Inflammatory bowel disease cancer risk, detection and surveillance

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IBD Cancer Risk, Detection and Surveillance

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Abstract

Ulcerative colitis (UC) is a chronic and relapsing inflammation of the colonic mucosa with variable extension from the rectum towards the cecum. The aim of medical treatment is to induce and maintain clinical remission. If no remission can be achieved continuous inflammation may repeatedly destroy the epithelial cells. This has to be compensated by epithelial increased proliferation which finally can lead to inflammation associated colorectal cancer. The risk of colitis associated colorectal cancer is increased after long disease duration, especially in patients with chronic active disease. This risk may be lower if long lasting mucosal healing can be achieved.

To early detect the development of dysplasia/intraepithelial neoplasia and colitis associated colorectal cancer, surveillance programs have been installed. However, the evidence for a success of those surveillance programs is limited. This is partially due to problems of detecting precancerous lesions in the colonic mucosa during those surveillance programs.

The specific problems of surveillance programs for the prevention of colorectal cancer and specific aspects of patient care in ulcerative colitis are reviewed in this article.

Key Words: ulcerative colitis; cancer risk; surveillance; dysplasia; intraepithelial neoplasia; colonoscopy; chromoendoscopy
1. **Risk of colorectal carcinoma in patients with ulcerative colitis**

It is well accepted that ulcerative colitis (UC) is associated with an increased risk to develop colorectal cancer. As the molecular pathways that change during the progression from normal epithelia to dysplasia and finally cancer are different from sporadic colorectal cancer (CRC) the term “colitis-associated cancer” frequently is used. It has been estimated in older studies that the risk for this inflammation-associated CRC in UC patients is about 7% at 20 years of disease \(^1-^3\), 7-14% at 25 years \(^4,^5\) and as high as 30% after 35 years. In more recent studies lower risks have been reported.

Eaden and co-workers have shown in a metaanalysis in 2001 based on 116 studies on 54,478 patients that there is an increased risk of cancer in pancolitis as compared to left sided colitis \(^6\) (figure 1). The overall prevalence of colorectal cancer in any patient with UC was shown to be 3.7%, in patients with pancolitis it was 5.4\(^6\). The cumulative CRC risk for any patient with UC was 2% at 10 years, 8% at 20 years and 18% at 30 years \(^6\) (figure 1). As the background risk in the normal population is about 5% during lifetime, this means that the risk to develop colorectal cancer at 30 years after initial diagnosis of ulcerative colitis is 3 to 4-fold increased at least. In ulcerative proctitis the cancer risk appeared not to be increased.

In a recent analysis in Denmark even no increased incidence of colorectal cancer was found \(^7\). Neither the overall cancer risk, nor the CRC risk, were increased in this population-based cohort in Copenhagen county after a median of 19 years of follow-up evaluation. This surprising finding, however, may be due to the higher rates of colectomy in this country and cohort respectively \(^7\). In a large cohort of
patients with extensive UC (600 patients over a 30 year period of observation) Rutter and co-workers reported cumulative incidences of CRC by colitis duration of 2.5% at 20 years, 7.6% at 30 years, and 10.8% at 40 years. Only 30/600 patients (5%) developed CRC. A recent Swedish analysis including 7,607 patients with UC diagnosed between 1954 and 1989 investigated frequency of CRC through 2004. The study indicates that over the past 35 years the risk of death from CRC declined markedly (table 1).

Most recently Jess and co-workers performed a meta-analysis on population based studies. In their analysis an average of 1.6% of patients with UC was diagnosed with CRC during 14 years of follow-up. Men with UC had a greater risk of CRC as compared to women. In the population-based (unbiased and unselected cohorts) the diagnosis of UC increased the risk of CRC 2.4-fold (which is clearly lower as compared to the Eaden data). The direct comparison of the Eaden- and Jess-data makes the differences obvious: In contrast to the above mentioned cumulative incidences of CRC of 2% at 10 years and 8% at 20 years of follow-up for any patient with UC, these figures were only 0.4% and 1.1%-5.3%, respectively, in the meta-analysis by Jess and co-workers. The analysis on non-population based data derived from specialized centers may have introduced some selection-bias into the analyses. The lower incidence of CRC in UC patients in more recent studies has also been explained with better control of inflammation and higher rates of mucosal healing. As this is hard to prove in clinical studies it will remain speculative.

