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Review

Inflammatory bowel disease related cancer

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1.THE NATURAL HISTORY OF IBD RELATED CANCER

The first case of rectal cancer complicating UC was reported in 1925.[1] The frequency of colorectal cancer in IBD patients has been reported to range from 0.6% to 17% in more than 50 articles published between 1928 and 1963. It is unknown whether colorectal cancer (CRC) in IBD patients behaves differently from regular CRC in non-IBD patients. Patients with IBD related CRC are 7 years younger than those without IBD. The distribution of CRC is not significantly different among subjects with UC and those without IBD .In patients with CD the majority of cancers are located in the proximal colon.[2] The mean time between UC onset and CRC development is 12 years. In CD, no differences regarding clinical phenotype at diagnosis and course between children and adults have been found.

The incidence of IBD is low in childhood. At the time of diagnosis, children with UC seem to have more widespread disease compared to adults. Childhood onset CD does not differ in clinical presentation, disease course or prognosis from the adult-onset CD. Those statements possibly cannot be copied and pasted when describing the natural history of IBD cancer in childhood.[3] The large variety of numbers in many studies reflects the changing natural history of IBD cancer through the years although not improving our knowledge to date regarding possible triggering factors.

2. DIFFERENT RISK OF CANCER IN IBD BEFORE AND AFTER THE 1970s?

An interesting retrospective study relates to the dramatic increase in the risk of colonic dysplasia or cancer in patients with long-standing UC with disease onset after 1972 compared to disease onset during or before 1972.[4]

The same study by suggests that less than 10% of patients with disease onset prior to 1972 had dysplasia or cancer, but more than 80% of patients with disease onset during or after 1972 had one or both of these conditions.

In addition, the changing IBD epidemiology, the North-South European disease pattern and the differences in therapeutic procedures cannot always explain these differences in disease course over time as far as IBD related colorectal cancer is concerned. On the other hand, increased longevity and the early IBD diagnosis may play an important role in answering this question.

Key words: Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, Dysplasia, Cancer, Colorectal cancer

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Abbreviations used in the text

IBDRC= inflammatory bowel disease related cancer
IBD= inflammatory bowel disease
UC= ulcerative colitis
CD= Crohn's disease
CRC= Colorectal cancer
SMR = standard mortality ratio
RR = relative risk
OR = odds ratio
CR = cumulative risk

3. MORTALITY-IN IBD AND MORTALITY RATES OF IBD RELATED CANCER

When stating that a death of an IBD patient was due to colorectal cancer in relation to IBD we must have in mind that some specific diagnostic criteria must be always be respected (Table 1).[5] The standardized mortality ratio in IBD is described as the following in tables 2 and 3.[6] In Mediterranean countries, mortality patterns of UC and CD are represented by the following numbers according to a retrospective study[7]: UC SMR= 0.6%, CD SMR= 1.9%. In addition, deaths caused directly by CD fell from 44% in the 1970's to 6% in the 1980's (fewer deaths from perforation and sepsis).[7] The ideal calculation of this rate is: deaths due to IBD-related cancer/ deaths in total IBD registry.[5]

The IBD cancer-related mortality may be influenced by the following risk factors: age (OR=1.16), male gender (OR=1.23), white race (OR=0.97) and history of NSAIDS consumption (OR=0,68).[2] However, the presence of IBD was not associated with a significant influence on CRC mortality (OR=1)[2] except for an increased mortality found among UC children.[3] This, sometimes-contradictory, evidence regarding the real influence of IBD cancer contribution to IBD mortality usually results from bias in the assessment of cancer risk, overall mortality and national or regional IBD surveillance programmes.

