**University of
Zurich^{UZH}**

**Zurich Open Repository and
Archive**

University of Zurich
University Library
Strickhofstrasse 39
CH-8057 Zurich
www.zora.uzh.ch

Year: 2012

Inflammatory bowel disease cancer risk, detection and surveillance

Rogler, Gerhard

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 (CRC). The risk of colitis-associated CRC is increased after a long disease duration, especially in patients with chronic active disease. This risk may be lower if long-lasting mucosal healing can be achieved. To detect the development of dysplasia/intraepithelial neoplasia and colitis-associated CRC early, surveillance programs have been installed. However, the evidence of success for 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 CRC and specific aspects of patient care in UC are reviewed in this article.

DOI: <https://doi.org/10.1159/000341893>

Posted at the Zurich Open Repository and Archive, University of Zurich

ZORA URL: <https://doi.org/10.5167/uzh-76206>

Journal Article

Accepted Version

Originally published at:

Rogler, Gerhard (2012). Inflammatory bowel disease cancer risk, detection and surveillance. *Digestive Diseases*, 30(Suppl. 2):48-54.

DOI: <https://doi.org/10.1159/000341893>

IBD Cancer Risk, Detection and Surveillance

Gerhard Rogler

Address for correspondence:

Gerhard Rogler, MD, PhD, AGAF

Division of Gastroenterology and Hepatology

Department of Visceral Medicine

University Hospital Zürich

Rämistrasse 100

CH-8091 Zürich

Switzerland

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 ⁸. Only 30/600 patients (5%) developed CRC ⁸. 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 ⁹ (table 1).

Most recently Jess and co-workers performed a meta-analysis on population based studies ¹⁰. In their analysis an average of 1.6% of patients with UC was diagnosed with CRC during 14 years of follow-up ¹⁰. 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 ¹⁰. 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 ^{6, 11-16}. 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 ¹⁷. 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 ⁶.

The risk to develop CRC is further increased in patients with primarily sclerosing cholangitis (PSC) ¹⁸⁻²⁷.

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 ^{16, 17, 28-31}. Collins and co-workers have published a Cochrane database systematic review in 2006 ³². 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 ³³, Choi in 1993 ³⁴ and Lashner in 1990 ³⁵ 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 ³³. This difference however did not reach statistical significance (RR = 0.29, 95% CI = 0.06 - 1.31) ³³. In the study of Choi in total 41 patients developed carcinoma of whom 19 had undergone colonoscopy surveillance and 22 had not ³⁴. 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 ³⁴. 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 colitis³². 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 ⁴³. 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 ^{12, 44, 45}. 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 ⁴⁶.

Despite the fact that ulcerative proctitis might have a slightly increased risk of carcinoma ⁴⁷ 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 ⁹. 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 ⁴⁷.

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 ⁴⁸. If the conditions of the colonoscopy are not perfect due to still present feces, the colonoscopy should be repeated ⁴⁸. 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 ⁴⁹. 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 ^{50, 51}. It even has been stated that upon excellent preparation most lesions will be macroscopically visible ^{50, 52}. If the mucosa is inflamed the macroscopic evaluation difficult ⁴⁹.

Targeted biopsies should be taken from all endoscopical suspect lesions ⁵⁰⁻⁵². 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 ⁵³. 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 ^{31, 37}. 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 ⁵⁴. Rutter in 2004 did not detect any intraepithelial neoplasias in 2906 random biopsies ⁵⁵. As with the new techniques of high resolutions endoscopy lesions may be visible much better as in former eras ^{50, 52} 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 ²⁹.

As an alternative a chromoendoscopy with targeted biopsies in all suspect areas may be recommended ⁵⁵⁻⁵⁸. The advantages of chromoendoscopy recently were confirmed in a multi-center study which detected more intraepithelial neoplasia as compared to conventional colonoscopy ⁵⁹. However, it should be kept

in mind the methylene blue which is frequently recommended for chromoendoscopy may cause DNA damage and contribute to CRC risk⁶⁰⁻⁶². Therefore, indigo carmine seems to be the better alternative for chromoendoscopy^{55, 60, 63}. 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 endoscopy⁶⁴. Irregular mucosa structures or elevated areas of the mucosa might be detected^{65, 66}. 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 inconclusive⁶⁷⁻⁷⁰.