The CRC risk increases with the duration of the disease and correlates positively with the severity of inflammation and extend of the disease. In fact there is no uniform and general accepted definition of disease-duration. Onset of symptoms has generally been used as starting point for disease-duration in the
studies that have identified this parameter as a risk factor. Based on the meta-analysis by Eaden et al., it is assumed that the risk for CRC begins to increase 8–10 years after onset of inflammation.

The risk to develop CRC is further increased in patients with primarily sclerosing cholangitis (PSC).

2. **Myths and facts about surveillance colonoscopy**

Generally it is believed that the colitis-associated mortality of CRC can be reduced by surveillance colonoscopy. Colonoscopic surveillance for dysplasia once a year or every 2 years with random biopsies has been advocated in many countries and in most guidelines. Collins and co-workers have published a Cochrane database systematic review in 2006. For their analysis they focused on 11 studies attempting to address the impact of surveillance colonoscopy on survival of patients with UC. Six of these studies were retrospective analyses lacking control groups. Three case control studies performed by Karlen in 1998 on 4,664 patients, Choi in 1993 and Lashner in 1990 are discussed in detail. In the first study, 2 out of 40 patients that died on colorectal cancer had undergone surveillance colonoscopy on at least one occasion as compared with 18 out of 102 of the controls. This difference, however, did not reach statistical significance (RR = 0.29, 95% CI = 0.06–1.31). In the study of Choi, in total 41 patients developed carcinoma of whom 19 had undergone colonoscopy surveillance and 22 had not. The 5 years survival rate was 77.2% for cancer of the surveillance group and 36.3% for the non-surveillance group (P=0.026), indicating that the cancers in the control group were more advanced as compared to the cancers in the surveillance group. In the study by Lashner, 4 out
of 91 patients in the surveillance group died from colorectal cancer as compared to 2 out of 95 patients in the non-surveillance group showing no difference between those groups \(^{35}\). However, it has to be mentioned that the benefit of surveillance could have been higher in these studies if multiple biopsies would have been performed. From the data outlined no clear evidence that surveillance colonoscopy prolongs survival in patients with extensive colitis can be obtained \(^{32}\). However, it may be concluded that cancers are detected at an earlier stage in patients who are undergoing surveillance, and that these patients have a correspondingly better prognosis \(^{32}\). Overall the Cochrane review is very cautious in its statements pointing to an indirect evidence that surveillance is likely to be effective at reducing the risk of death from IBD-associated colorectal cancer and indirect evidence that it may be acceptably cost-effective \(^{32}\). Therefore, also in the ECCO guidelines the recommendation for surveillance is not strong: In the manuscript by Biancone and colleagues it is stated – similar to the Cochrane review - that surveillance colonoscopy may permit earlier detection of CRC, with a corresponding improved prognosis \(^{17}\). Further, it is noted that unequivocal evidence that surveillance colonoscopy prolongs survival in patients with UC is lacking \(^{17}\).

3. **When and how should surveillance colonoscopy be performed?**

Generally it is recommended that for surveillance all of colitis patients shall undergo a complete ileo-colonoscopy 8 – 10 years after the initial symptoms \(^{17}\). As outlined above this recommendation is mainly based on meta-analyses that downscale the wide variation in reported CRC risk in different studies \(^{6, 36}\). It should be emphasized here that this time-point is referred to the initial symptoms and not to the first diagnosis, as patients might have had the disease for several years before it
being diagnosed. In patients with extensive colitis it is recommended that surveillance should start after screening colonoscopy (8 - 10 years after onset of disease) and then be performed every other year up to year 20 of disease, then annually or annually from 10 years of disease duration on 16, 17, 30, 31, 37.