4. INCIDENCE AND RISK FACTORS OF IBD-RELATED CANCER

There is convincing evidence that the incidence of colorectal cancer is increased in patients with UC, particularly in those with extensive and longstanding disease. However, the magnitude of this risk still remains controversial.[8] Smoking habits contribute significantly to the increased mortality observed in CD while neoplasms represent the first cause of death in IBD, involving almost the quarter of all causes of death in IBD patients.[7]

Factors that probably influence the variability of assessing cancer risk in IBD are: patient selection bias, bias due to the small numbers of patients, starting-time bias, prevalence and incidence bias, the operation rate bias, completeness of case recruitment and ascertainment, completeness of follow up, duration of follow-up, differences in method of analysis and differences in endoscopic and other facilities.[8]

The following risk factors are supposed to be related to IBD-related cancer: age (OR=1.45), sclerosing cholangiitis (OR=3.41),[9] history of a disease associated with consumption of NSAIDS (OR=0.84). Moreover, proximal small bowel disease (jejunal), 6-mercaptopurine use and hazardous occupations are associated with cancer of the small bowel in patients with CD and can also be added to the long list of suspected risk factors.[10] The protective role of sulphasalazine or 5-ASA formulations has been shown in one study.[11] Sex, race and type of IBD do not exert, at the moment, a significant impact on cancer development.[2] It has been suggested that the most significant predictors for malignancy in IBD are the presence of dysplasia or DALM (dysplasia associated mass or lesion) in colonic biopsies, the time since disease onset and the extent of colonic involvement.[12]

It has also been proposed that the risk for IBD related cancer is greater if the diagnosis is made before the age of 15, if there is a family history of sporadic colorectal cancer,[12] and if there are anorectal fistulas or abscesses in case of Crohn's disease.[13] The calculated risk with respect to the extent of the disease has been proposed as follows (x times the expected incidence of colorectal cancer in the general population): proctitis x 1.7, left sided colitis x 2.8, pancolitis x 14.8; however no attempt risk assessment in small bowel disease was made[12]. As natural history of IBD and cancer differs between countries, cancer risk in IBD has to be investigated and measured in each country separately using standard methods and compared with the expected risk in that population[8].

A child younger than 15 years of age or an elderly patient with pancolitis and proximal small bowel disease, with abscess and fistulas diagnosed at least 15 yearsearlier, treated for many years with 6-MP and not with NSAIDS, working in a hazardous occupation, having a family history of sporadic colorectal cancer with high grade dysplasia or dysplasia associated with mass lesion (DALM) at biopsy and coexisting sclerosing cholangitis is the hypothetic at ideal patient to develop IBD-related cancer.

The following tables present a scenario for the proposed risk of colorectal cancer in IBD (Tables 4, 5, 6, 7).[6]

5. AGE-RELATED IBD CANCER EPIDEMIOLOGY

Older UC patients tend to die of routine aging diseases whereas young UC patients are more likely to die of UC complications or colorectal cancer. The lower number of colorectal cancer deaths in older UC patients may reflect either effective screening programmes for cancer or total colectomy as therapy of choice in early disease stages. Children with IBD, especially those with

Table 1. Specific diagnostic criteria for assigning causes of death by reviewing death certificates and hospital charts. (Adapted from Nordenoholtz K.E., et al: Am J Gastroenterol, 1995; 90(6):927-932.)

Group I:	Causes of death directly related to IBD	
	Group Ia	Causes of death primarily related to IBD with IBD listed on death certificate: perforation, obstruction, fistulae, sepsis, electrolyte impalance, massive bleeding, toxic megacolon, cardiac arrest, or cardiac arrhythmia specified as secondary IBD
	Group Ib	Cause of death secondarily related to IBD: sclerosing cholangitis, pyoderma gangrenosum, malnutrition, fistulae, or cancer of the bowel
	Group Ic	Death caused by medical complication acutely related to IBD, with IBD listed on the death certificate
	Group Id	Death caused by surgical complication acutely related to IBD, with IBD listed on death certificate
Group II:	Causes of death possibly related to IBD	
	Group IIa	Medical problem: pulmonary embolism (with IBD listed on death certificate), osteoporosis, gallstones, deep venous thrombosis, or suicide
	Group IIb	Death caused by surgical complication, not related to IBD, but occurring after IBD-related surgery. Surgical complications were defined as postsurgical events occurring in the hospital within 30 days and as logical consequence of that particular surgical procedure.
Group III:	Causes of death not related to IBD	

We defined the following causes of death as having no relationship to IBD: trauma, remote MI/ASHD/CAD, respiratory failure, senility, fractures, and cancer unrelated to colon

Table 2. Mortality in ulcerative colitis (adapted from Travis S.P.L. Alim Pharmacol Ther, 1997; 11: 51-59.)