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^{16, 17, 30, 31, 37}. 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%⁷¹. 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-fold⁷². 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 pathologists⁷³. The variability is especially high for low grade dysplasia⁷³. 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 found⁷². The positive predictive value for low grade dysplasia including DALM for concurrent advanced lesions was 37%⁷². The positive predictive value for low grade dysplasia in the presence of a DALM for concurrent advanced lesions was 41%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.

References

1. Gyde SN, Prior P, Allan RN, Stevens A, Jewell DP, Truelove SC, Lofberg R, Brostrom O, Hellers G. Colorectal cancer in ulcerative colitis: a cohort study of primary referrals from three centres. *Gut* 1988;29:206-17.
2. Brostrom O, Lofberg R, Nordenvall B, Ost A, Hellers G. The risk of colorectal cancer in ulcerative colitis. An epidemiologic study. *Scand J Gastroenterol* 1987;22:1193-9.
3. Porschen R, Strohmeyer G. [Risk of colorectal cancer in ulcerative colitis--monitoring strategies and identification of risk patients]. *Z Gastroenterol* 1992;30:585-93.
4. Collins RH, Jr., Feldman M, Fordtran JS. Colon cancer, dysplasia, and surveillance in patients with ulcerative colitis. A critical review. *N Engl J Med* 1987;316:1654-8.
5. Lofberg R, Brostrom O, Karlen P, Tribukait B, Ost A. Colonoscopic surveillance in long-standing total ulcerative colitis--a 15-year follow-up study. *Gastroenterology* 1990;99:1021-31.
6. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;48:526-35.
7. Winther KV, Jess T, Langholz E, Munkholm P, Binder V. Long-term risk of cancer in ulcerative colitis: a population-based cohort study from Copenhagen County. *Clin Gastroenterol Hepatol* 2004;2:1088-95.
8. Rutter MD, Saunders BP, Wilkinson KH, Rumbles S, Schofield G, Kamm MA, Williams CB, Price AB, Talbot IC, Forbes A. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. *Gastroenterology* 2006;130:1030-8.
9. Soderlund S, Brandt L, Lapidus A, Karlen P, Brostrom O, Lofberg R, Ekblom A, Askling J. Decreasing time-trends of colorectal cancer in a large cohort of patients with inflammatory bowel disease. *Gastroenterology* 2009;136:1561-7; quiz 1818-9.

10. Jess T, Rungoe C, Peyrin-Biroulet L. Risk of Colorectal Cancer in Patients With Ulcerative Colitis: A Meta-Analysis of Population-Based Cohort Studies. *Clin Gastroenterol Hepatol* 2012.
11. Lashner BA, Provencher KS, Bozdech JM, Brzezinski A. Worsening risk for the development of dysplasia or cancer in patients with chronic ulcerative colitis. *Am J Gastroenterol* 1995;90:377-80.
12. Rutter M, Saunders B, Wilkinson K, Rumbles S, Schofield G, Kamm M, Williams C, Price A, Talbot I, Forbes A. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. *Gastroenterology* 2004;126:451-9.
13. Loftus EV, Jr. Epidemiology and risk factors for colorectal dysplasia and cancer in ulcerative colitis. *Gastroenterol Clin North Am* 2006;35:517-31.
14. Ha CY, Newberry RD, Stone CD, Giorba MA. Patients with late-adult-onset ulcerative colitis have better outcomes than those with early onset disease. *Clin Gastroenterol Hepatol* 2010;8:682-687 e1.
15. Eaden J. Review article: colorectal carcinoma and inflammatory bowel disease. *Aliment Pharmacol Ther* 2004;20 Suppl 4:24-30.
16. Farraye FA, Odze RD, Eaden J, Itzkowitz SH, McCabe RP, Dassopoulos T, Lewis JD, Ullman TA, James T, 3rd, McLeod R, Burgart LJ, Allen J, Brill JV. AGA medical position statement on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology* 2010;138:738-45.
17. Biancone L, Michetti P, Travis S, Escher JC, Moser G, Forbes A, Hoffmann JC, Dignass A, Gionchetti P, Jantschek G, Kiesslich R, Kolacek S, Mitchell R, Panes J, Soderholm J, Vucelic B, Stange E. European evidence-based Consensus on the management of ulcerative colitis: Special situations. *J Crohns Colitis* 2008;2:63-92.
18. Brentnall TA, Haggitt RC, Rabinovitch PS, Kimmey MB, Bronner MP, Levine DS, Kowdley KV, Stevens AC, Crispin DA, Emond M, Rubin CE. Risk and natural history of

