However, no significant excess risk was observed when UC and CD patients were analysed as a single group.[77] A large Finnish study that included 21 964 IBD patients and 236 129 person-years of follow-up found a slightly increased risk of Hodgkin lymphoma among UC patients [SIR 2.45, 95% CI, 1.06–4.81]. The likelihood of NHL was slightly increased in patients with CD [SIR 2.09, 95% CI, 1.00–3.48], but the risk was more pronounced in those over 75 years of age who had had CD for more than 3 years [SIR 7.22, 95% CI, 1.97–18.5].[84] A study that included 21 964 IBD patients and 236 129 person-years of follow-up found a slightly increased risk of Hodgkin lymphoma among UC patients [SIR 2.45, 95% CI, 1.06–4.81]. The likelihood of NHL was slightly increased in patients with CD [SIR 2.09, 95% CI 1.00–3.48], but the risk was more pronounced in those over 75 years of age who had had CD for more than 3 years [SIR 7.22, 95% CI, 1.97–18.5]. Similarly, the risk for lymphoma was increased only in CD patients [SIR 3.01, 95% CI, 1.21–6.19] in a Danish population-based study.[55] On the whole, these observations suggest that considering CD and UC as one group may be of limited use in estimating excess risk for haematological malignancies, given the organ-specific patterns of the two IBDs.

The increased risk of lymphoma in CD patients, as compared with the general population and with UC patients, also emerged from a Swedish population-based cohort study, which prospectively evaluated data recorded for 47 000 patients.[85] The SIRs [calculated using expected case data derived from the SEER database] for malignant lymphoma were 1.00 [95% CI, 0.8–1.3] and 1.3 [95% CI, 1.0–1.6] for UC and CD patients, respectively. These figures are consistent with population-based data from Canada, which show excess risk for lymphoma in CD patients [particularly males], with an incidence and rate ratio [IRR] of 3.63 [95% , 1.53–8.62%].[86] Finally, a meta-analysis of 34 studies on the cancer risk associated with CD found an increased risk of lymphoma (relative risk [RR] 1.47, 95% CI, 1.09–1.98, $p = 0.01$; 18 790 patients) but not of 'all haematopoietic' malignancies [RR 1.13, 95% CI, 0.83–1.53, $p = 0.45$; 9112 patients]. In 9462 immunosuppression-naïve CD patients, the risk of lymphoma was twice as high as that of the general population, suggesting that the excess risk is indeed related to CD itself.[87]

Although lymphoma rates seem to be lower in patients with UC, the latter are at increased risk for developing leukaemia. Using matched data from four population-based studies, Askling *et al.* found that leukaemia occurred significantly more often than expected

in UC patients [SIR 1.8].[85] Another population-based study analysed SEER-Medicare data to determine the risk of myeloid malignancies in patients over 67 years of age with autoimmune diseases. This risk of acute myeloid leukaemia was increased in patients with UC [OR 1.72, 95% CI, 1.28–2.31] but not those with CD.[88] These data were confirmed in another population-based study with an increased risk of chronic myelogenous leukaemia [OR 3.5, 95% CI, 1.1–11] and acute myeloid leukaemia [OR 3.8, 95% CI, 1.1–13].[89]

Haematological malignancies-related mortality in IBD patients, particularly those with UC, may also be higher than that of the general population. In 1986, a standardised mortality ratio [SMR] of 5.3 [95% CI, 1.7–12.3] was reported in a cohort of 1248 UC patients with acute myeloid leukaemia.[90] More recently, a nationwide study conducted on 2066 UC patients in Italy reported an SMR of 2.8 [95% CI, 1.0–6.1] in those with NHL or multiple myeloma.[91] A multi-national study conducted by the Porto Paediatric IBD Group found that cancer is the second cause of mortality in paediatric IBD patients,[92] but the specific impact of haematological malignancies was not analysed in detail.

3.2. IBD-specific risk factors

ECCO Statement 3B

Early disease onset, male gender, and age >65 are risk factors for haematological malignancies in IBD patients [EL 3]

Inflammation and immune activation are involved in lymphogenesis. The increased risk of haematological malignancies observed in patients with autoimmune diseases[93] suggests that these disorders may also play a role in IBD-associated tumourogenesis. Lymphoproliferative malignancies tend to affect organs where autoimmune responses occur.[81,93] Recent reports of increased rates of intestinal lymphatic malignancies at sites of active IBD highlight the role of chronic antigen stimulation in the development of HM.[83] Harewood *et al*. reported pancolitis in over 90% of their UC patients with haematological malignancies.[94] In addition, the incidence of these malignancies among IBD patients in centre/hospital-based series [who are more likely to have active/severe disease] is higher than that for IBD patients collected from other databases.[95]

The risk is increased by Epstein-Barr virus [EBV] infection,[96,97,98] and most IBD patients who develop haematological malignancies after initiating thiopurine therapy are EBV-positive.[81,99] Cases of EBV-related lymphoproliferative disorders have also been described in immunosuppressed IBD patients.[96,97,98]

In the largest case-control study conducted thus far on lymphoma and IBD [80 lymphoma patients and 159 matched controls], age [per decade] [OR 1.83, 95% CI, 1.37–2.43] and male sex [OR 4.05, 95% CI, 1.82–9.02] were strongly associated with the development of lymphoma [$p < 0.001$]. Current immunosuppressive therapy also increased the risk [OR 4.20, 95% CI, 1.35–13.11, $p = 0.01$]. Smoking appeared to exert a protective effect [OR 0.43, 95% CI, 0.20–0.92, $p = 0.03$], although this finding probably stemmed from a selection bias.[97] Male patients with early IBD onset are also at increased risk of haematological malignancies.[81,88,99,100]

Fibrostenotic/complicated CD and the early development of disease requiring surgery have been associated with *NOD2*, which plays an important role in bacterial autophagy in the intestine.[101] Homozygote variants of the *NOD2* gene predispose the carrier to CD, but they may also facilitate the development of haematological malignancies. Homozygotic carriers of the *NOD2* variant rs2066847 are reportedly at higher risk for developing NHL [OR 3.1, 95% CI, 1.1– 8.8][102] and marginal zone lymphoma [OR 8.82, 95% CI, 2.33–33].[103] Impaired lymphocyte apoptosis caused by unresponsiveness to increased tumour necrosis factor [TNF]-alpha signalling is thought to represent a pathogenetic link between leukaemia and IBD.[104] It is also important to note that patients with haematological malignancies often suffer from gastrointestinal disturbances, including IBD.[105]

3.3. Clinical Presentation and Diagnosis

ECCO Statement 3C

The possibility of haematological malignancies should be considered for any IBD patient with persistent haematological changes that are unresponsive to treatment, unexplained fever, adenopathy, or hepatosplenomegaly. A complete workup and haematological consultation are advised [EL 3]

Specific criteria for early diagnosis of haematological malignancies in IBD patients are lacking.[81,83,91,97,106,107] Common signs include anaemia, abnormal leucocyte counts, and abnormal morphology of peripheral blood leucocytes. Fever, weight loss, and night sweats are typical symptoms. Haematological malignancies should be suspected if an IBD patient develops unexplained headache, fatigue, acquired adenopathy, hepatosplenomegaly, or an unexplained biological inflammatory syndrome, with or without increase in blood lactate dehydrogenase levels.[81,83] These features are also associated with acute inflammatory flares, so differential diagnosis is important to avoid significant delays in the diagnosis of the haematological malignancy.[81,83,91,97,106,107] Persistent anaemia without signs or symptoms of active intestinal inflammation should also raise the suspicion of haematological malignancy.[55,81,91,94,108] A complete workup, assessment of the EBV load, and a haematology consultation may be justified.[81,83,91,106,107,109]

Intestinal and extra-intestinal malignancies may present with venous thromboembolism,[110] which is known to occur with increased frequency in IBD patients. Nevertheless, episodes of deep venous thromboembolism that occur without other clear predisposing factors or while the intestinal disease is in remission may be a marker of occult haematological malignancy and therefore warrant appropriate workup.

