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Cancer Prevention in Patients with Inflammatory Bowel Disease

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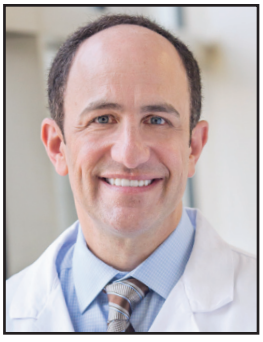

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INRODUCTION

Inflammatory bowel disease (IBD) is associated with increased rates of malignancies; some are disease-related (like colorectal cancer) and some are primarily associated with therapy exposures. Although there may be an overlap between disease- and therapy-related cancers, the general strategy for prevention of cancer in patients with IBD lies in understanding the risk factors for these malignancies, educating patients about the recommended screening and surveillance practices, and incorporating general screening recommendations into routine IBD care. An important limitation to our understanding of the effectiveness of our intervention and prevention strategies is the lack of studies assessing mortality benefit, but in part also a reflection of the low mortality in our IBD population. In practice, it is imperative to weigh the risks of cancer or other treatment-related complications in the context of disease progression as a result of lack of or ineffective treatment for IBD when tailoring a management plan for each patient. This review article summarizes the major cancers of concern in patients with IBD and presents a summary of the known risks and prevention strategies. (Table 1)

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Colorectal Cancer and Dysplasia in IBD

It is well described that dysplasia and adenocarcinoma of the colon and rectum (CRC) are associated with longstanding colitis, and this is a feared complication of the disease. The longest standing database and registry for understanding this risk is at the St. Mark's Hospital in the United Kingdom.[1] In their updated publication of their long-standing surveillance registry of over 40

years, they have demonstrated that the incident rate of CRC appears to have decreased over the years, and that when it is being diagnosed, it is being detected in earlier stages. The reasons for this have been postulated and may represent effective therapy controlling inflammation, effective surgery removing patients who are at highest risk from the analyses, or possibly the effect of secondary prevention strategies of performing screening and surveillance colonoscopies and therefore identifying dysplasia or early stage cancers. Therefore, whether it is that secondary prevention is effective by endoscopic interventions, or primary prevention by therapies controlling inflammation, or maybe there is even chemo-protective properties of some of the treatments we use to control IBD, the role of careful and effective surveillance remains paramount.

Table 1. Cancers Associated with Inflammatory Bowel Disease and Recommended Prevention Strategies

CANCER	WHO IS AT RISK	RECOMMENDED PREVENTION STRATEGIES
Adenocarcinoma of the Colon and Rectum	• Chronic colitis of extent greater than rectosigmoid • PSC • Cumulative inflammatory burden • Family history of CRC • Men more than women • Prior history of colonic neoplasia	Control of inflammation Screening and surveillance colonoscopies to identify dysplasia and early-stage cancers
Skin Cancer	• Thiopurine therapy, other immunosuppressants (increased risk for NMSC) • Crohn's disease, anti-TNF therapies (increased risk for melanoma)	Sun avoidance and sun protection Annual skin exams by a dermatologist
Lymphoma	• Crohn's disease • Thiopurine therapy • Possibly anti-TNF therapy (debated) • EBV infection while on thiopurines	Consider avoiding thiopurines in patients who are EBV negative (those under age 21) Consider treatment adjustment in patients who have been receiving thiopurines and are older than 60-65 years old
Cervical Cancer	• HPV infection • Immune suppression	HPV vaccination in people from 9-45 years of age Annual Pap smears
Anal Cancer	• HPV infection • Anal strictures • Receptive anal intercourse • Perianal fistulas	HPV vaccination in people from 9-45 years of age Careful perianal and digital rectal examination Anal Pap smears, exam under anesthesia, biopsies of suspicious areas

Abbreviations: CRC: colorectal cancer; PSC: primary sclerosing cholangitis; NMSC: non-melanoma skin cancer; EBV: Epstein Barr Virus; HPV: human papilloma virus; TNF: tumor necrosis factor.