- colonic neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis. *Gastroenterology* 1996;110:331-8.
19. Broome U, Lofberg R, Veress B, Eriksson LS. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology* 1995;22:1404-8.
 20. Kornfeld D, Ekblom A, Ihre T. Is there an excess risk for colorectal cancer in patients with ulcerative colitis and concomitant primary sclerosing cholangitis? A population based study. *Gut* 1997;41:522-5.
 21. Leidenius MH, Farkkila MA, Karkkainen P, Taskinen EI, Kellokumpu IH, Hockerstedt KA. Colorectal dysplasia and carcinoma in patients with ulcerative colitis and primary sclerosing cholangitis. *Scand J Gastroenterol* 1997;32:706-11.
 22. Nuako KW, Ahlquist DA, Sandborn WJ, Mahoney DW, Siems DM, Zinsmeister AR. Primary sclerosing cholangitis and colorectal carcinoma in patients with chronic ulcerative colitis: a case-control study. *Cancer* 1998;82:822-6.
 23. Shetty K, Rybicki L, Brzezinski A, Carey WD, Lashner BA. The risk for cancer or dysplasia in ulcerative colitis patients with primary sclerosing cholangitis. *Am J Gastroenterol* 1999;94:1643-9.
 24. Moayyeri A, Daryani NE, Bahrami H, Haghpanah B, Nayyer-Habibi A, Sadatsafavi M. Clinical course of ulcerative colitis in patients with and without primary sclerosing cholangitis. *J Gastroenterol Hepatol* 2005;20:366-70.
 25. Terg R, Sambuelli A, Coronel E, Mazzuco J, Cartier M, Negreira S, Munoz A, Gil A, Miguez C, Huernos S, Romero G, Goncalvez S, Levi D, Abecasis R. Prevalence of primary sclerosing cholangitis in patients with ulcerative colitis and the risk of developing malignancies. A large prospective study. *Acta Gastroenterol Latinoam* 2008;38:26-33.

26. Pekow JR, Hetzel JT, Rothe JA, Hanauer SB, Turner JR, Hart J, Noffsinger A, Huo D, Rubin DT. Outcome after surveillance of low-grade and indefinite dysplasia in patients with ulcerative colitis. *Inflamm Bowel Dis* 2010;16:1352-6.
27. Navaneethan U, Venkatesh PG, Lashner BA, Remzi FH, Shen B, Kiran RP. Temporal trends in colon neoplasms in patients with primary sclerosing cholangitis and ulcerative colitis. *J Crohns Colitis* 2012.
28. Obrador A, Ginard D, Barranco L. Review article: colorectal cancer surveillance in ulcerative colitis - what should we be doing? *Aliment Pharmacol Ther* 2006;24 Suppl 3:56-63.
29. Kaltz B, Bokemeyer B, Hoffmann J, Porschen R, Rogler G, Schmiegel W. [Surveillance colonoscopy in ulcerative colitis patients in Germany]. *Z Gastroenterol* 2007;45:325-31.
30. Farraye FA, Odze RD, Eaden J, Itzkowitz SH. AGA technical review on the diagnosis and management of colorectal neoplasia in inflammatory bowel disease. *Gastroenterology* 2010;138:746-74, 774 e1-4; quiz e12-3.
31. Dignass A, Preiss JC, Aust DE, Autschbach F, Ballauff A, Barretton G, Bokemeyer B, Fichtner-Feigl S, Hagel S, Herrlinger KR, Jantschek G, Kroesen A, Kruis W, Kucharzik T, Langhorst J, Reinshagen M, Rogler G, Schleiermacher D, Schmidt C, Schreiber S, Schulze H, Stange E, Zeitz M, Hoffmann JC, Stallmach A. [Updated German guideline on diagnosis and treatment of ulcerative colitis, 2011]. *Z Gastroenterol* 2011;49:1276-341.
32. Collins PD, 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:CD000279.
33. Karlen P, Kornfeld D, Brostrom O, Lofberg R, Persson PG, Ekblom A. Is colonoscopic surveillance reducing colorectal cancer mortality in ulcerative colitis? A population based case control study. *Gut* 1998;42:711-4.

