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REVIEW ARTICLE

Surveillance for colorectal cancer and chemoprevention in ulcerative and Crohn's colitis: The need for clinical strategies to increase effectiveness

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Abstract

This review considers why current strategies for surveillance and the prevention of colorectal cancer as a long-term complication are ineffective. The role of endoscopists, pathologists, and patients are investigated. Colorectal cancer is linked to poor compliance with therapy, and attention may be better directed at improving adherence to treatment than strengthening current surveillance programs. Clearly, 5-ASA compounds, particularly mesalazine, are the most appropriate agents to choose, but there may also be a place for the daily intake of folic acid. Currently, the evidence in support of ursodeoxycholic acid is mixed, and it cannot be recommended, in general, to patients for the prophylaxis of colorectal cancer risk. An alternative approach through better concordance with medications is considered. The situation in Crohn's colitis is less clear. Although the risk of colorectal cancer mirrors that in ulcerative colitis, there are no published community-based studies that exclusively assess the effects of surveillance on the early detection of cancer, and the benefits of 5-ASA compounds in treatment seem less certain than in ulcerative colitis. In addition, there have been no assessments of the effects of any medications on cancer risk in Crohn's disease.

Introduction

Cancer has been recognized as a potential complication of ulcerative colitis since the description of such a case by Burrill Crohn in the 1920s.[1] However, there have always been discussions regarding the magnitude of the risk and the role of surveillance in its early detection. Although it is difficult to establish when the concept of monitoring patients with ulcerative colitis for early cancer first became "good practice," gastroenterologists used radiology in the form of barium enemas in the 1960s and 1970s to assess the risk in patients with extensive and long-standing disease. In this review, the magnitude of the risk, the role and effectiveness of surveillance, and the place of medication in the prevention of colorectal cancer will be considered. These questions are particularly relevant because it is clear that, when colorectal cancer is detected during surveillance colonoscopy in ulcerative colitis, it is usually at an earlier stage and associated with a better outcome than for those cancers not so detected.[2] This review will deal specifically with ulcerative colitis, but naturally, the question arises as to whether the findings are also applicable to patients with Crohn's colitis. This is particularly relevant as NICE Guidelines recommended:

> "Offer colonoscopic surveillance to people with inflammatory bowel disease (IBD) whose symptoms started 10 years ago and have:
>
> - Ulcerative colitis (but not proctitis alone) or
> - Crohn's colitis involving more than one segment of colon"[3]

Cancer risk in ulcerative colitis

In a review of more than 100 papers dealing with cancer risk in ulcerative colitis, Eaden *et al.*[4] were able to confirm the growing risk of colorectal cancer with time. At 20 years, 10% of patients with ulcerative colitis had developed a colorectal cancer, and this figure rose to almost 20% at 30 years. These studies, of course, were retrospective and reflect the approach to treatment adopted between the 1960s and 1980s. However, a review of changes with time has suggested that there has been no significant improvement in the cancer risk of patients with this condition. Indeed, the overall risk of developing cancer between the 1950s and 2000 remained constant in a study that compared mortality from cancer in different regions across the world.[4] Having therefore established that cancer risk in ulcerative colitis is still a significant problem, the question arises as to whether the surveillance offered by most gastroenterologists is effective or not.

Cancer risk in Crohn's disease

In a meta-analysis of patients with Crohn's disease, Canavan *et al.*[5] demonstrated that overall colorectal cancer relative risk in

Crohn's disease was 4.5 (1.3–14.9) for patients with colonic disease, and the incidence was similar to that previously described by Eaden *et al*.[4] for ulcerative colitis. Although there have been no studies that assessed the benefit of screening a community-based cohort, and thus taking account of defaulters from the program, there is one long-term hospital-based series. This study demonstrated a similar risk for the development of dysplasia.[6]

Effectiveness of surveillance

Surveillance programs in colonic disease have three main elements:

1. The endoscopist
2. The pathologist
3. The patient

In the 1980s, a study from High Wycombe demonstrated that surveillance was quite ineffective.[7] In this study, most patients who developed colorectal cancer had not attended the surveillance program. Cancer of the colon in ulcerative colitis might, therefore, be linked with poor adherence to treatment and management regimes. However, if patients had attended, can we be reassured that early abnormalities would have been detected and treated, thus preventing the development of cancer? To develop an understanding of these potential limitations requires an assessment of the effectiveness of both the endoscopist and pathologist.