Study	Country	N	Period	Prognosis
Persson et al. 1996	Stockholm, Sweden	1547	1955-90	*Overall SMR*: 1.37 (95% CI: 1.20-1.54) after 15 years *Duration of follow-up*: 0-?35 y (median not stated) *Effect of age*: 75% relative survival >60 years, 101% relative survival age <40 years at diagnosis *Effect of extent*: -3% relative survival for proctitis. -7% relative survival for pancolitis
Probert et al. 1993	Leicester, UK	1014	1972-89	*Overall SMR*: 0.93 (95% CI: 0.75-1.14) *Duration of follow-up*: 0-18 years (median not stated *Effect of age*: 96% relative survival >60 years. 113% relative survival <60 years at diagnosis *Effect of extent*: SMR 0.8 for proctitis, 0.85 for pancolitis, but 2.37 for undefined extent
Langholz et al. 1992	Copenhagen, Denmark	1161	1962-87	*Overall SMR*: 121 deaths/113.4 expected (1.06, P=0.25) relative risk 2.4 in first year (P<0.001) *Duration of follow-up*: 0-26 y (median 12 y) *Effect of age*: no significant effect *Effect of extent*: SMR= 1.68 for pancolitis (P<0.02)
Ekbom et al. 1992	Uppsala, Sweden	2509	1965-83	*Overall SMR*: 1.4 (95% CI: 1.2-1.5) after 10 years *Duration of follow-up*: 0-?21 years (median not stated) *Effect of age*: not examined *Effect of extent*: SMR= 1.0 for proctitis, 1.9 (95% CI: 1.7-2.2) for pancolitis
Stannington et al. 1987	Minnesota, USA	182	1979-85	*Overall SMR*: same as general population *Duration of follow-up*: ?range (median 14 y) *Effect of age*: not examined *Effect of extent*: not examined

Table 3. Mortality in Crohn's disease (adapted from Travis S.P.L. Alim Pharmacol Ther, 1997; 11: 51-59.)

Study	Country	N	Period	Prognosis
Persson et al. 1996	Stockholm, Sweden	1251	1955-90	*Overall SMR:* 1.51 (95% CI: 1.29-1.75) *Duration of follow-up:* 0-?35 years (median not stated) *Effect of site:* 93% survival for ileal disease at 15 years, 96% for colonic (N.S.)
Munkholm et al. 1993	Copenhagen, Denmark	373	1962-87	Overall SMR: 41 deaths/31 expected (P=N.S.) relative risk increased for 5 years in patients 20-29 years at diagnosis (P=0.04) *Duration of follow-up:* 1-25 years (median 8.5 years) *Effect of site:* relative risk 3.6 (P=0.03) for jejunoileal and 5.9 (P=0.007) for gastroduodenal disease
Probert et al. 1992	Leicester, UK	610	1972-89	*Overall SMR:* 0.72 (95% CI: 0.49-1.01). Mortality highest in first 4 years after diagnosis *Duration of follow-up:* 1-18 years (median not stated) *Effects of site:* SMR= 2.10 (95% CI: 0.44-6.21) for duodenal or jejunal disease. SMR=0,53 for ileal and 1.03 for colonic disease
Gollop et al. 1988	Minnesota, USA	103	1943-82	*Overall SMR:* Same as general population *Duration of follow-up:* ?range (median 9 y) *Effect of site:* no difference between ileal and colonic disease

Table 4. Risk of intestinal cancer in Crohn's disease *(adapted from Travis S.P.L. Alim Pharmacol Ther, 1997; 11: 51-59)*

