

ECCO GUIDELINE: Inflammatory Bowel Disease and Malignancies

Presented by Dr.Khafaf , fellowship of Taleghani hospital

ECCO Guideline/Consensus Paper

European Evidence-based Consensus: Inflammatory Bowel Disease and Malignancies

**Vito Annese,^a Laurent Beaugerie,^b Laurence Egan,^c Livia Biancone,^d
Claus Bolling,^e Christian Brandts,^f Daan Dierickx,^g Reinhard Dummer,^h
Gionata Fiorino,ⁱ Jean Marc Gomet,^j Peter Higgins,^k
Konstantinos H Katsanos,^l Loes Nissen,^m Gianluca Pellino,ⁿ
Gerhard Rogler,^o Franco Scaldaferri,^p Edyta Szymanska,^q Rami Eliakim;
on behalf of ECCO**

^aUniversity Hospital Careggi, Department of Gastroenterology, Florence, Italy ^bDepartment of Gastroenterology, AP-HP Hôpital Saint-Antoine, and UPMC Univ Paris 06, Paris, France ^cPharmacology and Therapeutics, School of Medicine, National University of Ireland, Galway, Ireland ^dUniversity Tor Vergata of Rome, GI Unit, Department of Systems Medicine, Rome, Italy ^eAgaplesion Markus Krankenhaus, Medizinische Klinik I, Frankfurt am Main, Germany ^fDepartment of Medicine, Hematology/Oncology, Goethe University, Frankfurt am Main, Germany ^gDepartment of Haematology, University Hospital Leuven, Leuven, Belgium ^hDepartment of Dermatology, University Zürich, Zürich, Switzerland ⁱGastroenterology Department, Humanitas Research Hospital, Rozzano, Italy ^jService d'hépatogastroentérologie, Hôpital Saint-Louis, Paris, France ^kUniversity of Michigan, Department of Internal Medicine, Ann Arbor, USA ^lDepartment of Gastroenterology, Medical School, University of Ioannina, Ioannina, Greece ^mDepartment of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands ⁿSecond University of Naples, Unit of Colorectal Surgery, Department of Medical, Surgical, Neurological, Metabolic and Ageing Sciences, Naples, Italy ^oKlinik für Gastroenterologie und Hepatologie, UniversitätsSpital Zürich, Zürich, Switzerland ^pUniversità Cattolica del Sacro Cuore, Department of Internal Medicine, Gastroenterology Division, Roma, Italy ^qDepartment of Pediatrics, Nutrition and Metabolic Disorders, Children's Memorial Health Institute, Warsaw, Poland ^rDepartment of Gastroenterology and Hepatology, Sheba Medical Center & Sackler School of Medicine, Israel




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.



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



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;

D: Management of IBD patients with a history of malignancy.

IBD and Solid Tumours

Colorectal cancer

■ ECCO Statement 2A

Patients with IBD are at increased risk of developing colorectal cancer [CRC] which, in the case of ulcerative colitis [UC], varies with

- 1.The extent and duration of the disease,
- 2.Family history of CRC,
- 3.Presence/absence of primary sclerosing cholangitis [PSC] .

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.



Two recent meta-analyses of cohort studies have clarified the increased risk of CRC in patients with IBD.

For those with Crohn's disease 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 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 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




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. Endoscopic surveillance and treatment tailored to the individual patient's risk factor profile are recommended.

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 and US guidelines, stress the importance of endoscopy for the surveillance and treatment of lesions in patients with IBD.


Long-term follow-up data show that proctocolectomy with removal of the entire colon reduces the risk of CRC, but other reports, including case series, suggest that cancer and/or de novo polyps can still develop in the anal transition zone [ATZ]



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


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



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

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%],

The frequency of unknown-stage tumours [10%] resembled that of non IBD-related CRC patients.



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.**


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

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



Anal adenocarcinomas arising from perianal fistulas are a **rare** complication in CD.

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.




- **ECCO Statement 2E**

Chronic active perianal fistulising disease may be associated with advanced cancer stage at the time of diagnosis .

Regular follow-up is recommended for CD patients with chronic persisting perianal fistulas, especially when symptoms change [eg new-onset pain] .

The optimum frequency and modalities of surveillance are not known.



Fistula-related cancer is associated with non-specific signs and symptoms. This complicates and often delays diagnosis, thereby worsening the prognosis.

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.

In patients with long-standing perianal CD, a change in symptoms should always raise the suspicion of cancer.


Regular surveillance for ano-rectal carcinoma should be requested for all patients with perianal CD. It should include routine biopsy of any suspicious lesion.

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.

Conservative proctocolectomy with IPAA has become the intervention of choice for severe UC requiring surgery.



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%])



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].


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 IPAA [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.**



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].