3.4. Prevention and risk reduction

There is no gold standard or clear algorithm for identifying IBD patients at risk of developing haematological malignancies. Given the increased risk observed in IBD patients receiving immunomodulators, combination of immunosuppressive therapies should be avoided in young men who are likely to require prolonged treatment. Early post-mononucleosis lymphoproliferation has been observed in EBV-seronegative patients under 35 years of age who were receiving thiopurines,[81] suggesting that combination treatment should be delayed in these patients or another drug [methotrexate] administered. Routine EBV testing may reduce the risks of treatment-related lymphoproliferative disease.[81]

IBD patients who develop lymphoma while on immunosuppressive drugs are often EBV-positive, suggesting a relation between the immunosuppression and lymphoma. The link might be due to cytotoxic effects on activated T cells and NK cells that diminish the anti-EBV immune response.[111]

Controlling active intestinal inflammation may also reduce the risk of inflammation-driven haematological malignancies.

3.5. Treatment and prognosis

The treatment and prognosis of haematological malignancies in IBD patients are similar to those in individuals without IBD. Haematopoietic

stem cell transplantation is an important therapy in patients of all ages. It can be performed with both autologous and allogeneic haematopoietic stem cells.[112] In CD patients with extra-nodal relapsing Hodgkin lymphoma, un-manipulated peripheral blood autologous transplants have reportedly led to complete treatment-free remission of both diseases.[113]

4. IBD AND SKIN MALIGNANCIES

4.1. Epidemiology

ECCO Statement 4A

It is unclear whether IBD is an independent risk factor for melanoma [EL2], but it increases the risk of non-melanoma skin cancers [NMSCs] [EL2]. Squamous-cell carcinoma [SCC] and basal-cell carcinoma [BCC] are the most common NMSCs occurring in IBD. Advanced age is associated with higher risk of NMSC [EL2]

Current estimates indicate that approximately one in five of the general population will develop skin malignancies [melanoma and/or NMSC] in the course of their lifetimes; 2% will develop melanomas, and 91.3% of these individuals will survive for 5 years after the diagnosis.[82,114]

Most population-based studies have found higher rates of NMSC in patients with IBD.[77,84,115,116,117] The risk seems to be higher in CD patients than in those with UC and it tends to increase with age.[115,116,118,119] Squamous-cell and basal-cell carcinomas [SCC and BCC, respectively] are the most common NMSCs diagnosed in IBD patients.[77,84,115,116,117] Long *et al.*[116] analysed data for 108 579 IBD patients and 434 233 random matched non-IBD controls using administrative data from the LifeLink Health Plan Claims Database. After adjusting for healthcare utilisation and comorbidities, the IBD group displayed a melanoma risk similar to that of the general population [adjusted HR 1.15, 95% CI, 0.97–1.36] but had a higher frequency of NMSCs [adjusted HR 1.34, 95% CI, 1.28–1.40]. The risk for NMSC was increased in both CD [adjusted HR 1.48, 95% CI, 1.39–1.58] and UC patients [adjusted HR 1.23, 95% CI, 1.16–1.31].[116]

Another large population-based study from Canada examined data on 9618 IBD patients and 91 378 matched controls. The risk of BCC was higher in the IBD group [BCC: HR 1.20, 95% CI, 1.03–1.40] and more pronounced in patients with CD [SIR 1.95, 95% CI, 1.50–2.50]. The CESAME group reported similar results, with IBD-related increases in the risk of NMSC [SIR 2.89, 95% CI, 1.98–4.08] but not of melanoma [SIR 0.64, 95% CI, 0.17–1.63] as compared with the general population.[121] Most studies concur that IBD *per se* does not increase the risk for melanoma,[55,77,84,86] but a very large sample size would be needed to detect a difference in an outcomes as rare as melanoma.

4.2. IBD-specific risk factors

Chronic inflammatory diseases increase the risk of carcinogenesis.[50,122] Smoking is a major risk factor for both CD and skin malignancies,[123] particularly SCC, and it may also increase the risk of NMSC in CD patients, although it has been associated with lower risk for acral melanoma.[123] Preliminary and experimental studies suggest that TNF-alpha signalling has a critical role in the protection of the skin against oxidative stress.[120] Consequently, the specific impact of IBD *per se* on the risk for developing skin malignancies is difficult to assess in studies including patients treated with TNF-alpha inhibitors. It is generally agreed that thiopurines increase the risk of NMSC, whereas biologicals increase the risk of melanoma, though indirect data debate this as well.[77,83,84,115,116,117,121] The latter risk is probably related to drug-induced increases in photosensitivity, and it increases with the duration of therapy.[116] The risk for skin cancers associated with thiopurines is related to 6-thioguanine DNA photoproducts, which result in selective sensitivity to UVA light.[124]

Sun exposure plays a pivotal role in most skin cancers.[125,126] The risk of melanoma is related to repeated burns developing with intermittent sun exposure,[125] whereas the risk for NMSC is related to cumulative sunlight exposure.[126]

A genetic predisposition toward skin cell alterations may underlie the development of some skin malignancies in IBD patients. Owens[127] suggested that certain genetic variants may be associated with predisposition to both IBD and keratin mutations associated with SCC, predisposing to both diseases. The genes encoding keratins 8 and 18 are located on chromosome 12q, whereas those for all other type I keratins are on chromosome 17. An association between K8 and IBD has been described.[128]

4.3. Diagnosis and treatment

The clinical presentation and diagnosis are similar to skin malignancies in patients without IBD, and no specific criteria are available for early diagnosis.[77,81,83,84,115,116,117]

Annual skin screening is important for IBD patients, particularly those taking immunosuppressants. The risk for NMSC increases with age, especially for IBD patients on thiopurines, so regular dermatological examination is particularly important in these older patients [> 50 years]. Patients should be taught to self-assess any visible skin alteration. The screening examination should not be limited to sun-exposed areas: it must include all areas, including those which the patient cannot readily see [ie scalp, back]. Ideally, screening should be performed by a dermatologist, but it can also be done by a general medical practitioner [GMP] or gastroenterologist.[81]

4.4. Prevention and risk reduction

IBD patients, especially those who are immunosuppressed, should avoid prolonged sun exposure and the use of sunbeds and always use adequate sunblock protection. IBD patients who have been successfully treated for skin malignancies are at risk for recurrence and need ongoing follow-up.[81] Combined immunosuppression should probably be avoided in these patients.