Study	Distribution	Overall	Comment
Persson et al. 1996	Any CD	SMR=0,30 (95% CI: 0.01-1.66)	No data on colonic disease alone
Munkholm et al. 1993	Any CD	4.2% at 25 years, RR 1.1	Increased risk of small bowel cancer (RR 50, 95% CI: 37.1-65.9)
Ekbom et al. 1992	Any CD	RR 2.5 (95% CI: 1.3-4.5)	SMR=1.7, NS. RR 1.0 for ileal disease
Ekbom et al. 1990	Colonic CD	RR 5.6 (95% CI: 2.1-12.2)	Some cases diagnosed pre-1940

CD: Crohn's disease

Table 5. Risk for colorectal cancer in ulcerative colitis (adapted from Travis S.P.L. Alim Pharmacol Ther, 1997; 11: 51-59.)

Study	Extent	Risk of colorectal cancer	Comment
Persson et al. 1996	Any UC	SMR=2.85 (95% CI: 1.59-4.69)	Population based. 35% total colitis at diagnosis
Langholz et al. 1992	Any UC	3.1% at 25% years (95% CI: 0.0-6.8) Relative risk 0.9	Population based. 18% total colitis. Unrelated to extent or duration of UC
Ekbom et al. 1992	Any UC	SMR=4.4 (95% CI: 3.2-5.9)	Population-based. 34% total colitis. Includes patients diagnosed pre-1940
Lennard Jones et al. 1990	Extensive	3% at 15 years, 5% at 20 years, 9% at 15 years	Referral centre, so not population-based
Gyde et al. 1988	Any UC	7% at 20 years, 17% at 30 years	Primary referrals to three referral centres 59% total colitis

CD, develop cancer extremely rarely.[3]

Patients with CD diagnosed before the age of 30, with colonic involvement at diagnosis, have a higher relative risk (20.9) of cancer compared to those diagnosed at older ages (relative risk= 2.2).[14]

Table 6. Cancer incidence in ulcerative colitis (adapted from Travis S.P.L. Alim Pharmacol Ther, 1997; 11: 51-59.)

	No. of patients			Cancer						
	Review	Whole	Extensive	Whole	Extensive	Cumulative cancer incidence, whole series, %				
References	period	series	colitis	series	colitis	10 years	15 years	20 years	25 years	30 years
Hospital studies										
De Dombal, Leeds	1952-63	428	210	8	8	5	-	21	42	-
Devroede, Rochester	1919-65	396	303 (T)*	52	-	3	-	23	-	40
					2	12	30	-	50 (T)	
Lennard Jones, London	1966-76	-	229	-	5	0	5	10.3	-	30.4 (E)
Greestein, N.Y	1960-76	267	158	26	21 (T)	0.4	2.5	13	-	34
Prior, Birmingham	1944-76	679	462	35	35	-	-	-	8	20 (E)
Population studies										
Kewenter, Gothenburg	1952-75	-	234	-	15	3	9.6	24.2	-	- (E)
Hendrikson, Copenhagen	1960-78	783	124 (T)	?	2 (T)	0.8	1.1	1.4	-	-
Brostrom, Stockholm	1955-79	-	1274 (T)	-	-	-	3	5	_	13 (T)
Gilat, Tel Aviv	1970-80	1053	147 (T)	26		0.2	2.8	5.5	-	13.5
				10	0.5	1.7	3.8	-	8.7 (E)	
				13 (T)	0	9.3	13.8	-	- (T)	
Gyde, Birmingham	1945-65	823	486	38	7	0.7	3.4	7.2	11.6	16.5 (E)

*T= total colitis, E= extensive colitis

Table 7. Cancer incidence in Crohn's disease (adapted from Travis S.P.L. Alim Pharmacol Ther, 1997; 11: 51-59.)