Effective surveillance for colon cancer and dysplasia in patients with IBD should be guided based on the individual patient's risk factors. These risk factors can be broken down into those that are (potentially) modifiable and those that are deemed immutable. Potentially modifiable risk factors include increased cumulative inflammatory activity, backwash ileitis (as a potential marker of more extensive colitis) and the presence of post inflammatory pseudopolyps (although this has been recently challenged by some newer data to suggest it may not be a risk).[2] Prior dysplasia is a risk for future and subsequent complications and having a mass or a stricture is certainly associated with a higher risk of neoplasia.[3] These are all markers of prior high-degrees of inflammation and more extensive disease. The risks that are unchangeable include male sex, longer disease duration, greater extent of colonic involvement, a family history of CRC (independent of a family history of IBD), primary sclerosing cholangitis and a younger age of diagnosis (independent of duration of disease).[3–7] Therefore, providers should develop an individualized screening and surveillance strategy for CRC in each patient.

Inflammation has been identified as an independent risk factor for neoplasia in ulcerative colitis. The St. Mark's group (London) demonstrated that cumulative inflammation is associated with colonic neoplasia in UC and developed an arithmetic model that accounts for the amount of inflammation over time based on the number of colonoscopies the patient had to demonstrate that cumulative inflammation correlates with the risk of colorectal neoplasia.[8] This has been subsequently validated in a smaller cohort of patients at the University of Chicago.[9] The implication of these findings are that by effectively treating inflammation over time this will reduce the overall risk for cancer and dysplasia in colitis. These findings further support ongoing "treating to a target" of colitis with the hope that better control of the inflammation reduces the long-term neoplasia risk.

We have come to appreciate that in the non-colitis population CRC is being diagnosed at younger ages. This has also been seen in the IBD population and led to changes in the ulcerative colitis guidelines for cancer prevention to begin 8 years from diagnosis.[10] The strategy of earlier surveillance aims to both identify more neoplasia and at an earlier stage. In fact, a model by Lutgens and colleagues suggests that by starting surveillance