The endoscopist. With the growth in medical litigation, the effectiveness of colonoscopists offering screening for cancer prevention will come under minute scrutiny. The development of a national screening program in the United Kingdom for the early detection of dysplasia or early-stage carcinoma of the colon means that patients who are screened need reassurance that the endoscopist will be able to detect these lesions. Published evidence from studies where patients underwent a double imaging does not give this reassurance.[8] Indeed, there is evidence that 12% of abnormalities, such as colonic polyps, will be missed on a single endoscopy. A recent study from the United States found that high-grade dysplasia or colorectal cancer undetected on colonoscopy but found at colectomy was as high as 29%.[9] The main distribution of such lesions was in the rectum and on the right side of the colon, possibly the least well-evaluated areas on routine colonoscopies.

When assessing the efficiency of endoscopists at detecting specific lesions in ulcerative colitis, a sensible benchmark can be obtained from national guidelines. These guidelines were developed by the British Society of Gastroenterology (BSG) and provide criteria to assess the effectiveness of endoscopists. In a study of endoscopists who were members of the BSG, it became clear that many endoscopists will biopsy normal mucosa under the impression that it is abnormal.[10] Up to 16% of endoscopists fell into this practice, and we have to consider that practitioners are often uncertain as to what constitutes an abnormal area in ulcerative colitis. This situation is also complicated by the fact that more recent studies have suggested that multiple biopsies have a very low yield in identifying dysplasia.[11] Although it has been recommended that as many as 32 biopsies should be taken, in practice, few endoscopists take anywhere near this number.[10] Even if surveillance is successful and identifies patients with dysplasia, there is no consistency in the management of such patients, which varies from center to center. To some extent, this depends on the practitioners' views about the significance of low-grade dysplasia. It is, therefore, quite clear that the approach to surveillance among British gastroenterologists is not uniform. Where guidelines exist, they are seldom followed.

The development of chromoendoscopy and narrow-band imaging has given renewed hope to colonoscopists that screening patients with ulcerative colitis for dysplastic lesions will be through a more effective approach. However, despite compelling evidence from randomized trials, a major recent study from Amsterdam has shown that, in clinical practice, chromoendoscopy for IBD surveillance did not increase dysplasia detection compared with targeted and random biopsy sampling.[11]

The pathologist. Unfortunately, there is no reassurance that, once biopsies have been obtained, there will be a uniform interpretation by histopathologists. Current best practice suggests that there should be two independent specialist gastrointestinal pathologists reviewing the biopsies with the intention being to reach a common conclusion. However, in practice, this is often not the case. In a study where pathologists were provided with biopsies alone and no clinical information, there was little agreement between specialist gastrointestinal pathologists, and surprisingly, nonspecialist pathologists had better agreement about the presence or absence of dysplasia.[12] Of 51 slides reviewed, in only four cases did all 13 pathologists on the board assessing the biopsies have a common opinion. These discrepancies in pathological reporting again undermine the value of surveillance.

Combined with the difficulties of interpretation experienced by colonoscopists, this means that surveillance in ulcerative colitis is not an effective approach to preventing the development of colorectal cancer in ulcerative colitis and, in some ways, contributes to the fact that there has been no significant change in the colorectal cancer rate over the last 40 years.

The patient. For any surveillance program to be effective, patients need to understand their role and be willing participants. In a review of patients with long-standing ulcerative colitis, 14% were unaware of the fact that there was a cancer risk, and 44% knew that it was possible to screen for cancer, but more than half did not realize that, if cancer or precancerous lesions were detected, this required surgical intervention.[13]

Education of patients with ulcerative colitis about surveillance and its value is sadly lacking in Europe. Clearly, an educational program is likely to improve compliance and would allow patients to understand its limitations.