			GIT cancers				Relative risk O/E		
	Review	No of		Small	Upper	Whole		Small	Upper
References	period	patients	Colorectal	bowel	GIT*	GIT	Colorectal	bowel	GIT
Hospital studies									
Weedon, Rochester	1919-72	449	8	1	0	-	26.6	-	-
Fielding, Birmingham	1944-68	295	1	2	4	3.5	-	100	17
Gyde, Birmingham	1944-76	513	9	1	8	3.3	4.0	-	3.2
Cooke, Birmingham	1944-76	174	3	1	6	2.1	-	-	-
Greenstein, New York	1960-76	579	7	7	3	5.0	6.9	100	-
Hamilton, Baltimore	1949-83	-	11	-	-	-	-	-	-
Kvist, Copenhagen	1964-83	473	3	2	-	-	-	-	-
Petras, Cleveland	1975-84	3500	7	4	-	-	-	-	-

*GIT= gastrointestinal tract

6. ULCERATIVE COLITIS VS CROHN'S DISEASE IN RISK OF DEVELOPING CANCER

There are many studies which to estimate the differences in risk of developing cancer between UC and CD. In UC, the ratio of observed/expected incidence of CRC was 5.7.[10] In UC, patients are more likely to die from colorectal cancer than CD patients.[5] In addition, this is more emphasized in children, where the occurrence of cancer is 12.5% in UC and 0% in CD respectively.[3] It has also been suggested that CD and UC result in similarly increased risk of colorectal cancer provided that cases of similar duration of disease and similar extent of colonic involvement are compared.[2] Another study suggests that the relative risk (RR) of colorectal cancer in CD reaches an overall 2.5 (terminal ileum RR=1, ileum + parts of colon RR=3.2, colon alone RR=5.6).[14] A zero to 10-fold increase in gastrointestinal malignancies in CD patients has been reported. The same study emphasizes the increased risk of small bowel adenocarcinoma, which has been estimated to occur 6 times more frequently compared to the general population.[1]

As conclusion, in UC the risk of developing cancer seems to be greater compared to that of the general population, despite which colectomy surely changes the magnitude of this risk. In CD with colonic involvement there is a "conflict" between investigators supporting the increased or otherwise risk of colorectal cancer[14,15] with studies from Denmark, Minnesota and Israel supporting that there is no increase in risk of colorectal cancer in CD patients.[6]

7. PRECANCEROUS LESIONS IN IBD

All precancerous lesions (dysplasia) are usually classified according to the grade of dysplasia and the co-existance with a dysplasia-associated lesion. Among all patients with high-grade dysplasia or dysplasia-associated lesion, 25-50% will develop carcinoma.[4] High-grade dysplasia or low-grade dysplasia in association with a lesion or mass is an indication for colectomy when confirmed by two pathologists. It is also very important to distinguish between colitis-associated and sporadic (adenomatous) dysplasia. The clinical distinction between ulcerative colitis-associated polypoid dysplastic lesion and sporadic adenomas is important because the former is an indication for colectomy whereas the latter is usually treated by simple polypectomy. There are a variety of clinical and pathological features that can be used to distinguish these lesions, but none of these features are entirely specific. Furthermore there is recent evidence to suggest that the molecular pathogenesis of UC-associated polypoid dysplasia is different in terms of the order and timing of genetic events in comparison to sporadic adenomas.[16] Which are the underlying causes of dysplasia? Can dysplasia be prevented? Those questions still remain unanswered, leaving a gap in the natural history of IBD cancer.

8. ALTERNATIVE MARKERS OF PREMALIGNANCY IN IBD

Many markers of premalignancy in IBD have been proposed. Inactivation of p53 tumor suppressor gene as a result of mutation or loss of heterozygosity has been found in many UC-associated neoplasms.Also microsatellite instability and transforming growth factor beta (TGF β) mutations have been described in a small number of UC-associated dysplasias and carcinomas. Some other markers of cell proliferation were also tested; Ki-ras mutations, CA 19-9, CA 50, carcinoembryonic antigen (CEA), adenomatous polyposis gene (APC gene), deletion in colon cancer gene (DCC) of C-scr tyrosine kinase, mucin-associated carbohydrate antigen sialosyl-Tn and Ki-67.