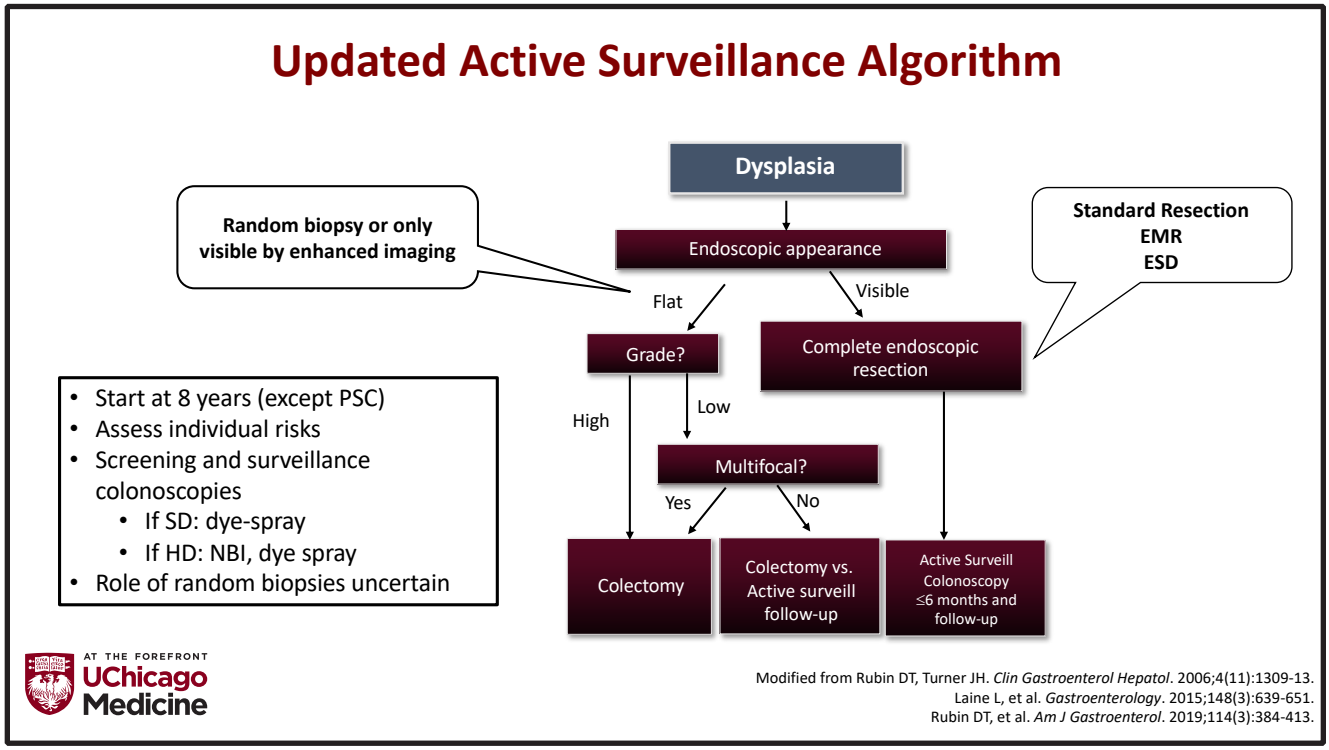

Figure 1. Algorithm For Endoscopic Dysplasia Surveillance In Inflammatory Bowel Disease

at 8 years from the diagnosis of colitis, one would identify additional 6% of cases.[11] An important exception should be made in patients who have IBD with concomitant PSC, in whom the risk of CRC is very high; their exams should start at the time of diagnosis of the PSC and performed annually thereafter.

Technology has advanced our visualization as well as our endoscopic techniques for prevention and management of neoplasia and its progression. A meta-analysis by Feuerstein and colleagues evaluated dye-based chromoendoscopy compared with white light endoscopy in the detection of colorectal neoplasia. In their analysis of randomized clinical trials in which patients were randomized to chromoendoscopy or white light endoscopy, the data demonstrated improved detection by chromoendoscopy compared with standard-definition white light (RR 2.12 [1.15-3.91]). However, when chromoendoscopy was compared with high-definition white light, there was no statistically significant difference between the two (RR 1.36 [0.84-2.18]). In their non-randomized trials analysis, which were primarily retrospective studies, a definite benefit of dye spray chromoendoscopy when compared with both standard-definition and high-definition was shown.[12] This shows the added benefit of chromoendoscopy in screening and surveilling high-risk patients to standard-definition white light endoscopy. However, in patients whose exam is performed using a high-definition endoscope, dye-based chromoendoscopy is not likely to be of significant added benefit. Given the added benefit of dye-based chromoendoscopy as well as the limitation to its use, it has been of great interest to understand virtual compared with dye-based chromoendoscopy. An additional meta-analysis by El-Dallal and colleagues suggests that, in fact, narrow band imaging may be as good as dye spray if you perform the colonoscopic exam with a high definition colonoscope in a well prepped colon and in a patient who is in remission.[13]

Another strategy to improve neoplasia detection has been performance of non-targeted biopsies in different segments of the colon. Prior guidelines had suggested we should be performing sequential sampling of the mucosa with random 4-quadrant biopsies every 10 cm. However, although there may be some benefit to this non-targeted biopsy approach, a study by the French GETAID group demonstrated this to be a low yield practice.[14] Of 1000 colonoscopies, 140 neoplastic sites were identified, 80% by targeted biopsies and only 20% by random biopsies. While the yield of random biopsies was low at 0.2% per biopsy, the yield in patients with history of neoplasia was significantly higher at 12.8%. Additional patient characteristics associated with detection of neoplasia by non-targeted biopsies included having tubular appearing colon (which is a surrogate of prior severe inflammation) and history of PSC. Another study by our group assessed the question whether we miss neoplasia using high-definition white light exams, and demonstrated that advanced neoplastic lesions are not missed.[15] In summary, non-targeted biopsies may be of highest yield in the higher risk patient population or in endoscopic exams limited to only standard-definition white light.