5. MALIGNANCIES RELATED TO IBD THERAPY

Patients with IBD are at risk for malignancy, attributable to chronic intestinal or biliary tract inflammation or to the carcinogenic effects of immunosuppressant drug therapy.[129,130] The latter mechanisms are sometimes interlinked, as in certain cases of intestinal primary lymphomas.[83] Cancers caused by immunosuppressant drugs represent a minority of the incident cancers observed in patients with IBD. The true risk of cancer related to IBD therapy has been investigated in analyses of large medico-administrative databases and data from the study of specifically-designed cohorts.

5.1 Overall excess risk of cancer

ECCO Statement 5A

Patients with IBD being treated with thiopurines are at increased risk for cancer [EL3]. There is currently no evidence that the overall risk of cancer is increased in patients being treated with anti-TNF agents alone [EL4]

Thiopurines

Thiopurine cytotoxicity is mediated by the incorporation of 6-thioguanine instead of guanine during DNA replication in target cells.

The error stimulates the mismatch repair system, but repair is incomplete and thus leads to cell death instead of recovery.[131] Thiopurines can promote cancer in a number of ways. Their ability to produce carcinogenic mutations of cell DNA is the putative mechanism for certain thiopurine-related skin cancers.[132] They also impair tumour-cell immunosurveillance [post-transplant state],[133] reduce the number and/or function of immune cells that prevent cells chronically infected by Epstein-Barr virus [EBV] from proliferating,[134] and facilitate the proliferation of cells with microsatellite instability, which evade the cytotoxic effects of thiopurines. The latter phenomenon is thought to be responsible for the excess risk of acute myeloid leukaemia caused by these drugs.[135,136]

Six studies conducted in IBD referral centres concluded, however, that long-term thiopurine use is not associated with any significant increase in the overall risk of cancer.[137,138,139,140,141,142] All these studies were underpowered to detect such an effect, but the issue has also been examined in three recent nationwide studies that were adequately powered.[143,144,145] The first, a nested case-control study conducted within the UK's General Practice Research Database, suggested that the risk of lymphoma, but not that of cancer in general, was significantly increased in current azathioprine users, but the design of the study did not allow identification of patients exposed to these drugs prior to entry into the study observational period.[143] In the other two studies, the risk associated with current thiopurine exposure of cancer in general was assessed by multivariate analysis with adjustments for age, sex, and IBD subtype. The excess risk in the CESAME cohort was 68%[144] and was 41% in the Danish study.[145] The difference between these figures is presumably related to the fact that BCCs were included among the cancers analysed in the former study but not in the latter. Past exposure to thiopurines was not associated with any excess risk of cancer in either of these studies.[144,145]

Anti-TNF agents

Tumour necrosis factor [TNF]-alpha is a cytokine produced by activated T cells and macrophages, which exerts necrotising effects on tumour cells in vitro. Inhibition of TNF-alpha has therefore been hypothesised to increase the overall cancer risk,[146] possibly in combination with impaired immunosurveillance of tumour cells. Since 1995, several studies have investigated the cancer risk associated with TNF-alpha antagonists used in IBD. The majority of patients treated with these agents in these studies also used [or had used] thiopurines, so it is difficult to attribute the findings to anti-TNF therapy alone. In addition, most of the studies were not adequately powered to demonstrate a mild anti-TNF induced increase in the overall risk of cancer. The results of the first meta-analysis that looked at this issue were published in 2008. Based on data from controlled trials of infliximab therapy for CD, the incidence of cancer [any type] was similar in patients treated with infliximab and those who received placebo.[148] Comparable findings have emerged from a more recent systematic review of pooled data from 22 randomised controlled trials, which found no significant difference between anti-TNF or placebo groups in terms of the frequency of malignancies diagnosed within the first year of treatment.[149] A pooled analysis of data from clinical trials of adalimumab in IBD was also published in 2014. It revealed no excess risk of cancer in general related to adalimumab monotherapy, but the risk was significantly increased in patients receiving adalimumab and immunomodulators.[150] Data from cohort and case-control studies also suggest that TNF-alpha antagonists alone do not significantly increase the overall cancer risk in IBD.[151,152,153,154,155,156] Finally, a recent adequately powered nationwide study in Denmark found no evidence that TNF-alpha antagonists increased the overall risk of cancer in IBD patients over a median follow-up of 3.7 years.[147] Within the confines allowed by these limitations, current evidence suggests that TNF inhibition alone does not significantly increase the overall long-term [up to 19 years] cancer risk of IBD patients.[147]

Methotrexate

No studies have focused specifically on the overall risk of cancer in IBD patients exposed to methotrexate monotherapy, largely because relatively few patients with IBD are currently treated with this drug alone.[157] Two studies have looked at the cancer risk in biological therapy-naive rheumatoid arthritis [RA] patients who were treated with methotrexate at doses similar to those used in IBD,[158,159] but neither was adequately powered to detect such risk.[160]

Calcineurin inhibitors [cyclosporin, tacrolimus]

Cyclosporin A and tacrolimus are used in a minority of patients with IBD and usually for short-to-intermediate periods of time. Consequently, reliable data on the risks of cancer associated with these drugs in IBD are lacking. Calcineurin inhibition is associated with an unequivocal excess risk of cancer in the post-transplant state.[133,161] The *de novo* malignancies that arise in organ transplant recipients vary with treatment duration: melanomas and lymphomas appearing first, followed by NMSCs and other solid tumours as therapy continues.[162] The overall excess risk of cancer attributable to the use of calcineurin inhibitors has not been well defined for populations being treated for specific autoimmune diseases.[163,164] This may be due to lower doses and shorter treatments episodes, since the malignancy risk associated with calcineurin inhibitors is dose and treatment duration dependent.[165]

5.2. Haematological malignancies

ECCO Statement 5B

In IBD patients treated with thiopurines, there is an excess risk of lymphoma [EL1], which can be reversed by drug withdrawal [EL3]. There is no evidence of an overall excess risk of lymphoma in IBD patients treated with anti-TNF agents alone [EL4]

Thiopurines with and without anti-TNF agents

In a recent meta-analysis[166] of eight population-based studies[143,145,157,167,168,169] and 10 referral studies,[78,109,138,139,141,170,171,172] the overall SIR for lymphoma considered in the population studies was significantly increased [5.7, 95% CI, 3.2 – 10.1] in IBD patients receiving thiopurines, but not in former users or patients who had never used these drugs. The absolute risks were globally multiplied by a factor of 2 to 3 in men compared with women, irrespective of age and drug exposure. Among thiopurine users, the highest absolute risks for lymphoma [any type] were found in patients over 50 [2.6/1000 patient-years] and in males under the age of 30 [estimated crude risk: 1-to-2/1000 patient-years]. The lowest absolute risks were observed in middle-aged IBD patients [0.3, 0.6, and 0.9/1000 patient-years for the 30–39, 40–49 and 50–59 year age classes, respectively]. In two studies that considered the potential impact of treatment duration, the SIR for lymphoma attributable to thiopurine exposure did not appear to increase substantially beyond the first year of treatment.