The frequency of aneuploidy increases with the degree of histological abnormality, from nonneoplastic epithelium through grades of dysplasia to carcinoma. The clinical importance of aneuploidy is that, when present without dysplasia, it is often an earlier marker of neoplastic change. When it occurs with indefinite or low grade dysplasia it adds a quantitative criterion that complements histological assessment.[1,17]

9. SMALL AND LARGE BOWEL IBD-RELATED CANCER

It is generally accepted that the large bowel is more accessible than the small intestine when using endoscopic facilities. This fact results in differences in diagnostic facilities, follow-up, therapeutical strategies and clinical outcome. Thus, small bowel cancer in IBD is less likely to be diagnosed at an early and curable stage (i.e. precancerous lesions). Moreover it may be that small bowel adenocarcinoma is the presenting symptom of Crohn's disease.[18]

10. CANCER PROGNOSIS IN IBD

This field is not well documented in studies which have been published to date. The 5-year cancer-specific survival rates in patients with UC-associated colorectal cancer are similar to the non-UC colorectal cancer patients and range from 41% to 72% in many specialized surgical departments.[1] Survival in Crohn's disease-related cancer has been less optimistically reported, mainly due to delayed diagnosis; however, more well designed prospective population based studies are needed. The method of staging and the therapeutical protocols for IBD-cancer prevention need to be further established and evaluated in long term prospective studies.

11. IBD ANTI-CANCER SURVEILLANCE AND DECISION FOR COLECTOMY

It is currently unknown whether colonoscopic surveillance reduces the risk of colorectal cancer in IBD. Biopsy surveillance after 8-10 years rather than total colectomy is proposed by some centers. Patients in remission should be followed annually or biannually and colectomy must be avoided indefinitely unless the patient develops evidence of dysplasia.[4] The same study also suggests that it would be too great a risk to allow patients with ulcerative pancolitis to postpone colectomy beyond about 15 years.[4]

The recommended frequency of colonoscopy varies in most series; a 2-year interval is used provided no abnormality is detected. It has been suggested that colonoscopy should be performed every 3 years for the first 12 years, then every 2 years for 6 years, then annually. Moreover it should be emphasized that, regardless of protocols, every patient with longstanding ulcerative colitis must undergo endoscopy 8-10 years after initial diagnosis. In case of dysplasia or dysplasia associated mass or lesion (DALM) colonoscopy must be performed within 3-6 months (Table 8).[1] The suggested management of dysplasia detected on colonoscopic surveillance is briefly presented in figure 1.

Table 8. Surveillance recommendations for patients with ulcerative colitis (adapted from Eaden JA, et al. Am J Gastroenterol 2000;95(10):2710-9)

Disease category	Colorectal cancer surveillance recommendations
Proctitis	Same as general population
Pancolitis	
<8 years	Same as general population
>8 years	A: Colonoscopic surveillance every 1-2 years with 2-4 biopsies every 10 cm, or
	B: Consider prophylactic colectomy

Colectomy is probably one of the most critical questions and therapeutical decisions. Strategies differ between countries and doctors. Consequently, colectomized patients may influence results from many studies reporting on the natural history of IBD-related cancer. This question still remains unanswered as the indications for colectomy in order to prevent IBD-related cancer are still under a lot of discussion worldwide.