Endoscopic management of dysplasia remains a challenge, but the approach is guided by whether the dysplasia is visible and discrete (See Figure 1). If the lesion is visible and endoscopically discrete such that it can be removed in its entirety, active surveillance and follow-up may be considered. On the other hand, if the dysplasia is either flat and is not easily discrete for endoscopic resection, or if it is multifocal or if it harbors high grade dysplasia or cancer, this would necessitate a surgical consultation and a discussion of whether a proctocolectomy or, a segmental resection with ongoing active surveillance would be more appropriate.[16]

Skin Cancer and IBD

Patients with IBD have an increased risk of non-melanoma skin cancer with a risk of 912 per 100,000 compared to those who do not have IBD whose risk is 623 per 100,000. It has also been shown that IBD patients may have an increased risk of melanoma, with the risk being 57.1 per 100,000 compared to the non-IBD population of 44 per 100,000. Melanoma also appears to be more prevalent among IBD patients. A meta-analysis by Singh and colleagues demonstrated an odds ratio of 1.37 (95% CI, 1.10-1.70) for the development of melanoma in the IBD population compared with

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non-IBD patients.[17] Additionally, patients with Crohn's disease appear to have a higher risk for developing melanoma than those with ulcerative colitis.[18]

It is well described that thiopurines are associated with an increased risk of non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma).[18–20] This risk increases with longer exposure to the therapies and there is little to no risk that has been reported in patients on the therapy for less than a year.[18] It is important to note that the increased risk of non-melanoma skin cancer with prolonged use of thiopurines does not appear to go away when you stop the therapy. Therefore these patients require close observation.[21] A retrospective cohort study and nested case control study using a large claims database by Long and colleagues assessed the overall risk of skin cancer as it related to therapies in IBD patients as a whole, as well as the individual risks associated with Crohn's disease and ulcerative colitis. The overall risk of melanoma was increased in IBD patients who are receiving biologics, which at the time was only anti-TNFs, and the risk of non-melanoma skin cancer was increased in patients who were receiving thiopurines. When Crohn's disease was isolated, the melanoma risk remained with biologic therapy and the non-melanoma skin cancer risk remained with thiopurines, but in ulcerative colitis the melanoma risk was not statistically significant while the non-melanoma skin cancer risk continued with thiopurines.[18] In summary, anti-TNF therapy appears to carry an increased risk of melanoma that is distinct from the independent increased risk of melanoma seen in Crohn's disease. Newer therapies such as the non-selective Janus kinase inhibitor tofacitinib and the anti-cytokine monoclonal antibody ustekinumab have had small numbers of non-melanoma skin cancer reported from their pivotal trials and long-term extension follow-up, but there has not appeared to be a significant signal when compared with patients who received placebo. Further study and ongoing vigilance for any immune therapies used in patients with IBD is advised.

When considering these risks and choosing therapies in clinical practice, it is also important to keep in mind other known risk factors for skin cancer such as fair skin, prior or current high amounts of ultraviolet radiation exposure, as well as personal or family history of skin cancer. Primary prevention and protection by sun avoidance and sun protection with sunscreens are recommended, although there are not studies demonstrating deceased rates of skin cancer or mortality in the IBD population. Furthermore, it is recommended that patients with IBD should see a dermatologist for annual skin cancer screening, should be educated about the need and importance of screening, and that this should be on providers' list for health maintenance discussions.

Lymphoma Risk in IBD

Crohn's disease alone appears to confer a small but significantly increased risk for non-Hodgkin lymphoma. Population-based studies in Denmark and in Canada have demonstrated an increased risk of lymphoma among Crohn's patients, with men having a higher risk than women, independent of medical therapy exposure.[22,23] Separately, thiopurine therapy appears to confer a 4-6-fold increased risk of lymphoma, compared with the risk in those who are not receiving thiopurines. In the CESAME inception cohort of IBD patients from France and Belgium of over 19,000 patients, the rates of lymphoma in patients with previous thiopurine use (0.20 per 1000 [95% CI, 0.02-0.72]) compared to no history of thiopurine use (0.26 per 1000 [95% CI, 0.10-0.57]) were similar, but in patients with current thiopurine use the rate was higher (0.90 per 1000 [95% CI, 0.5-1.49]). Importantly, as demonstrated in CESAME as well as other studies including a nationwide cohort study of 36,891 VA patients, the risk of lymphoma increases with increased duration of therapy, but importantly, the risk also returns to baseline non-exposed rates after discontinuation of the thiopurine.[24–27]