In patients with left sided colitis also a new staging colonoscopy should be performed 8 years after disease onset to identify patients with a spreading of inflammation from left sided to more extensive disease. Patients who still have left sided colitis should start surveillance 15 years after first manifestation 16, 17, 30, 31, 37. Patients with now extension to pancolitis should have their surveillance colonoscopy every 2 years after the index-colonoscopy at 8 years (as mentioned above for extensive disease). In all guidelines the consensus on this strategy is strong 17, 31, 37 despite the lack of robust efficacy data.

If a PSC is present, annual surveillance colonoscopies should be started independent of the disease activity and extent right after the diagnosis of UC and PSC. In patients with PSC, the risk of developing a CRC is particularly high and has been reported to occur early (median 2.9 years) after symptom onset 19, 20, 23, 38-42. Despite robust data showing a clear advance for this strategy it is obvious that these patients at high risk for CRC should enter in a more intensive surveillance programme once diagnosed.

The Cochrane review clearly showed that surveillance colonoscopy cannot completely abolish the risk to have colorectal cancer in patients with ulcerative colitis 32. However, it is likely that those colorectal cancers are detected earlier improving the 5 year survival rate as indicated above. On the other hand a study from The Netherlands indicated that up to 20% of patients may have a colitis associated colorectal cancer before the index colonoscopy at 8 years after symptom
onset. If the patients with concomitant PSC are subtracted from this group, the frequency of CRC occurring without this risk factor before the 8 years margin is still alarming 10 to 15%. The severity of inflammation may be relevant with respect to this. Therefore, it may be justified to include patients with chronically active disease in a surveillance program earlier. The interval between 2 surveillance colonoscopies should be longer than 2 years as in this time frame interval carcinoma might occur.

Despite the fact that ulcerative proctitis might have a slightly increased risk of carcinoma, there is no consensus on regular proctologic examination. In a study by Söderlund and co-workers the risk of CRC was much greater in patients with UC pancolitis (SIR, 5.6; 95% CI, 4.4–7.0) when compared with the general population. The standardized incidence ratio was lower when compared to UC patients with proctitis, raising the possibility that UC proctitis might be associated with an increased risk of CRC.

4. **How should surveillance colonoscopies be performed?**

Crucial factors for surveillance colonoscopies are one hand the number of biopsies taken and on the other hand the time taken for the evaluation of the colon. A further important point is with respect to the conditions of the colonoscopy whether the cleansing of the gut has been done successfully. If the conditions of the colonoscopy are not perfect due to still present feces, the colonoscopy should be repeated. Further it appears to be important that the colonoscopy is done during a remission phase of the colitis as the histomorphological discrimination of inflamed and neoplastic changes is difficult. Low grade dysplasia may be missed as inflamed mucosa is present or on the other hand inflamed mucosa may be
misinterpreted as dysplastic mucosa. Of course the general aim of surveillance colonoscopies is to detect neoplasias with high sensitivity and specificity. Macroscopic evaluation of the gut is therefore very helpful. It even has been stated that upon excellent preparation most lesions will be macroscopically visible. If the mucosa is inflamed the macroscopic evaluation difficult.

Targeted biopsies should be taken from all endoscopical suspect lesions. In addition blind and non-targeted biopsies should be taken every 4cm in all quadrants as up to 20% of dysplastic lesions may not be visible macroscopically. A mathematical modelling was done by Rubin and co-workers indicating that 34 random biopsies will result in a 90% confidence interval to detect CRC or high grade dysplasia, 64 biopsies will be necessary for a 95% probability of detection. Despite the fact that this is only a modelling based on a questionable basis and that the evidence is weak similar numbers for random biopsies during surveillance colonoscopy can now be found in a number of guidelines. To achieve a 90% security for the detection of dysplasia/neoplastic lesions it is recommended that 4 biopsies are taken every 10 cm. Kiesslich in 2003 found only 2 intraepithelial neoplasias in 598 random biopsies. Rutter in 2004 did not detect any intraepithelial neoplasias in 2906 random biopsies. As with the new techniques of high resolutions endoscopy lesions may be visible much better as in former eras, this point is still a matter of discussion. In reality the number of random biopsies taken during surveillance colonoscopy in UC patients is usually much lower.