12. INSURANCE ASPECTS AND QUALITY OF CARE IN IBD-RELATED CANCER

Ulcerative colitis is generally twice as common as CD. In health care numbers and insurance aspects these roles are dramatically reversed.[19-21] Colectomy is strongly recommended by some centers in all IBD patients with pancolitis after 15 years of disease, rather than to subject them to the discomfort, dread and cost of annual coloscopy, the fear of developing cancer and the expense and side effects of medication.[4] Additionally, the randomized controlled trials of surveillance programmes are highly unlikely in view of the low prevalence of IBD in the population, the long period of observation required and the probability of confusing surveillance programs with routine colonoscopy performed for assessment of disease activity.[1]

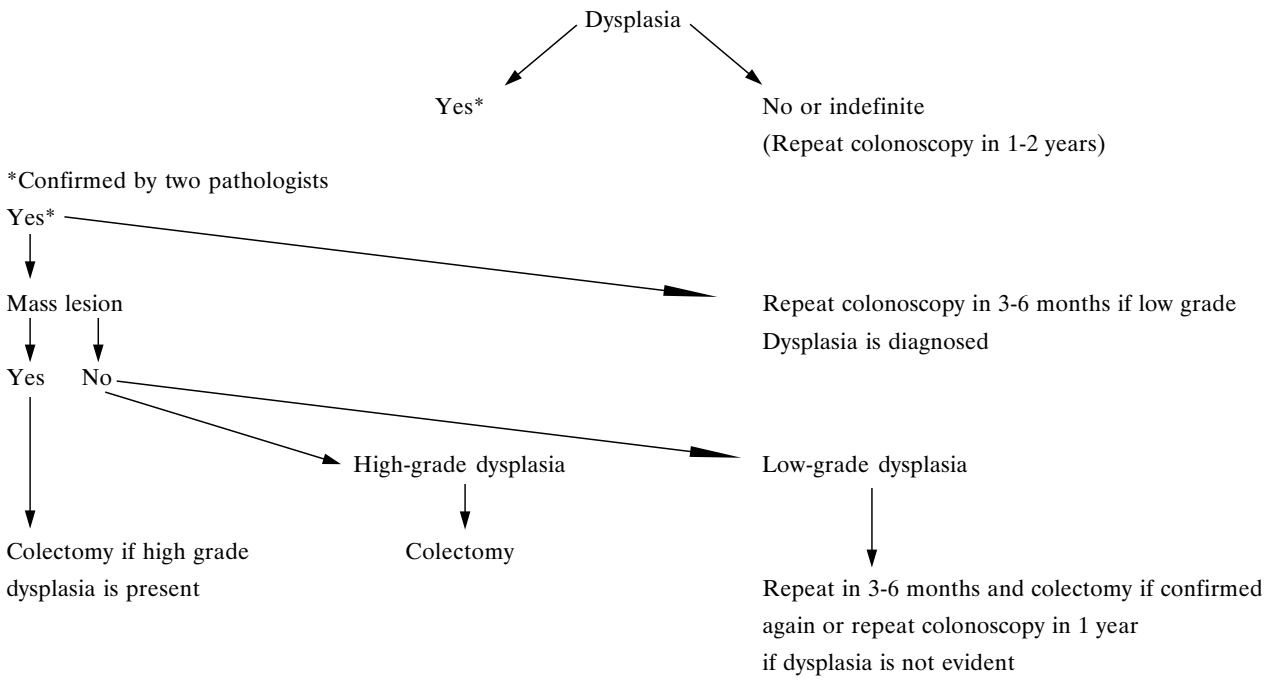

Figure 1. Suggested management of dysplasia detected on colonoscopic surveillance. (From Itzkowitz SH. Inflammatory bowel disease and cancer. Gastroenterol Clin North Am 1997;26: 129-39)

On the other hand, the insurance policy for IBD patients seems to be no different from that for the general population, taking into account of course the high probability of a non-surgical long-term disease outcome. Insurance costs for IBD patients vary among insurance companies and from country to country. These differences in insurance risks result mainly from the following bias of assessment of cancer and mortality risk in IBD,

- Incidence/prevalence bias
- Referral/institutional bias
- Ascertainment bias

Although observational studies[22-35] have given some hint as to which patients with IBD are at a higher risk of cancer, further studies are urgently needed to better characterize this group of patients. In addition, it seems that IBD-related cancer has to be reinvestigated and probably measured in each country separately, using standard methods of estimation. Further studies are, therefore, urgently needed.

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