It is not clear whether concomitant anti-TNF treatment increases the risk of thiopurine-associated lymphoma, except for the hepatosplenic T-cell variety, as discussed below. In two nationwide cohort

studies,[157,167] the absolute risk of lymphoma in patients receiving TNF inhibitors and thiopurines was similar to that of patients treated with thiopurines alone. However, in both studies the proportions of patients on combined treatment were too low to allow detection of significant differences. Indirect evidence is given in the meta-analysis of Siegel *et al.*[173] The relative risk of NHL in CD patients being treated with TNF antagonists, many of whom were also receiving thiopurines, was not significantly greater than the pooled risk for lymphoma observed in patients receiving thiopurines alone.[173]

Thiopurines may also increase the long-term risk of acute myeloid leukaemia and severe myelodysplastic syndromes secondary to the proliferation of blood cells whose defective mismatch repair system allows them to escape the cytotoxic effect of these drugs.[136] In the CESAME cohort, the risk for these disorders in former thiopurine users [0.3/1000 patient-years] was significantly higher than that of never users.[135]

The 2009 meta-analysis by Siegel *et al.* found that combined therapy for CD with anti-TNF agents and thiopurines was associated with an increased risk of NHL, with SIRs of 3.2 vs general population [CI, 1.5–6.8] and 1.7 vs CD patients on immunomodulator therapy alone [CI, 0.5–7.1].[173] In 2011, however, an analysis of data in the Kaiser Permanente database found similarly increased incidence rates of lymphoma in IBD patients exposed to thiopurines alone and in those on thiopurines plus anti-TNF agents, suggesting indirectly that TNF-antagonist monotherapy is not associated with any real excess risk of lymphoma.[167] The results of some other studies [population-based,[153] single-centre,[155] case-control[151,152]] also suggest that anti-TNF therapy alone is not associated with an increase in the risk of lymphoma, leukaemia, or other haematological malignancies.[151,152,153,155] However, many of the patients treated with anti-TNF agents in these studies were also current or former thiopurine users. Finally, in the Danish cohort published in 2014, anti-TNF therapy was associated with an adjusted OR for cancers of haematopoietic and lymphoid tissues of 0.9 [CI, 0.4–1.9].[147]

Methotrexate

Thus far, no study has looked specifically at the overall excess risk of lymphoma in IBD patients exposed to methotrexate monotherapy. Patients with RA have a higher risk of lymphoma than the general population, but it is mainly attributed to the severe, chronic inflammation that characterises the disease rather than to its treatment.[93] A 3-year prospective nationwide study conducted in France found that the incidence of lymphoma in RA patients treated with methotrexate was similar to that expected in the general population.[174]

Calcineurin inhibitors

No data are available on the risk for haematological malignancies in IBD patients exposed to calcineurin inhibitors, but use of these drugs during the post-transplant state is known to carry an excess risk for NHL.[133,175] Compared with post-transplant lymphomas linked to thiopurine use, those related to calcineurin inhibitor therapy occur earlier, are more likely to involve the lymph nodes and small intestine and less likely to occur in the brain, and regress more frequently after reduction of immunosuppression.[133,176]

5.2.1. Thiopurine-related lymphomas

Clinicopathological characterisation of lymphomas diagnosed in patients with IBD has distinguished three types of lymphomas that are attributable to thiopurine use.[157,177] They include: a] post transplant-like lymphomas,[178] which can develop in any patient with chronic latent EBV infection and seropositivity—in other words, the majority of teenagers and almost all adults over the age of 30; b] post-mononucleosis lymphomas, which occur exclusively in males who convert from being EBV-seronegative[111,179]; and c] hepatosplenic T-cell lymphomas, which occur mainly in men under the age of 35 who receive thiopurines, alone or with anti-TNF agents, for more than 2 years.[180]

5.2.2. Post transplant-like lymphomas

ECCO Statement 5C

Post transplant-like lymphomas caused by the reactivation of chronic latent EBV infection cannot be prevented in adult IBD patients treated with thiopurines [EL 5]

Post transplant-like lymphomas account for almost all thiopurine-related lymphomas that develop in IBD adults over the age of 30.[157] They are EBV-related and caused primarily by reactivation of a chronic latent EBV infection.[134] In the early post-transplantation phase, the clinical onset of these lymphomas in hematopoietic stem cell recipients is usually preceded by a progressive rise in the systemic EBV viral load.[181] The latter parameter thus requires close monitoring in this patient population,[182] and various strategies for preventing or curing this early post-transplant lymphoproliferation have been developed.[183] These approaches have not been evaluated in patients with IBD, and their use should not currently be considered in clinical practice. Attempts should be made, however, to promptly detect EBV-associated lymphoproliferation in IBD patients. The presenting symptoms of these malignancies may be non-specific [unexplained fever or fatigue, isolated lymphadenopathy],[184] and they are sometimes accompanied by mild or overt biological signs of haemophagocytic lymphohistiocytosis.[185] When these signs/symptoms develop, measurement of the systemic EBV viral load should be part of the diagnostic workup, which should ideally be coordinated jointly with the haematology staff.

5.2.3. Post-mononucleosis lymphomas

ECCO Statement 5D

Given the risk of post-mononucleosis lymphoma, alternatives to thiopurine therapy should be considered in young male IBD patients who are EBV-seronegative [EL5]

These are typically fatal early post-mononucleosis lymphoproliferations that mimic X-linked lymphoproliferations.[111] They have been reported exclusively in young males who are EBV-seronegative [10% to 20% of all males under the age of 30] and have been exposed to thiopurines. In this subgroup of the CESAME study population, the absolute risk of this rare form of lymphoma was estimated at 3/1000 patient-years.[177] These lymphomas can be prevented by using anti-TNF agents or other immunosuppressants instead of thiopurines in the IBD subgroup known to be at risk.

5.2.4. Hepatosplenic T-cell lymphomas

ECCO Statement 5E

The risk of hepatosplenic T-cell lymphoma in young males being co-treated with thiopurines and anti-TNF agents can be reduced by limiting the duration of the combined treatment to 2 years [EL5]

Hepatosplenic T-cell lymphomas [HSTCLs] occur almost exclusively in males under the age of 35 who are exposed to thiopurines.[180] In this subgroup of the CESAME population, the absolute risk for

HSTCL was approximately 0.1/1000 patient-years in individuals treated with thiopurines alone and 0.3/1000 patient-years for those treated with thiopurines and anti-TNF agents. In the latter group, over 80% of the cases of HSTCL occur after the first 2 years of combination therapy.[180] The risk can therefore be reduced by limiting the duration of combination therapy in this population to 2 years, whenever possible.[177]

5.3. Skin cancers

5.3.1. Non melanoma skin cancer

ECCO Statement 5F

IBD patients who are receiving thiopurines are at increased risk for NMSC [EL3], but it is not clear whether the excess risk persists after thiopurine withdrawal [EL3]. It is also unclear whether the risk of NMSC is increased by anti-TNF monotherapy for IBD [EL3]

NMSCs, which include BCCs and SCCs, are more common than all other types of cancer. It is uncertain whether IBD is intrinsically associated with an increased risk of NMSC.[77,116,186]

Thiopurines

Post-transplant patients exposed to thiopurines are at increased risk for NMSC, with a predominance of SCCs[187] [whereas BCCs are more common in the general population]. Data suggesting an excess risk of NMSC in IBD patients being treated with thiopurines have emerged from several studies conducted in the past 5 years.[115,116,117,186] The suspicion has recently been confirmed in a meta-analysis, which found a pooled adjusted HR for NMSC in thiopurine-treated IBD patients of 2.3. There was a trend towards increased ratios in studies from referral centres. In studies detailing NMSC subtypes, BCCs were more frequent than SCCs, but the BCC:SCC ratio was nonetheless lower than that observed in the general population.[188] The carcinogenic effect of thiopurines has been attributed to increased UVA-induced DNA damage, increased production of reactive oxygen species in skin epithelial cells,[124] and possibly also direct induction of mutations of the PTCH gene[132]. One nationwide study found a significant excess risk of NMSC in IBD patients with past exposure to thiopurines, suggesting that the carcinogenic effect of these drugs might persist after withdrawal.[186] However, this issue requires further investigation since no persistent risk was noted in a nested case-control study in the Manitoba population[117] or in a recent analysis of data from the US Veterans Affairs database[189].