34. Choi PM, Nugent FW, Schoetz DJ, Jr., Silverman ML, Haggitt RC. Colonoscopic surveillance reduces mortality from colorectal cancer in ulcerative colitis. *Gastroenterology* 1993;105:418-24.
35. Lashner BA, Kane SV, Hanauer SB. Colon cancer surveillance in chronic ulcerative colitis: historical cohort study. *Am J Gastroenterol* 1990;85:1083-7.
36. Eaden JA, Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. *Gut* 2002;51 Suppl 5:V10-2.
37. Hoffmann JC, Zeitz M, Bischoff SC, Brambs HJ, Bruch HP, Buhr HJ, Dignass A, Fischer I, Fleig W, Folsch UR, Herrlinger K, Hohne W, Jantschek G, Kaltz B, Keller KM, Knebel U, Kroesen AJ, Kruis W, Matthes H, Moser G, Mundt S, Pox C, Reinshagen M, Reissmann A, Riemann J, Rogler G, Schmiegel W, Scholmerich J, Schreiber S, Schwandner O, Selbmann HK, Stange EF, Utzig M, Wittekind C. [Diagnosis and therapy of ulcerative colitis: results of an evidence based consensus conference by the German society of Digestive and Metabolic Diseases and the competence network on inflammatory bowel disease]. *Z Gastroenterol* 2004;42:979-83.
38. Broome U, Lindberg G, Lofberg R. Primary sclerosing cholangitis in ulcerative colitis--a risk factor for the development of dysplasia and DNA aneuploidy? *Gastroenterology* 1992;102:1877-80.
39. Choi PM, Nugent FW, Rossi RL. Relationship between colorectal neoplasia and primary sclerosing cholangitis in ulcerative colitis. *Gastroenterology* 1992;103:1707-9.
40. Loftus EV, Jr., Aguilar HI, Sandborn WJ, Tremaine WJ, Krom RA, Zinsmeister AR, Graziadei IW, Wiesner RH. Risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis following orthotopic liver transplantation. *Hepatology* 1998;27:685-90.