Whether anti-TNF therapy increases the risk of lymphoma has been a subject of great concern and debate. In a large study by Lemaitre and colleagues using a French nationwide insurance database of 189,289 patients, in which 23,069 were anti-TNF and thiopurine naïve, 50,405 were receiving thiopurine monotherapy, 30,294 receiving anti-TNF monotherapy, and 14,229 receiving combination thiopurine and anti-TNF therapy, the incidence of

IBD Checklist for Monitoring & Prevention™

CORNERSTONES HEALTH

Name: _____

MR#: _____ D.O.B.: _____

Vaccine Preventable Illnesses	Dates Completed
Varicella (Chicken Pox – Live Vaccine) Check Varicella Zoster Virus IgG. If negative consider vaccination. Can be considered in patients on "low dose" immunosuppression (prednisone ≤20mg/day, MTX, 6-MP, azathioprine), but not on biologics. Can administer > 4 weeks prior to starting biologics.	
Herpes Zoster (Shingles – Non-Live Recombinant Vaccine (RZV)) Recommended for patients taking low-dose immunosuppressive therapy and persons anticipating immunosuppression. Recommendations regarding the use of RZV in patients already on higher does immunosuppression have not yet been made by the CDC.	
MMR (Live Vaccine) Contraindicated in immunosuppressed patients and those planning to start immunosuppressants within 4 weeks.	
Diphtheria and Pertussis (Non-Live Vaccine) Vaccinate with Tdap if not given within last ten years, or if Td ≥ 2 years.	
Influenza (Non-Live Vaccine) One dose annually to all patients during flu season. Avoid intranasal live vaccine in immunosuppressed patients.	
HPV (Non-Live Vaccine) Related to cervical and anal cancer. Three doses approved for females and males ages 9-26 (regardless of immunosuppression).	
Hepatitis A (Non-Live Vaccine) Safe to administer to at-risk patients regardless of immunosuppression.	
Hepatitis B (Non-Live Vaccine) Check hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody before initiating anti-TNF therapy. If non-immune consider vaccination series with non-live hepatitis B vaccine, 3 doses. If active viral infection or core Ab positive, check PCR and withhold anti-TNF therapy until active infection is excluded or treated appropriately.	
Meningococcal Meningitis (Non-Live Vaccine) Vaccinate at-risk patients (college students, military recruits) if not previously vaccinated regardless of immunosuppression.	
Pneumococcal Pneumonia (Non-Live Vaccine) If not immunosuppressed: Consider vaccination with PSV23 (Pneumovax®). If immunosuppressed: Vaccinate with PCV13 (Prevnar®) followed by PSV23 (Pneumovax®) ≥ 8 weeks later followed by PSV23 booster after 5 years.	

Bone Health	Dates Completed
Vitamin D 25-OH Level Serial monitoring of vitamin D levels, supplement if deficient.	
Bone Density Assessment Assess bone density if the following conditions are present: **1.** Steroid use > 3 months; **2.** Inactive disease but past chronic steroid use of at least 1 year within the past 2 years; **3.** Inactive disease but maternal history of osteoporosis; **4.** Inactive disease but malnourished or very thin; **5.** Inactive disease but amenorrheic; **6.** Post menopausal women; regardless of disease status.	
Prescription of Calcium & Vitamin D Co-prescription of calcium and vitamin D tablets for all patients with each course of oral corticosteroids and if vitamin D deficient or insufficient.	