Anti-TNF agents

A meta-analysis showed that anti-TNF therapy for RA is associated with an increased risk of NMSC.[190] Data from a case-control study suggest that the risk for these cancers is also significantly increased in IBD patients exposed to these drugs.[115] However, this result was not confirmed in a study of data from a large medico-administrative database,[116] and a similar picture emerged from a recent meta-analysis of controlled trial data on adalimumab.[150] The latter study revealed a significant excess risk of NMSC in patients receiving combination therapy with anti-TNF agents and immunomodulators, but not in those treated with adalimumab alone. In light of these conflicting data, it is currently impossible to draw any meaningful conclusions on the risk of NMSC related to anti-TNF monotherapy.

Methotrexate

There are no specific data on the risk of NMSC related to methotrexate in IBD.

Calcineurin inhibitors

There are no specific data on the risk of NMSC related to calcineurin inhibitor therapy for IBD. However, these drugs are associated with an increased risk for NMSC in post-transplant settings[133] and in autoimmune diseases other than IBD.[164,191]

5.3.2. Melanoma

ECCO Statement 5G

In patients with IBD, the risk of cutaneous malignant melanoma is increased 1.32-fold in those treated with anti-TNF agents [EL2], but does not seem to be affected by thiopurine exposure [EL3]

The incidence of melanoma is increasing in developed countries. The results of a recent meta-analysis indicate that the risk of melanoma is mildly increased [37%] in IBD patients, independently of the use of biological therapy.[192]

Thiopurines

In two nationwide studies that assessed the impact of immunosuppressant therapy on skin cancer risk,[116,193] the incidence of melanoma in IBD patients with ongoing exposure to thiopurines was similar to that expected in the age- and gender-matched general population, before and after adjustment for concurrent anti-TNF treatment.

Anti-TNF agents

In a large nested case-control study performed with data from a large health insurance claims database, the use of TNF-alpha antagonists was independently associated with an increased melanoma risk in patients with IBD [OR 1.9, 95% CI, 1.1–3.3].[116] In the Danish cohort, the adjusted odds ratio was non-significant [OR 1.3, 95% CI, 0.6–2.7].[147] The most recent systematic reviews in the field of rheumatology indicate that the risk of melanoma in patients with RA exposed to anti-TNF agents is slightly higher than that of patients receiving conventional disease-modifying anti-rheumatic drugs [DMARDs].[158,190]

Methotrexate

No data are available for IBD, but in a small prospective study of patients with RA, those treated with methotrexate exhibited a significant 3-fold increase in the incidence of melanoma as compared with the general population. However, there was no comparator group of patients with RA who were not treated with methotrexate.[194]

Calcineurin inhibitors

There are no specific data on the risk of melanoma related to calcineurin inhibitors therapy for IBD but, in solid organ transplant recipients, there is an excess risk attributable to post-transplant use of immunosuppressants, including calcineurin inhibitors.[133,195] A recent review of over 35 years of dermatological experience found no significant risk of melanoma related to cyclosporin A [at the lower dosages used to treat autoimmune disorders].[196]

5.3.3. Prevention and detection of skin cancers related to immunosuppressant therapy

ECCO Statement 5H

As soon as IBD is diagnosed, patients should be instructed on the lifelong use of sun protection measures [EL5], and regular full-body skin examinations should also be considered [EL5]

Risk factors for skin cancers [Bowen's disease, BCC, SCC, and melanoma] include smoking, older age, male sex, fair skin type and eyes, red hair, cumulative sun exposure, a childhood history of painful or severe sunburns, outdoor occupation and family history of skin cancer, Caucasian race, geographical area, atypical moles, and several genetic factors [*p53* polymorphisms, variations in genes encoding enzymes involved in free-radical metabolism].[81,187] All should be taken into account when immunosuppressant therapy is being considered for a patient with IBD. Given the background excess risk of skin cancers associated with various immunosuppressants [see above], drugs other than anti-TNF agents and calcineurin inhibitors might be safer for use in melanoma survivors and patients at high risk for these tumours. Alternatives to thiopurines should also be considered in patients with histories of SCC, multiple BCCs, or premalignant skin lesions [eg solar keratosis].

In transplant recipients, lifelong sun protection and a yearly full-body skin examination are recommended. In patients with IBD, sun protections also recommended given the excess risk of melanoma related to IBD, and especially if certain medicines are utilised [thiopurines, calcineurin inhibitors, anti-TNF agents]. Skin surveillance by a dermatologist is reasonable; however, the patients to be examined and the frequency of examination must be defined. In the meantime, it is reasonable to provide surveillance at intervals as defined by a dermatologist on the basis of the patient's specific risk factors for skin cancer [genetic and environmental] and the expected impact of the immunosuppressant drugs being used.

5.4. Human papiloma virus (HPV)-related dysplasia and cancer of the uterine cervix

In female IBD patients, current smoking, age at diagnosis < 20 years, extensive disease, and exposure to > 10 prescriptions of oral contraceptives have been identified as risk factors for HPV-related cancer and dysplasia of the uterine cervix.[197,198]

Thiopurines and methotrexate

In organ transplant recipients, the use of thiopurines is associated with an increased risk of HPV-related cancer of the uterine cervix.[133] Studies that have addressed the independent role of immunomodulators in the occurrence of HPV-related cervical abnormalities in IBD patients have produced conflicting results. A mildly increased risk of cervical abnormalities in women with IBD exposed to corticosteroids and immunosuppressants was observed in a nested case-control study in a population-based cohort,[198] and similar findings [odds ratio: 1.5] emerged from a case-control study conducted in a tertiary care centre.[199] No significant excess risk was independently associated with thiopurine exposure in four other studies [a nested case-control study in a tertiary care population,[79] a population-based study that included only a limited number of patients exposed to thiopurines,[55] and two studies of large medico-administrative databases,[197,200] one of which also included chronic inflammatory diseases other than IBD[200]]. No data are available regarding the use of methotrexate alone in IBD.

Anti-TNF agents

Six studies addressed the impact of immunosuppressant therapy on the risk of cervical abnormalities in women with IBD,[55,79,197,198,199,201] but none were able to estimate the specific risk associated with anti-TNF therapy because the number of patients treated with TNF antagonists, alone or with thiopurines, was too small.