41. Soetikno RM, Lin OS, Heidenreich PA, Young HS, Blackstone MO. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. *Gastrointest Endosc* 2002;56:48-54.
42. Lindberg J, Stenling R, Palmqvist R, Rutegard J. Early onset of ulcerative colitis: long-term follow-up with special reference to colorectal cancer and primary sclerosing cholangitis. *J Pediatr Gastroenterol Nutr* 2008;46:534-8.
43. Lutgens MW, Vleggaar FP, Schipper ME, Stokkers PC, van der Woude CJ, Hommes DW, de Jong DJ, Dijkstra G, van Bodegraven AA, Oldenburg B, Samsom M. High frequency of early colorectal cancer in inflammatory bowel disease. *Gut* 2008;57:1246-51.
44. Gupta RB, Harpaz N, Itzkowitz S, Hossain S, Matula S, Kornbluth A, Bodian C, Ullman T. Histologic inflammation is a risk factor for progression to colorectal neoplasia in ulcerative colitis: a cohort study. *Gastroenterology* 2007;133:1099-105; quiz 1340-1.
45. Hefti MM, Chessin DB, Harpaz NH, Steinhagen RM, Ullman TA. Severity of inflammation as a predictor of colectomy in patients with chronic ulcerative colitis. *Dis Colon Rectum* 2009;52:193-7.
46. Connell W. What is the optimal interval of surveillance colonoscopy in patients with long-standing ulcerative colitis? *Inflamm Bowel Dis* 2008;14 Suppl 2:S194-5.
47. Peyrin-Biroulet L, Phelip JM, Roblin X. Is ulcerative colitis proctitis associated with an increased risk of colorectal cancer? *Gastroenterology* 2009;137:1857-8; author reply 1858.
48. Thomas-Gibson S, Rogers P, Cooper S, Man R, Rutter MD, Suzuki N, Swain D, Thuraisingam A, Atkin W. Judgement of the quality of bowel preparation at screening flexible sigmoidoscopy is associated with variability in adenoma detection rates. *Endoscopy* 2006;38:456-60.
49. Toruner M, Harewood GC, Loftus EV, Jr., Sandborn WJ, Tremaine WJ, Faubion WA, Schroeder KW, Egan LJ. Endoscopic factors in the diagnosis of colorectal dysplasia in chronic inflammatory bowel disease. *Inflamm Bowel Dis* 2005;11:428-34.

50. Blonski W, Kundu R, Lewis J, Aberra F, Osterman M, Lichtenstein GR. Is dysplasia visible during surveillance colonoscopy in patients with ulcerative colitis? *Scand J Gastroenterol* 2008;43:698-703.
51. Rubin DT, Rothe JA, Hetzel JT, Cohen RD, Hanauer SB. Are dysplasia and colorectal cancer endoscopically visible in patients with ulcerative colitis? *Gastrointest Endosc* 2007;65:998-1004.
52. Rutter MD, Saunders BP, Wilkinson KH, Kamm MA, Williams CB, Forbes A. Most dysplasia in ulcerative colitis is visible at colonoscopy. *Gastrointest Endosc* 2004;60:334-9.
53. Rubin CE, Haggitt RC, Burmer GC, Brentnall TA, Stevens AC, Levine DS, Dean PJ, Kimmey M, Perera DR, Rabinovitch PS. DNA aneuploidy in colonic biopsies predicts future development of dysplasia in ulcerative colitis. *Gastroenterology* 1992;103:1611-20.
54. Kiesslich R, Fritsch J, Holtmann M, Koehler HH, Stolte M, Kanzler S, Nafe B, Jung M, Galle PR, Neurath MF. Methylene blue-aided chromoendoscopy for the detection of intraepithelial neoplasia and colon cancer in ulcerative colitis. *Gastroenterology* 2003;124:880-8.
55. Rutter MD, Saunders BP, Schofield G, Forbes A, Price AB, Talbot IC. Pancolonoscopic indigo carmine dye spraying for the detection of dysplasia in ulcerative colitis. *Gut* 2004;53:256-60.
56. Kiesslich R, Galle PR, Neurath MF. Endoscopic surveillance in ulcerative colitis: smart biopsies do it better. *Gastroenterology* 2007;133:742-5.
57. Kiesslich R, Goetz M, Lammersdorf K, Schneider C, Burg J, Stolte M, Vieth M, Nafe B, Galle PR, Neurath MF. Chromoscopy-guided endomicroscopy increases the diagnostic yield of intraepithelial neoplasia in ulcerative colitis. *Gastroenterology* 2007;132:874-82.