In patients with high-risk features or who have been operated on for dysplasia or cancer, pouch surveillance may be conducted.

If dysplasia is noted early after surgery, careful annual pouch surveillance is needed, with multiple biopsies of the ileal reservoir and the anorectal mucosa below the ileo-anal anastomosis.



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.



Carcinoid tumours

Carcinoids are rare in IBD, 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.



Small bowel cancers

- **ECCO Statement 2G**

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



About 2% of all gastrointestinal cancers affect the small bowel, and a high percentage of these are adenocarcinomas.

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.

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.



- **ECCO Statement 2H**

Prolonged duration of **stricturing** disease may be associated with the development of small-bowel cancer in patients with CD.

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,
Environmental factors



In almost all case series reported thus far, small-bowel adenocarcinomas tended to develop in inflamed intestinal segments.

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.


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.

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 or as a short segment of stenosis mimicking benign fibrostenosis.



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%.

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.



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.




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.


Data from the Swedish Hospital Discharge Register and the Swedish Cancer Registry indicate a strong association between UC and extrahepatic bile duct cancer.



Danish population-based studies have revealed that extrahepatic cholangiocarcinoma is increased in patients with UC as well as those with CD.

However, in patients who do not have PSC, there is no evidence linking cholangiocarcinoma to IBD.

The effects of IBDs on the natural history of PSC and its complications [including cholangiocarcinoma] have not been well characterised



Survival after a diagnosis of cholangiocarcinoma is **poor**, even in patients without IBD.



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. 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, a GIST of the rectum in a patient with UC in remission, and a *DOG1*-expressing GIST found in a surgical specimen, 20 cm from the adenocarcinoma, from a patient with long-standing UC.


There is no convincing evidence of an association between IBD and GIST.

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.

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** , and UC is associated with an increased risk of **liver-biliary tract** cancers and **leukaemia**.



A meta-analysis of population-based cohort studies comprising a total of 17052 patients with IBD revealed no increased risk of cancer at any site in the IBD population.


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 [particularly the **stomach**], the **lungs**, and **the urinary bladder**, as well as for squamous-cell skin cancer.



Fistulising forms of CD also seem to be associated with an increased risk of extra-intestinal cancer.

The meta analysis also found patients with UC to be significantly more likely to develop liver–biliary cancer and leukaemia, although their risk of developing lung cancer is reduced.

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.



Tumours of the **cervix, ovary, pancreas, breast, kidney,** and **brain** have not been found to be associated with IBD.


IBD AND HAEMATOLOGICAL MALIGNANCIES

Patients with IBD are at increased risk for intestinal cancers, 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.

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.




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%.

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.



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.

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




A large Finnish study that included 21964 IBD patients and 236129 person-years of follow-up found a slightly increased risk of Hodgkin lymphoma among UC patients.

The likelihood of **NHL** was slightly increased in patients with **CD**, but the risk was more pronounced in those **over 75 years** of age who had had CD for **more than 3 years**.

A study that included 21964 IBD patients and 236129 person-years of follow-up found a slightly increased risk of **Hodgkin lymphoma among UC patients**.



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.



Although lymphoma rates seem to be lower in patients with UC, the latter are at increased risk for developing leukaemia.

Four population-based studies, Askling *et al.* found that leukaemia occurred significantly more often than expected in UC patients.

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 but not those with CD.



Haematological malignancies-related mortality in IBD patients, particularly those with UC, may also be higher than that of the general population.

A multi-national study conducted by the Porto Paediatric IBD Group found that **cancer is the second cause of mortality in paediatric IBD patients**, but the specific impact of haematological malignancies was not analysed in detail.



IBD-specific risk factors

- **ECCO Statement 3B**

Early disease onset, male gender, and age >65 are risk factors for haematological malignancies in IBD patients.

Inflammation and immune activation are involved in lymphogenesis. The increased risk of haematological malignancies observed in patients with autoimmune diseases suggests that these disorders may also play a role in IBD-associated tumourogenesis.


Lymphoproliferative malignancies tend to affect organs where autoimmune responses occur.



Harewood *et al.* reported **pancolitis** in over 90% of their UC patients with **haematological malignancies**.

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.

The risk is increased by Epstein-Barr virus [EBV] infection, and most IBD patients who develop haematological malignancies after initiating thiopurine therapy are EBV-positive.




In the largest case-control study conducted thus far on lymphoma and IBD [lymphoma patients and 159 matched controls]:

Age [per decade] and **male sex** were strongly associated with the development of lymphoma.

Smoking appeared to exert a protective effect , although this finding probably stemmed from a selection bias.

Male patients with early IBD onset are also at increased risk of haematological malignancies.



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.

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.

It is also important to note that patients with haematological malignancies often suffer from gastrointestinal disturbances, including IBD.

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.