Currently, there is no clear evidence that surveillance is effective in ulcerative colitis. Although two Cochrane Reviews have suggested that surveillance ***may*** have some benefit for those people who participate in screening, the evidence was considered to be of low quality, and they failed to adequately address the problem of patients who do not attend or consider how compliance with the program could be increased.[14,15] Therefore, the question arises regarding whether prevention might be a better approach than surveillance. There is now growing evidence that this might be the case. Clearly, such an approach will need significant input by patient educators such as clinicians and nurses.

In a study of 156 patients from Birmingham, only 50% of the patients were aware of any link of their condition to bowel cancer; 79% of patients felt their concordance and understanding would be improved if they were informed of the chemoprophylactic potential of the medication. [16]

Prevention

Prevention can essentially take one of two forms:

1. Colectomy.
2. Chemoprophylaxis.

Colectomy. Clearly, prophylactic colectomy will prevent death from colorectal cancer. This approach was, at one time, popular in Scandinavia and allowed patients to be confident that they would not develop a neoplasm.[17] However, colectomy is not without risk and is not acceptable for many patients. Despite this, patients should be allowed to choose which management plan they wish to follow. Currently, this choice lies between prophylactic colectomy, surveillance, and chemoprevention. Prophylactic colectomy certainly has a place in dysplasia, sclerosing cholangitis, and long-standing symptomatic pancolitis. Ekbom has also suggested that it may also be useful for those patients who have an associated family history of colorectal cancer.[17]

Chemoprevention. Currently, there are three compounds that can be effective in prevention. They are:

1. 5-Aminosalicylic acid (5-ASA) compounds
2. Ursodeoxycholic acid
3. Folic acid supplements

In the mid 1990s, Moody *et al.*[18] noted that patients who complied with treatment with 5-ASA compounds such as sulphasalazine had a colorectal cancer risk of 3% compared with noncompliant patients, where the risk was 31%. This work was subsequently confirmed by Eaden *et al.*,[19] who conducted a case–control investigation comparing 102 patients who developed colorectal cancer with matched controls. In this study, it was clear that regular 5-ASA therapy reduced cancer risk by 75%. When a dose of 1.2 g mesalazine was taken daily, this risk was reduced by 81%. Quite clearly, the regular use of 5-ASA compounds can reduce cancer risk in ulcerative colitis, and this has been confirmed in several subsequent studies.[20] In a recent meta-analysis of 17 studies covering more than 1500 patients, there was evidence of reduced risk, especially with higher doses of aminosalicylates.[21]

There may be some link between the regular use of medication and concerns of individuals about their health and welfare. It is now clear that regular attendance at hospital clinics was also associated with reduced cancer risk. It seems likely that such patients are also going to take their medication regularly. There is also some support from the High Wycombe study that was described earlier.

This then raises the question regarding adherence and the role of adherence in the prevention of cancer in ulcerative colitis. Research by Stone *et al.*[22] has shown that, in a community from central England, adherence among patients with ulcerative colitis to 5-ASA compounds was as low as 42%. With this level of adherence, duration of treatment becomes an important question. However, the number of studies of long-term use of 5-ASA compounds is quite limited.[23] There have been 16 placebo-controlled studies that looked at 2500 patients and lasted more than 6 months. Indeed, there is only one study of 5-ASA compounds in ulcerative colitis, which lasted for 18 months. We know that, with time, adherence to treatment weakens, and this fact has yet to be taken into account in an assessment of the efficiency of 5-ASA compounds in reducing cancer risk. It is possible that even a short duration of treatment might be beneficial to reducing cancer risk. However, this does not fit in with our biological understanding of colorectal cancer and the protective role of aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs) in the general population.