58. Kiesslich R, Neurath MF. Chromoendoscopy: an evolving standard in surveillance for ulcerative colitis. *Inflamm Bowel Dis* 2004;10:695-6.
59. Marion JF, Waye JD, Present DH, Israel Y, Bodian C, Harpaz N, Chapman M, Itzkowitz S, Steinlauf AF, Abreu MT, Ullman TA, Aisenberg J, Mayer L. Chromoendoscopy-targeted biopsies are superior to standard colonoscopic surveillance for detecting dysplasia in inflammatory bowel disease patients: a prospective endoscopic trial. *Am J Gastroenterol* 2008;103:2342-9.
60. Davies J, Burke D, Olliver JR, Hardie LJ, Wild CP, Routledge MN. Methylene blue but not indigo carmine causes DNA damage to colonocytes in vitro and in vivo at concentrations used in clinical chromoendoscopy. *Gut* 2007;56:155-6.
61. Hardie LJ, Olliver JR, Wild CP, Dexter S, Sahay P. Chromoendoscopy with methylene blue and the risk of DNA damage. *Gastroenterology* 2004;126:623; author reply 623-4.
62. Olliver JR, Wild CP, Sahay P, Dexter S, Hardie LJ. Chromoendoscopy with methylene blue and associated DNA damage in Barrett's oesophagus. *Lancet* 2003;362:373-4.
63. Hurlstone DP, Sanders DS, Lobo AJ, McAlindon ME, Cross SS. Indigo carmine-assisted high-magnification chromoscopic colonoscopy for the detection and characterisation of intraepithelial neoplasia in ulcerative colitis: a prospective evaluation. *Endoscopy* 2005;37:1186-92.
64. van den Broek FJ, Fockens P, van Eeden S, Reitsma JB, Hardwick JC, Stokkers PC, Dekker E. Endoscopic tri-modal imaging for surveillance in ulcerative colitis: randomised comparison of high-resolution endoscopy and autofluorescence imaging for neoplasia detection; and evaluation of narrow-band imaging for classification of lesions. *Gut* 2008;57:1083-9.
65. Bernstein CN. ALMs versus DALMs in ulcerative colitis: polypectomy or colectomy? *Gastroenterology* 1999;117:1488-92.
66. Odze RD. Adenomas and adenoma-like DALMs in chronic ulcerative colitis: a clinical, pathological, and molecular review. *Am J Gastroenterol* 1999;94:1746-50.

67. East JE, Suzuki N, von Herbay A, Saunders BP. Narrow band imaging with magnification for dysplasia detection and pit pattern assessment in ulcerative colitis surveillance: a case with multiple dysplasia associated lesions or masses. *Gut* 2006;55:1432-5.
68. Matsumoto T, Kudo T, Jo Y, Esaki M, Yao T, Iida M. Magnifying colonoscopy with narrow band imaging system for the diagnosis of dysplasia in ulcerative colitis: a pilot study. *Gastrointest Endosc* 2007;66:957-65.
69. Rodrigues S, Pereira P, Magro F, Lopes S, Albuquerque A, Lopes J, Carneiro F, Macedo G. Dysplasia surveillance in an ulcerative colitis patient: successful detection with narrow band imaging and magnification. *J Crohns Colitis* 2011;5:54-6.
70. Watanabe K, Sogawa M, Yamagami H, Watanabe J, Ajioka Y, Arakawa T. Endoscopic differential diagnosis between ulcerative colitis-associated neoplasia and sporadic neoplasia in surveillance colonoscopy using narrow band imaging. *Dig Endosc* 2011;23 Suppl 1:143-9.
71. Taylor BA, Pemberton JH, Carpenter HA, Levin KE, Schroeder KW, Welling DR, Spencer MP, Zinsmeister AR. Dysplasia in chronic ulcerative colitis: implications for colonoscopic surveillance. *Dis Colon Rectum* 1992;35:950-6.
72. Thomas T, Abrams KA, Robinson RJ, Mayberry JF. Meta-analysis: cancer risk of low-grade dysplasia in chronic ulcerative colitis. *Aliment Pharmacol Ther* 2007;25:657-68.
73. Odze RD, Goldblum J, Noffsinger A, Alsaigh N, Rybicki LA, Fogt F. Interobserver variability in the diagnosis of ulcerative colitis-associated dysplasia by telepathology. *Mod Pathol* 2002;15:379-86.

Figure 1

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:

	10 years	20 years	30 years
Pancolitis	1.5	3.8	7.6
UC	1	2.3	5.2
CD	0.5	1.4	2.2

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)