Therapy Related Testing	Dates Completed
Mesalamines Annual renal function monitoring.	
Corticosteroids – See Bone Health Document plan and use of corticosteroid-sparing therapy. Consider ophthalmology exam.	
Thiopurines TPMT, CBC, and liver function prior to initiating therapy. Routine CBC and liver function monitoring while on therapy.	
Methotrexate CBC, liver, and renal function prior to initiating therapy. Routine CBC, liver, and renal function monitoring while on therapy.	
Anti-TNFα/Anti-IL-12/23 Tuberculosis (TB) screening prior to initiating therapy with PPD skin testing and/or QuantiFeron-TB Gold assay. Chest X-Ray if high-risk and/or indeterminate PPD or QuantiFeron-TB Gold. Perform annual TB risk assessment and consider re-testing if high risk (including travel to endemic region). See Hepatitis B vaccine. CBC, liver, and renal function prior to initiating therapy and periodic monitoring while on therapy.	
Natalizumab Enrollment in TOUCH program. Check JCV antibody and treat if negative. Retest JCV antibody q 4-6 months prior to initiating therapy. Routine CBC and liver function monitoring while on therapy.	
Vedolizumab CBC, liver, and renal function prior to initiating therapy and periodic monitoring while on therapy.	
Tofacitinib CBC, liver, fasting lipid profile, and tuberculosis (TB) screening with PPD skin testing and/or QuantiFeron-TB Gold assay prior to initiating therapy. Chest X-Ray if highrisk and/or indeterminate PPD or QuantiFeron-TB Gold. Perform annual TB risk assessment and consider re-testing if high risk (including travel to endemic region). Routine CBC and liver function monitoring while on therapy. Fasting lipid profile 4-8 weeks after initiating therapy.Screen for risks of thrombosis at https://www.mdcalc.com/caprini-score-venous-thromboembolism-2005. Consider alternative therapies if high risk. History of prior varicella (chicken pox) infection, varicella vaccination or seropositive for varicella: vaccination against HZV should be strongly considered when treating with tofacitinib. The recombinant non-live vaccine is preferred, and necessary if the patient is already on immunosuppresive therapy.	

Cancer Prevention	Dates Completed
Colon Cancer If ulcerative colitis beyond the rectum or Crohn's is present in at least 1/3 of the colon, perform annual or biannual surveillance colonoscopies for neoplasia detection after 8 years of disease. High definition scopes preferred; augmented imaging (NBI or dye-spray) and targeted biopsies recommended.	
Cervical Cancer Annual PAP smears if immunocompromised.	
Skin Cancer Annual visual exam of skin by dermatologist if immunocompromised and recommend sun exposure precautions.	

Miscellaneous	Dates Completed
Assessment of anatomic location and activity	
Smoking Cessation Discuss at every visit.	
Nutritional Assessment B12 if ileal disease or resection, iron panel. Assess for risk of malnutrition.	
Behavioral Health Screen and address mental health co-morbidities.	

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2. *https://www.cdc.gov/vaccines/vpd/shingles/hcp/index.html, accessed Feb 9, 2020.*

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Figure 2. Checklist for Health Maintenance in Inflammatory Bowel Disease Patients
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lymphoma was 0.54 per 1000 person-years (95% CI, 0.41-0.67) in patients receiving thiopurine monotherapy and 0.41 per 1000 person-years (95% CI, 0.27-0.55) in patients receiving anti-TNF monotherapy. Combination therapy was associated with an even higher incidence of 0.95 per 1000 person-years (95% CI, 0.45-1.45). A multivariable Cox model comparing treatment-exposed patients with non-exposed patients identified an adjusted hazard ratio (aHR) of 2.6 (95% CI, 1.96-3.44) for those receiving thiopurines alone, aHR of 2.4 (95% CI, 1.60-3.64) for those receiving anti-TNF alone and aHR of 6.11 (95% CI, 3.46-10.8) for those who were receiving combination therapy.[28] Interestingly, in a multivariable analysis controlling for disease type, Crohn's disease treated with anti-TNF monotherapy was associated with a persistent elevated risk (aHR 2.75 [95% CI, 1.74-4.33]), but ulcerative colitis did not have a statistically significant elevated risk (aHR 1.73 [95% CI 0.74-4.01]), which raises the possibility that the increased aHR for lymphoma for those receiving anti-TNF monotherapy was driven by the Crohn's disease itself. This is further supported by numerous additional studies which did not identify increased risk of lymphoma with anti-TNF monotherapy, including a study by Deepak and colleagues, who looked specifically at TNF inhibitors with and without thiopurines, and in which thiopurines drove the predominant risk of lymphomas and hepatosplenic T-cell lymphomas; TNF inhibitors as monotherapy did not have an increased risk.[29] The newer classes of biological therapies such as the anti-integrin therapy vedolizumab and the anti-cytokine therapy ustekinumab do not appear to have a risk of lymphoma associated with their use.