As an alternative a chromoendoscopy with targeted biopsies in all suspect areas may be recommended. The advantages of chromoendoscopy recently were confirmed in a multi-center study which detected more intraepithelial neoplasia as compared to conventional colonoscopy. However, it should be kept
in mind the methylene blue which is frequently recommended for chromoendoscopy may cause DNA damage and contribute to CRC risk. Therefore, indigo carmine seems to be the better alternative for chromoendoscopy. The other techniques that have been investigated in recent years should not be used as stand-alone strategies.

A number of studies in recent years could demonstrate that the higher number of intraepithelial neoplasias can be detected with high-resolution endoscopy. Irregular mucosa structures or elevated areas of the mucosa might be detected. However, presently the published data are not sufficient to completely omit the recommendation for random biopsies. As a potential replacement of chromoendoscopy virtual chromoendoscopy techniques such as NBI, FICE or I-SCAN have been recommended, however the data published so far are inconclusive.

5. **What to do if dysplasia/ intraepithelial neoplasia has been found?**

If an intraepithelial neoplasia has been detected, an external and independent second opinion by a pathologist should be achieved. The presence of a low grade intraepithelial neoplasia should be re-investigated by colonoscopy control after increase of anti-inflammatory therapy within 3 months.

The grading of the intraepithelial neoplasias is very important for the CRC risk in patients with UC. If a patient underwent colectomy due to CRC random biopsies in the colectomy specimen detect intraepithelial neoplasia in up to 74%. This indicates that there may be several additional neoplasias in UC colon that already has developed CRC at one location. A meta-analysis has shown that in low grade intraepithelial neoplasias and low grade dysplasia the risk for CRC is at least 9-fold. Therefore the detection of low grade dysplasia and low grade intraepithelial
neoplasias has important consequences for further treatment. However, there is a high inter-observer variability within pathologists\textsuperscript{73}. The variability is especially high for low grade dysplasia\textsuperscript{73}. Due to the therapeutic consequences therefore an independent second opinion is mandatory. In the meta-analysis by Thomas and co-workers based on 20 studies with 508 patients with low grade dysplasia an up to 12-fold risk of developing advanced lesions such as high grade dysplasia or CRC as compared to patients without low grade dysplasia was found\textsuperscript{72}. The positive protective for low grade dysplasia including DALM for concurrent advanced lesions was 37\%\textsuperscript{72}. The positive protective value for low grade dysplasia in the presence of a DALM for concurrent advanced lesions was 41\%\textsuperscript{72}. If a second external pathologist confirms the diagnosis of low grade dysplasia or low grade intraepithelial neoplasia, the patient should be informed about his risk and procto-colectomy should be recommended. As an alternative a tight surveillance colonoscopy program every 3 months might be acceptable. Adenoma associated dysplasia (ALM) however has to be treated differently. A clear adenoma-like lesion with intraepithelial neoplasia, which is classified as ALM by the pathologist, should be resected endoscopically.


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Cumulative risk of developing CRC:

- 2% at 10 yrs,
- 8% at 20 yrs and
- 18% at 30 yrs

Figure 1: Meta-analysis of 116 studies assessing the risk of CRC in CU patients: Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut 2001;48:526-535, Ref 6
Table 1: Risk of colorectal cancer in 3 population based Swedish cohorts (1954 – 1989) including 7 607 patients with IBD (198 227 patient-years). 196 CRCs were found in 188 patients. (Söderlund S, Brandt L, Lapidus A, Karlen P, Broström O, Löfberg O, Ekbom A, Askling J. Decreasing Time-Trends of Colorectal Cancer in a Large Cohort of Patients With Inflammatory Bowel Disease, Gastroenterology 2009;136:1561-1567, Ref 9)

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