5.4.1. Prevention

HPV infection is considered to be the necessary aetiological agent for cervical cancer and intra-epithelial neoplasia. Preventive measures include HPV vaccination and regular Pap-test screening.[202] These measures will not be discussed here since they are extensively reviewed in the 2014 Second European Evidence-based Consensus on the prevention, diagnosis, and management of opportunistic infections in inflammatory bowel disease, published in 2014.[203]

5.5. Urinary tract cancers

Transplant recipients exposed to immunosuppressants, including thiopurines, are at increased risk for developing urinary tract cancers [including those of the bladder and kidney][133,204] and, if the cancer is successfully treated, there is a high risk of recurrence during thiopurine therapy.[205] To the best of our knowledge, the relative risk of urinary tract cancer in IBD patients associated with thiopurine exposure status has been assessed in only one study from Denmark. The adjusted risk was significantly increased [2.4-fold] in current users as compared with non-users, whereas the relative risk for former users [1.7] was not significantly different from that of non-users.[145]

6. Management of IBD patients with past history of malignancy

The lifetime risk of cancer is rising due to increasing life expectancy and the increased incidence associated with advanced age.[206] For patients who have apparently been cured of cancer, the risk of local recurrence or metastatic spread of the original neoplastic disease must always be considered. In addition, data from registries in the SEER Programme suggest that individuals who survive cancer are 14% more likely to develop a second malignancy than those in the general population, and the development of a first cancer during childhood increases the lifelong risk of a second malignancy 6-fold.[207]

For gastroenterologists caring for patients with IBD, managing the disease in patients with a history of cancer or those who develop neoplastic disease for the first time can be challenging. Oncologists are often uncertain how to deal with IBD in their cancer patients. The best course involves joint management by specialists from both fields with case-by-case decision making based on the characteristics and expected evolution of the index cancer, the probable impact of IBD therapy on cancer evolution, and the intrinsic severity of the IBD.

In this context, three major questions require urgent attention and will be analysed in the pages that follow. First, what effects [if any] do the medical therapies prescribed for IBD have on the progression or recurrence of cancer? Second, how should medical therapy for IBD be managed for patients with a history of cancer, newly diagnosed cancer, or recurrent neoplastic disease? Third, what effects [if any] do the treatments used for cancer have on the course of concomitant IBD?

6.1. The effects of IBD drug therapy on the risks of malignancy progression or recurrence

ECCO Statement 6A

In IBD patients with a history of cancer, the risk of developing new or recurrent cancer is increased 2-fold relative to that of IBD patients who have never had cancer, regardless of whether or not they receive immunosuppressants [EL 2]

ECCO Statement 6B

Physicians must be aware of the potential impact of immunosuppressants on cancers and on the risk of developing a second malignancy in cancer survivors [EL 3]

The development or recurrence of cancer in an IBD patient may be unrelated to IBD or its treatment. Alternatively, it may be related to the chronic intestinal inflammation that characterises IBD and/or be influenced by the immunosuppressant drugs used to treat IBD [Section 6]. Consensus guidelines have not been issued on the management of IBD patients with a history of cancer, although several expert opinions on this issue have been published recently.[129,208,209] Clinical data on the potentially detrimental effects of immunosuppressant therapy come mainly from observational studies of patients with rheumatological disease or solid organ transplant recipients. The thiopurines are known to have both carcinogenic and anticancer properties[210] and, until the 1990s, they were widely administered to organ transplant recipients. Renal transplant recipients with pre-transplant diagnoses of cancer have been shown to be at increased risk for cancer occurrence or recurrence compared with patients without previous cancer history.[205,211] The risk of recurrence exceeded 20% for patients who had had melanomas or NMSCs and was highest [54%] in the 2 years following completion of chemotherapy, decreasing progressively thereafter [to 33% at 2–5 years and 13% after 5 years]. As shown in Table 1, the relative risk of cancer recurrence in the renal transplant recipients studied by Penn *et al.*[205] varied with the type of cancer. More recently, melanoma patients receiving immunosuppressants at the time of diagnosis for various reasons have been found to have similar relapse rates but significantly higher cancer-related mortality rates [owing to more aggressive disease] than controls who had never received these drugs [42% vs 23%, respectively, $p = 0.01$].[212] Furthermore, in some patients diagnosed with malignancies while using thiopurines, withdrawal of the latter drugs has reportedly been followed by spontaneous resolution of the cancer.[213,214]

Table 1. Risk of cancer recurrence [adapted from Penn I, 1993.[205]]

Risk	Organ/type of cancer
Low [< 10%]	Incidental asymptomatic renal tumour
	Lymphomas
	Testicle
	Uterine cervix
	Thyroid
Intermediate [11-25%]	Uterine body
	Colon
	Prostate
	Breast
High [> 25%]	Bladder
	Sarcoma
	Melanoma and non-melanoma skin cancer
	Myeloma
	Symptomatic renal carcinoma

The CESAME study group recently reported the results of a prospective assessment of the risk of new or recurrent cancer in patients with IBD and pre-existing cancer who were or were not receiving immunosuppressants.[215] The original cohort consisted of 17047 patients who were enrolled between May 2004 and June 2005 and followed up through December 2007; 405 patients had a cancer diagnosis before study entry. Incident cancer rates during follow-up were 21.1/1000 patient-years [PY] and 6.1/1000 PY in patients with or without a history of cancer, respectively. The former subgroup had a multivariate-adjusted HR for incident cancer of 1.9 [95% CI, 1.2–3.0, $p = 0.003$] as compared with patients without cancer diagnoses. Within the group with prior malignancy, the potential impact of immunosuppressant therapy on the cancers was investigated by survival analysis and a nested case-control study. The 93 [23%] cancer patients who received immunosuppressants had appreciably higher rates of new and recurrent neoplastic disease [23.1/1000 PY and 3.9/1000 PY, respectively] than the 312 [77%] without prior cancer diagnoses [13.2/1000 PY and 6.0/1000 PY, respectively]. However, these differences were not statistically significant, even when analysis was restricted to patients with recently diagnosed cancer [< 2 years before study entry] or when those with NMSCs were excluded. The authors concluded that whereas prior cancer increases the risk of new/recurrent incident cancer in IBD patients, immunosuppressant therapy has no real impact on this risk.

These findings should be considered with caution, however, because the subset of patients with previous cancer in this cohort was relatively small, and the data obtained are clearly in contrast with those emerging from more extensive experience in organ transplant recipients. In addition, 77 [83%] of the 93 patients with prior cancers who were receiving immunosuppressants at study entry were on thiopurines. It is possible that these drugs were used with greater caution in patients with histories of lymphoma or NMSCs [generally considered the most common immunosuppressant-promoted cancers], and this might have biased the results. The number of patients on anti-TNF agents [$n = 7$] or methotrexate [$n = 10$] at study entry were far too small to allow any conclusions on the risk associated with these immunosuppressant drugs.