Ursodeoxycholic acid. Other compounds that have been shown to prevent cancer in ulcerative colitis include ursodeoxycholic acid. A study conducted by Tung *et al.*[24] showed that regular use of this compound reduced the frequency of dysplasia to 13% compared with 12% among patients who were not receiving it. Of course, it is used specifically in sclerosing cholangitis, and when this condition is associated with ulcerative colitis, there is a significant increase in the risk of colorectal cancer. However, it is possible that it may be of some benefit in reducing cancer risk in patients with ulcerative colitis but without sclerosing cholangitis. However, there are no adequate trials on which to base a general recommendation.

Folic acid. Folic acid is associated with the reduced risk of colorectal cancer in people with ulcerative colitis, and this can be achieved with a dose as low as 1 mg daily.[25,26] This important observation requires further substantiation. In practice, it would be easy to recommend folic acid to those patients already on maintenance therapy with 5-ASA compounds, and there is a possibility it might enhance their protective role.

Conclusion

In summary, we know that patients with ulcerative colitis and Crohn's disease are at significant risk of cancer. In ulcerative colitis, this is linked to poor compliance with therapy, and attention may be better directed at improving adherence to treatment than strengthening current surveillance programs. This is especially so following the poor performance of chromoendoscopy in clinical practice compared to randomized trials. Clearly, 5-ASA compounds, particularly mesalazine, are the most appropriate agents to choose for chemoprevention, but there may also be a place for the daily intake of folic acid. Currently, the evidence in support of ursodeoxycholic acid is mixed, and it cannot be recommended, in general, to patients for the prophylaxis of colorectal cancer risk. Perhaps the most disturbing current observation is that of colorectal cancer in Crohn's colitis, and this mirrors that in ulcerative colitis.[5] However, few gastroenterologists offer surveillance to patients with Crohn's disease, although this has been recommended in NICE Guidelines.[3] Indeed, with the mucosal abnormality that characterizes this disease, it would be difficult to target biopsies. In addition, there have been no studies which indicate that any of the compounds discussed have any benefits in reducing cancer risk in Crohn's colitis. There is, perhaps, some urgency to look at the benefits of mesalazine in

this disease, particularly as their role in the treatment and prevention of acute flare ups is less clear than in ulcerative colitis.