Hepatosplenic T-cell lymphoma (HSTCL) is a rare lymphoma that is nearly uniformly fatal. It is associated with thiopurine therapy in the IBD population with a risk of <1:20,000 person-years. HSTCL occurs almost exclusively in men < 35 years of age who are receiving thiopurines or combination therapy of anti-TNF and thiopurine, but no cases have been reported of HSTCL with anti-TNF monotherapy or anti-TNF therapy in combination with methotrexate.[30] The concern over HSTCL has led to a change in practice in the US by pediatricians, and avoidance of thiopurine therapy in young male patients.

It is important to note that one of the other risk factors for the development of lymphoma appears to be Epstein-Barr virus (EBV) infection. EBV was first discovered due to its association with the pathogenesis of Burkitt lymphoma, but later found to be linked to a range of lymphoproliferative disorders. Patients who were infected with EBV at the time of thiopurine therapy appear to have the greatest risk of developing a difficult lymphoproliferative disease. Therefore, although this is not currently recommended for all patients, in male patients younger than 21 years old, and in whom thiopurine therapy is being considered, we advise serologic assessment for prior EBV exposure and avoidance of thiopurines in those with negative serology.

In summary, the risk of lymphoma is increased in Crohn's disease, higher in male patients, and primarily driven by thiopurine therapy. The risk with anti-TNF therapy remains inconclusively demonstrated but should be discussed in the context of the disease activity when considering treatment options for IBD. The evolving practical understanding of the timing of thiopurines and lymphoma in patients with IBD suggests that the therapy may be used for short-term to optimize anti-TNF therapy and subsequently withdrawn if the patient is stable, achieves deep remission, and has sufficient serum concentrations of drug, with no subsequent accrued risk of lymphoma.

Cervical Dysplasia

HPV, primarily 16 and 18, is responsible for all cases of cervical cancer and it is therefore recommended that people from 9-45 years of age receive vaccination against HPV. It is important also to understand that cervical dysplasia precedes cervical cancer, with a long lead time of 10-30 years, therefore, when primary prevention is not possible, adequate screening is likely to successfully prevent cervical cancer or death from cervical cancer.[31] IBD, among other immune-mediated disorders that are treated with or result in immune suppression, such as rheumatoid arthritis (RA), HIV, and organ transplantation, have been shown to have a higher rate of progression to cervical dysplasia because of the decreased ability to clear HPV. This is particularly true in patients with IBD who are smokers and those receiving

immunosuppressants.[32] There have been no specific studies that have confirmed the increased risk of cervical cancer in patients with IBD, but multiple studies have identified an increased risk of cervical dysplasia in the IBD population compared with those without IBD.[32-38] Therefore, in addition to vaccination against HPV, it is recommended to perform annual Pap smears in women with IBD who are sexually active and receiving immune modifying therapies.

Anal Cancer

There is higher prevalence of anal cancer among patients with IBD, and this has been linked to HPV infections, severe perianal inflammation from Crohn's disease, receptive anal intercourse, and the immunosuppression associated with HIV or organ transplantation.[39,40] It has been proposed that patients with perianal Crohn's should be screened for anal cancer, which may be performed by anal Pap smear and under anesthesia. The diagnosis of anal cancer in patients with IBD is often delayed due to a misdiagnosis of benign anal stricture.[39] Therefore, a careful digital rectal exam in a patient with perianal Crohn's disease and the finding of exuberant perianal tissue or nonhealing ulcers in this region should raise a concern for possible anal cancer and prompt biopsy of the area.[40]

CONCLUSIONS

In summary, cancer prevention in patients with IBD requires an understanding of the risks of cancer in this patient population, education of our colleagues and patients about those risks, an understanding of screening, surveillance, and prevention strategies that are currently recommended, and implementation into routine practice in a systematic way. The use of checklists (Figure 2) by both providers and patients and routine "healthy visit" appointments may improve adherence to these strategies. This is especially important when patients are in remission and when they may not know of the need for routine follow-up and these strategies for prevention and good health. ■

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