The risk of new or recurrent cancer during anti-TNF therapy has been investigated in a few small, generally underpowered studies involving patients with RA. Using data from the British Society for Rheumatology Biologics registry, Dixon *et al.* analysed the risk of cancer recurrence in 294 RA patients with prior cancer.[216] The incident malignancy rate was 25.3/1000 PY in the 177 receiving anti-TNF therapy vs 38.3/1000 PY in the 117 on conventional DMARDs [OR for the former approach 0.58, 95% CI, 0.23–1.43]. It is important to note, however, that the anti-TNF group had more remote history of malignancy and a higher rate of incident malignancies among patients whose previous tumours were melanomas [3/17, 18% vs 0/10 in the DMARD group]. In another study, this one based on data from the German biologicals registry RABBITT,[217] prior malignancy was reported by 122 of the 5120 RA patients making up the total cohort: at study entry, 58 were receiving anti-TNF therapy and the other 55 were on DMARDs. The crude incidence rates of new or recurrent malignancies in these two groups were not significantly different [45.5/1000 PY vs 31.4/1000 PY, $p = 0.6$], but the numbers in both arms are small. A similar picture emerged from an observational study of Swedish RA patients with first primary cancers, which revealed no significant differences in cancer stage at diagnosis, prognosis, or cancer-related mortality between the 314 who, at the

time of cancer diagnosis, were receiving or had received anti-TNF therapy and 586 matched biologicals-naïve controls.[218]

Data on anti-TNF therapy in IBD patients with histories of cancer come exclusively from small case series and have thus far been presented only in abstract form.[219,220] The largest of these cohorts is the one studied by the Groupe d'Etudes Thérapeutiques des Affections Inflammatoires Digestives [GETAID]: it comprised 79 IBD patients with recent [< 5 year] history of cancer who were exposed to TNF antagonists. Cancer-free survival rates at 1, 2, and 5 years were 96%, 86%, and 72%, respectively.[221] More recently, data from seven academic medical centres in the USA have been presented with 255 IBD patients with previous history of cancer and subsequent exposure to anti-TNF, thiopurines or methotrexate [antimetabolite arm] or without subsequent immunosuppression exposure [control arm].[222] Patients in the control group were more likely to have later stage primary cancers compared with the other study arms [$p = 0.0003$]. Incident cancer rate per 100 person-years for patients exposed to anti-TNF was: 2.6 with 795 person-years of follow-up; 14.8 with 122 person-years of follow-up for patients in the antimetabolite arm; and 8.52 with 422 person-years of follow-up for controls. There was a significant difference in time to subsequent cancer between groups, with patients exposed to anti-TNF being less likely to develop a new or recurrent cancer compared with controls [$p = 0.0110$].

In contrast, a predictive statistical model based on the Adverse Event Reporting System of the US Food and Drug Administration [currently described only in abstract form] estimated that the risk of a second cancer increased 11-fold after 9.5 years of anti-TNF therapy.[223] Anti-TNF therapy should definitely be avoided in patients with a history of melanoma [see section 5.3.2].

ECCO Statement 6C

Preliminary data on immune-mediated inflammatory diseases and IBD demonstrate no obvious excess risk of developing a second [new or recurrent] cancer while being treated with anti-TNF therapy [EL 4]

6.2. Managing IBD therapy in patients with cancer or a history of cancer

ECCO Statement 6D

All cases of cancer in IBD should be managed with multidisciplinary support. In general, thiopurines, calcineurin inhibitors, and anti-TNF agents should be stopped at least until cancer therapy is completed [EL 5]

There is a dearth of solid data on this issue. Therefore, for patients with IBD who develop cancer or have had cancer in the past, treatment decisions require close collaboration between gastroenterologists and oncologists, and they must be based on a thorough knowledge of the individual case, including the activity of the IBD, concomitant therapy, patient age, and the type and stage of the cancer. The development of a second neoplasm in cancer survivors is one of the most serious and lethal complications of cancer therapy. These tumours account for about 18% of the incident cancers in the USA and are thus more common than first cancers of the breast, lung, and prostate.[207] Second cancers are not always caused solely by cytotoxic treatment of the first tumour: they may also reflect the persistence of risk factors [eg lifestyle, host factors, genetic predisposition]. Interest is growing in the effects of behavioural and environmental factors. More work is needed to define the roles played by certain factors [eg diet, physical activity, weight management, sun exposure]. However, the influence of excessive alcohol consumption and tobacco use have been much more thoroughly explored, and the findings can and should be used to influence clinical practice.[224]

ECCO Statement 6E

Thiopurines should be withdrawn in IBD patients who develop squamous-cell carcinomas, aggressive forms of basal-cell carcinomas, and multiple synchronous or sequential lesions. In patients with sporadic non-aggressive basal cell carcinoma, thiopurines can be continued if no satisfactory therapeutic alternatives are available [EL 5]

Given the mechanism of action of immunosuppressant agents and epidemiological data extrapolated from the organ-transplant literature, it is generally agreed that—except in certain cases, which will be discussed below--immunosuppressants should be stopped until the cancer is controlled. Oncologists prefer to stop thiopurines when cancer is diagnosed, in part because of their presumed ability to aggravate the bone marrow suppression produced by cytotoxic chemotherapy. For patients with incident carcinoma that has been successfully treated endoscopically or surgically and carries no risk of recurrence [eg sporadic colon polyp], there is no need to withdraw immunosuppressant therapy. Greater caution is needed, however, for in situ dysplastic lesions of the uterine cervix caused by HPV.[81] After the cervical lesion has been successfully treated, thiopurines can be resumed in these cases with close gynaecological monitoring. Prompt discontinuation is indicated if the dysplasia recurs.

NMSCs are very common, and stopping thiopurines does not eliminate the risk of their recurrence [as it does with lymphomas].[81,225] Therefore, the risks and benefits of continuing these drugs should be weighed carefully in light of the severity of the IBD and the characteristics of the neoplastic lesions [eg number, disfiguring potential]. More specifically, in the presence of more aggressive BCC histotypes [sclerosing, metatypic] and/or cancers that are not amenable to surgery due to the risk of disfiguration,[186,226] possible alternatives to thiopurine therapy [eg methotrexate or anti-TNF agents] should be discussed with the patient and used with close dermatological follow-up.

A review of the literature clearly shows that the concomitant presence of IBD and cancer often leads oncologists and/or gastroenterologists to alter their standard treatment plans. For this reason, close cooperation between specialists in the two fields is highly recommended. An observational study conducted in Denmark found that breast cancer patients with CD received radiotherapy less frequently and had higher mortality rates than their non-IBD counterparts,[227] and retrospective cohort studies in several countries[219,220,228] indicate cancer diagnosis in IBD patients is often followed by marked reduction [but rarely complete withdrawal] of immunosuppressant therapy and more frequent recourse to surgery and use of steroids.

ECCO Statement 6F

In patients with active IBD and a history of malignancy, 5-aminosalicylates, nutritional therapies, and local corticosteroids can be safely used [EL 3]. In more severe flares that do not respond to these treatments, the use of anti-TNF, methotrexate, short-term systemic corticosteroids, and/or surgery should be considered on a case-by-case basis [EL 5]

In general, 5-aminosalicylates [5-ASA], nutritional therapies, and local corticosteroids [eg budesonide] can be safely used in patients with active IBD and a history of malignancy. For more severe flares that do not respond to these treatments, anti-TNF agents, methotrexate, a short course of systemic corticosteroids, and/or surgery should be considered on a case-by-case basis. Regardless of the expected duration of the immunosuppressant drug withdrawal period, the choice of an immunosuppressant drug that can be initiated or resumed after cancer therapy has been completed must be based on the type of cancer.