References

1 Crohn B, Rosenberg H. The sigmoidoscopic picture of chronic ulcerative colitis (non-specific). *Am. J. Med. Sci.* 1925; **170**: 220–8.
2 Cole EB, Shah Y, McLean LP, Yang YX, Khan N. Frequency of surveillance and impact of surveillance colonoscopies in patients with ulcerative colitis who developed colorectal cancer. *Clin. Colorectal Cancer*. 2018; **17**: e289–92.
3 NICE. *Colonoscopic Surveillance for Preventing Colorectal Cancer in Adults with Ulcerative Colitis, Crohn's Disease or Adenomas. NICE Guidelines (CG118).* 2011. Cited 22 Feb 2017. Available from URL: https://www.nice.org.uk/guidance/cg118
4 Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*. 2001; **48**: 526–35.
5 Canavan C, Abrams KR, Mayberry JF. Meta-analysis: colorectal and small bowel cancer risk in patients with Crohn's disease. *Aliment. Pharmacol. Ther.* 2006; **13**: 1097–104.
6 Friedman S, Rubin PH, Bodian C, Harpaz N, Present DH. Screening and surveillance colonoscopy in chronic Crohn's colitis:results of a surveillance program spanning 25 years. *Clin. Gastroenterol. Hepatol.* 2008; **6**: 993–8.
7 Jones HW, Grogono J, Hoare AM. Surveillance in ulcerative colitis: burdens and benefit. *Gut*. 1988; **29**: 325–31.
8 Pickhardt RJ, Nugent PA, Mysliwiec RA, Choi JR, Schindler WR. Location of adenomas missed by optical colonoscopy. *Ann. Intern. Med.* 2004; **141**: 352–9.
9 Eluri S, Parian AM, Limketkai BN *et al*. Nearly a third of high-grade dysplasia and colorectal cancer is undetected in patients with inflammatory bowel disease. *Dig. Dis. Sci.* 2017; **62**: 3586–93.
10 Eaden JA, Ward BA, Mayberry JF. How gastroenterologists screen for colonic cancer in ulcerative colitis; an analysis of performance. *Gastrointest. Endosc.* 2000; **51**: 123–8.
11 Mooiweer E, van der Meulen-deJong AE, Ponsioen CY *et al*. Chromoendoscopy for surveillance in inflammatory bowel disease does not increase neoplasia detection compared with conventional colonoscopy with random biopsies: results from a large retrospective study. *Am. J. Gastroenterol.* 2015; **110**: 1014–21.
12 Eaden I, Abrams K, McKay H, Denley H, Mayberry J. Inter-observer variation between general and specialist gastrointestinal pathologists when grading dysplasia in ulcerative colitis. *J. Pathol.* 2001; **194**: 152–7.
13 Robinson RI, Hart AR, Mayberry LF. Cancer surveillance in ulcerative colitis: a survey of patients' knowledge. *Endoscopy*. 1996; **28**: 761–2.
14 Bye WA, Nguyen TM, Parker CE, Jairath V, East JE. Strategies for detecting colon cancer in patients with inflammatory bowel disease. *Cochrane Database Syst. Rev.* 2017; **9**: CD000279. https://doi.org/10.1002/14651858.CD000279.pub4.
15 Collins RD, Mpofu C, Watson AJ, Rhodes JM. Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. *Cochrane Database Syst. Rev.* 2006; https://doi.org/10.1002/14651858.CD000279.
16 Low A, Love M, Walt R, Kane K, Eksteen B, Goh J. Understanding of chemoprophylaxis and concordance in inflammatory bowel disease. *World J. Gastroenterol.* 2010; **16**: 578–82.
17 Ekbom A. Motion-colonoscopic surveillance is more cost effective than colectomy in patients with ulcerative colitis: arguments against the motion. *Can. J. Gastroenterol.* 2003; **17**: 122–4.
18 Moody GA, Jayanthi V, Probert CS, MacKay H, Mayberry JF. Long-term therapy with sulphasalazine protects against colorectal cancer in ulcerative colitis: a retrospective study of colorectal cancer risk and compliance with treatment in Leicestershire. *Eur. J. Gastroenterol. Hepatol.* 1996; **8**: 1179–83.
19 Eaden J, Abrams K, Ekbom A, Jackson E, Mayberry J. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment. Pharmacol. Ther.* 2000; **14**: 145–53.
20 Stange EF. Review article: the effect of aminosalicylates and immunomodulation on cancer risk in inflammatory bowel disease. *Aliment. Pharmacol. Ther.* 2006; **24**(Suppl. 3): 64–7.
21 Zhao L-N, Li J-Y, Yu T, Chen G-C, Yuan Y-H, Chen QK. 5-Aminosalicylates reduce the risk of colorectal neoplasia in patients with ulcerative colitis: an updated meta-analysis. *PLoS One*. 2014; **9**: e94208. https://doi.org/10.1371/journal.pone.0094208.
22 Stone M, Baker R, Mayberry J. Prevalence and management of inflammatory bowel disease: cross sectional study from central England. *Eur. J. Gastroenterol. Hepatol.* 2003; **15**: 1275–80.
23 Moshkovska T, Mayberry JF. Duration of treatment with 5ASA compounds. *World J. Gastroenterol.* 2007; **13**: 4310–15.
24 Tung BY, Emond MJ, Haggitt RC *et al*. Ursodiol use is associated with lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Ann. Intern. Med.* 2001; **134**: 89–95.
25 Lashner BA, Heidnreich PA, Su GL *et al*. Effect of folate supplementation on the incidence of dysplasia and cancer in chronic ulcerative colitis. *Gastroenterologv*. 1989; **97**: 255–9.
26 Lashner BA, Provencher KS, Seidner DL, Knesebeck A, Brzezinski A. The effect of folic acid supplementation on the risk for cancer or dysplasia in ulcerative colitis. *Gastroenterology*. 1997; **112**: 29–32.