Specific criteria for early diagnosis of haematological malignancies in IBD patients are lacking.



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.



Persistent **anemia** without signs or symptoms of active intestinal inflammation should also raise the suspicion of haematological malignancy.

A complete workup, **assessment of the EBV load**, and a haematology consultation may be justified.

Intestinal and extra-intestinal malignancies may present with venous thromboembolism, 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

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, 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

IBD patients who develop lymphoma while on immunosuppressive drugs are often EBV-positive, suggesting a **relation between the immunosuppression and lymphoma**

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



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.

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**.



IBD AND SKIN MALIGNANCIES

Epidemiology

ECCO Statement 4A

It is unclear whether IBD is an independent risk factor for melanoma, but it **increases the risk of non-melanoma skin cancers [NMSCs]** .

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**.



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.

Most population-based studies have found **higher rates** of **NMSC** in patients with IBD.


The risk seems to be **higher in CD** patients than in those with UC and it tends to increase with age.



Squamous-cell and basal-cell carcinomas [SCC and BCC, respectively] are the most common NMSCs diagnosed in IBD Patients.

After adjusting for healthcare utilisation and comorbidities, the IBD group displayed a melanoma risk similar to that of the general population but had a higher frequency of NMSCs .

The risk for NMSC was increased in both CD and UC patients.



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 and **more pronounced in patients with CD.**

IBD-specific risk factors

Chronic inflammatory diseases increase the risk of carcinogenesis.

Smoking is a major risk factor for both CD and skin malignancies, 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.

Preliminary and experimental studies suggest that TNF-alpha signalling has a critical role in the protection of the skin against oxidative stress



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 TNFalpha 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.

A genetic predisposition toward skin cell alterations may underlie the development of some skin malignancies in IBD patients.

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.

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**.

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.

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. **Combined immunosuppression** should probably be **avoided** in these patients.



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

Cancers caused by immunosuppressant drugs represent a minority of the incident cancers observed in patients with IBD



Overall excess risk of cancer

ECCO Statement 5A

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

Thiopurines

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

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.

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

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.


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.

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.



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.

Data from cohort and case-control studies also suggest that TNF-alpha antagonists alone do not significantly increase the overall cancer risk in IBD.



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.

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.


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.

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.**



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.

Haematological malignancies

In IBD patients treated with thiopurines, there is an excess risk of lymphoma [EL1], which can be reversed by drug withdrawal

There is no evidence of an overall excess risk of lymphoma in IBD patients treated with anti-TNF agents alone.

It is not clear whether concomitant anti-TNF treatment increases the risk of thiopurine-associated lymphoma, except for the hepatosplenic T-cell variety.



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.

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


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.

Post transplant-like lymphomas account for almost all thiopurine related lymphomas that develop in IBD adults over the age of 30.



They **are EBV-related** and caused primarily by reactivation of a chronic latent EBV infection.

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



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**], and they are sometimes accompanied by mild or overt biological signs of haemophagocytic lymphohistiocytosis.

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.

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.

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.



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.

Hepatosplenic T-cell lymphomas [HSTCLs] occur almost exclusively in males under the age of 35 who are exposed to thiopurines.



Skin cancers

Non melanoma skin cancer

- **ECCO Statement 5F**

IBD patients who are receiving thiopurines are at increased risk for NMSC, but it is not clear whether the excess risk persists after thiopurine withdrawal.

It is also unclear whether the risk of NMSC is increased by anti-TNF monotherapy for IBD.

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 , but does not seem to be affected by thiopurine exposure .

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 , and regular full-body skin examinations should also be considered.

Urinary tract cancers

Recipients exposed to immunosuppressants, including thiopurines, are at increased risk for developing urinary tract cancers [including those of the bladder and kidney]

If the cancer is successfully treated, there is a high risk of recurrence during thiopurine therapy



Human papilloma 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

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.

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.

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.**




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.

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?


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.

- **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.



The development or recurrence of cancer in an IBD patient may be unrelated to IBD or its treatment.

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.

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




- **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.

- **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



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 data knowledge:

- 1:the activity of the IBD,
- 2:concomitant therapy,
- 3:patient age,
- 4: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



- **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.



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.



- **ECCO Statement 6F**

In patients with **active IBD** and a history of malignancy, **5-aminosalicylates, nutritional therapies, and local corticosteroids** can be safely used .

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



- **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 .**

The delay can be extended to 5 years if the cancer is associated with an intermediate or high risk of recurrence



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 .

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] . The impact of targeted anticancer therapy on IBD remains unknown.

Table 2. Immunosuppressant therapies to use or avoid in IBD patients with a history of cancer [adapted from Beaugerie L 2014²¹⁵]

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.

The **strongest predictor** of disease flare was the use of **hormone therapy**, alone or with cytotoxic chemotherapy.



