ECCO Statement 6G

Based on data in transplant recipients, physicians should consider delaying the resumption of immunosuppressant therapy for IBD in patients being treated for cancer, because of the risk of recurrent neoplastic disease, for 2 years following the completion of cancer treatment [EL 3]. The delay can be extended to 5 years if the cancer is associated with an intermediate or high risk of recurrence [EL 3]

The decision to resume immunosuppressant therapy in a patient who has had cancer should be carefully evaluated, case by case, in a multidisciplinary fashion. Particular emphasis should be placed on the individual risk of cancer recurrence [Table 1], the potential risk posed by each immunosuppressant drug in the setting of the specific cancer history [Table 2], and most importantly the amount of time that has passed since completion of cancer therapy.

The effects of TNF and anti-TNF agents on malignancy are unpredictable.[129] TNF can trigger apoptosis through the extrinsic pathway by activating caspases 8 and 10,[229] and this raises the concern that TNF inhibition might facilitate tumour recurrence, growth, and/or metastasis. TNF may also favour neoplastic-cell survival and proliferation by activating signalling through the nuclear factor κB pathway,[230] and inhibition of this effect would thus have positive repercussions. Several groups have investigated the potential effects on advanced cancer of anti-TNF therapy, alone or combined with chemotherapy.[231,232,233,234] The use or addition of anti-TNF therapy has not been shown to produce any clear benefits thus far, but neither has it been shown to accelerate cancer progression or worsen overall survival. Infliximab has been successfully used to treat severe colitis induced by ipilimumab, a monoclonal antibody used to treat melanoma, which is directed against cytotoxic T cell-associated antigen 4,[235,236,237,238,239] and it was not found to adversely affect the clinical outcome of the cancer. However, these experiences should be evaluated with caution, since all the studies were conducted on relatively small patient populations and the findings are based exclusively on short-term follow-up [given the generally poor prognoses]. Furthermore, Lees *et al.* have described a case of non small-cell lung carcinoma which developed during adalimumab therapy for IBD and regressed spontaneously after the anti-TNF therapy was withdrawn.[240]

The use of systemic corticosteroids in this setting is controversial, although these drugs are frequently used by oncologists. In theory, they can enhance tumour-cell resistance to apoptosis and decrease immune surveillance in general.[241] Data from population-based studies suggest that prolonged corticosteroid exposure is associated with an excess risk for lymphoma, NMSC, and breast cancer.[242,243,244] Additional data are thus needed for proper evaluation of the safety of corticosteroids in the management of active IBD in patients with cancer.

In summary, during the first 2 years after completion of anticancer therapy, the first-line therapy for IBD should consist of 5-ASA, local steroid therapy, nutritional therapy, antibiotics, and possibly surgery. If these approaches are ineffective, therapy with immunosuppressants can be considered. It is important to recall, however, that for patients who have had cancer, immunosuppressant therapy is best avoided unless absolutely necessary [Table 2]. Experiences with organ transplant recipients [Table 1] indicate that, when the cancer is associated with an intermediate or high risk of recurrence, it is wiser to wait 5 years before starting immunosuppressants. The recommended durations of both waiting periods are empirical. These data apply mainly to thiopurine therapy, whereas evidence for anti-TNF agents and especially vedolizumab is much more limited. Resumption of immunosuppressant therapy should be preceded by in-depth discussion of risks and alternatives with the oncologist and the patient, and it should be initiated with a cautious step-up approach, starting with monotherapy [preferably methotrexate when appropriate] [Table 2]. Anecdotal data, however, suggest that cautious resumption of thiopurines or anti-TNF therapy can be attempted as early as 3 months after cessation of chemotherapy.[209] Data from small, relatively underpowered series indicate that, in patients with metastatic disease, cancer progression is not dramatically accelerated by anti-TNF agents. When disabling IBD occurs in this setting, improving the patient's quality of life is probably the top priority, which outweighs the above-mentioned contraindications to anti-TNF therapy.

6.3. Influence of chemotherapy on IBD

ECCO Statement 6H

Limited evidence indicates that IBD can be aggravated by hormonal therapy, chemotherapy-induced mucositis, or immune system-activating therapy, alone or in combination [EL 4]. In patients with active disease at cancer diagnosis, remission can be induced and maintained thanks to the immunosuppressant effects of cancer treatment [despite withdrawal of immunosuppressant therapy for IBD] [EL 4]. The impact of targeted anticancer therapy on IBD remains unknown [EL 5]

Table 2. Immunosuppressant therapies to use or avoid in IBD patients with a history of cancer [adapted from Beaugerie L 2014[215]]

Type of cancer	Avoid	Use with caution	Can be used
Lymphoma	Thiopurines	Anti-TNF, methotrexate, steroids	
Acute myeloid leukaemia and severe myelodysplastic disorders	Thiopurines	Anti-TNF	Methotrexate, steroids
Melanoma	Anti-TNF	Thiopurines, steroids	Methotrexate
Non-melanoma skin cancer	Thiopurines	Anti-TNF, steroids	Methotrexate
Urinary tract cancer	Thiopurines	Anti-TNF	Methotrexate, steroids
Other tumours		Thiopurines, anti-TNF	Methotrexate, steroids

TNF, tumour necrosis factor.

Limited data are available on the impact of cancer treatment on the course of IBD. Axelrad *et al*. followed 84 IBD patients who had just completed chemotherapy for extra-intestinal solid tumours.[222] Of the 69 patients whose IBD was inactive at baseline, 12 [17.4%] experienced flare-ups during 5 years of follow-up. The strongest predictor of disease flare was the use of hormone therapy, alone or with cytotoxic chemotherapy. In contrast, 10 [67%] of the 15 patients with active disease at baseline achieved clinical remissions in the months following completion of their cancer treatments. Only one of these 10 patients had received hormonal monotherapy as opposed to all 5 of those who did not achieve remission. In a French case-control study,[228] the median percentage of years with active disease was not different before and after cancer diagnosis [27% vs 19%], and it was not significantly different from that of IBD patients without a cancer history. However, several groups have reported the development or exacerbation of colitis after docetaxel therapy for breast cancer,[245] ipilimumab for melanoma,[235,246,247] sunitinib and sorafinib for renal cell carcinoma,[248] and rituximab.[249,250,251] In contrast, imatinib therapy for GISTs has occasionally been reported to exert beneficial effects on UC[252] and CD.[253]

Conflict of Interest

ECCO has diligently maintained a disclosure policy of potential conflicts of interests [CoI]. The conflict of interest declaration is based on a form used by the International Committee of Medical Journal Editors [ICMJE]. The CoI statement is not only stored at the ECCO Office and the editorial office of *JCC* but also open to public scrutiny on the ECCO website [https://www.ecco-ibd.eu/about-ecco/ecco-disclosures.html] providing a comprehensive overview of potential conflicts of interest of authors.

Acknowledgments

Contributors: VA and RE acted as convenors of the Consensus; VA, LB, LE, and RE contributed equally to this work. Members of the working parties:

We are particularly grateful to Mrs Marian Kent and Dr Marcus Harbord for careful and extensive revision of the manuscript for English style and consistency, and to Dr Loes Nissen for extensive evaluation of the accuracy of references.

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