Colorectal Cancer in Ulcerative Colitis: Effect of Cancer Prevention Strategy on Survival

Dr. Ahmet K. GÜRBÜZ, Dr. Francis M. GIARDIELLO, Dr. Theodore M. BAYLESS, Dr. Steven N. GOODMAN, Dr. John H. YARDLEY

Özet: *ÜLSERATİF KOLİT'TE KOLOREKTAL KANSER : KANSER ÖNLEME STRATEJİSİNİN YAŞAM SÜRESİNE ETKİSİ*

Ülseratif kolitli hastalarda kolorektal adenokarsinom riski genel popülasyona oranla 20-40 kat daha fazladır. Kolorektal malignite ve displazi (premalign lezyon) gelişme riskine karşı takip programları önerilmiş olmakla birlikte bu tip bir yaklaşımın yahut profilaktik kolektominin ülseratif kolit vakalarındaki kolorektal kanser mortalitesini azaltıcı etkisi halen ispatlanmamış olup bu tip takip programları bazı araştırmacılar tarafından kabul görmemektedir.

Biz bu çalışmada 1956-1991 yılları arasında Johns Hopkins hastanesinde tanı konmuş kolorektal adenokarsinom ve ülseratif kolitli 40 hastanın prognozunu inceledik. Hastalar iki gruba ayrıldı. Kolorektal kanser açısından asemptomatik 18 hastada kolonoskopi, displazi için biyopsi, kolon grafisi gibi testlere dayalı takip programı yahut profilaktik kolektomi uygulanmıştı. Kalan 22 hastada ise ilerlemiş kanseri önleyici diagnostik testler veya profilaktik kolektomi uygulanmamıştı. I ve II. evredeki kolorektal kanserlerin oranı koruyucu takip programı uygulanan hastalarda %67 (12/18), bu tedbirlerin uygulanmadığı hastalarda ise % 9 (2/22) idi (Wilcoxon test p < 0,01). Bu gruplarda kolorektal kansere bağlı 5 yıllık yaşam ise sırayla %89 (Güv. Ara. % 61-97) ve %19 (Güv. Ara. %6-39) idi (p<0.001).

Sonuç : Koruyucu strateji uygulanarak izlenen ülseratif kolitli hastalarda saptanan kolorektal kanserler koruyucu takip programları uygulanmayan gruptakilere oranla anlamlı derecede erken evrede yakalanmakta ve daha uzun yaşam süresini mümkün kılmaktadırlar.

Anahtar kelimeler: Kolorektal kanser, korunma, ülseratif kolit, yaşam süresi.

Meyerhoff Digestive Disease and Inflammatory Bowel Disease Center, The Johns Hopkins University School of Medicine and Hospital.

This paper has been presented as an abstracat at 1'st United European Gastroenterology Week 1992 in Athens-Greece.

Summary: *Patients with ulcerative colitis are at 20 to 40 times increased risk for colorectal adenocarcinoma compared to the general population. Although surveillance for colorectal malignancy and dysplasia (a premalignant lesion) has been recommended, a benefit in reducing mortality from colorectal cancer via surveillance or prophylactic colectomy remains unproven and is still challenged by some authors.*

We reviewed the outcome of 40 consecutive ulcerative colitis patients with colorectal adenocarcinoma diagnosed between 1956-1991 at the Johns Hopkins Hospital. Patients were divided into two groups. Eighteen asymptomatic patients had received diagnostic testing (colonoscopy, biopsies for dysplasia, or barium enema) or had undergone "prophylactic" colectomy as part of a colorectal cancer prevention strategy (Prevention Group) while 22 patients did not undergo cancer prevention testing or prophylactic surgery (Nonprevention Group). Colorectal cancer was diagnosed at a statistically significantly earlier cancer stage in the Prevention Group [12 of 18 (67%) at stage I or II] compared with the those in the Nonprevention Group [2 of 22 (9%) at stage I or II] (Wilcoxon test p < 0.01). Colorectal cancer 5 year survival in the Prevention Group was 89% (CI 61-97%) and in the Nonprevention Group 19% (CI 6-39%) (p < 0.001).

Conclusion : Ulcerative colitis patients with colorectal cancer discovered as part of a prevention strategy had malignancies that were less invasive and showed greatly increased survival compared to patients not undergoing colon cancer prevention.

Key words: Colorectal cancer, prevention, ulcerative colitis, survival.

Although estimates vary between studies, patients with ulcerative colitis are at a 20 to 40 fold increased risk for colorectal cancer compared with the general population (1-8). Increased risk correlates with greater extent (2, 9-13), duration of disease (4,8,9), and young age of onset (2). The presence of colorectal mucosal dysplasia, a premalignant lesion, (14-21) is strongly associated with colorectal cancer, being present in over 90% of patients.

A widely cited recommendation for patients with chronic ulcerative colitis is colonoscopic biopsy surveillance for dysplasia and early cancer (19,20,22-25). However, some medical writers have strongly criticized this surveillance strategy because of the lack of comparative mortality data, arguing, among other points, that most cancers found are quite advanced. Also, there is no compelling evidence that surveillance for dysplasia does improve survival from colorectal cancer (1,26). This debate has left both patients and physicians confused.

In 1993, Choi and colleagues from the Lahey Clinic published retrospective data indicating that colonoscopic surveillance does indeed reduce mortality from colorectal cancer in ulcerative colitis (27). An earlier abstract from the Cleveland Clinic came to a similar conclusion (28).

The purpose of the present study was to determine if a management strategy of colorectal cancer prevention in ulcerative colitis patients actually reduced colorectal cancer mortality compared to an expectant management approach. Since it is unlikely that a prospective study of surveillance will be done, we analyzed retrospectively the TNM stage and survival of consecutive patients with ulcerative colitis and colorectal cancer seen at The Johns Hopkins Hospital between 1956 and 1991. In addition, potential sources of bias influencing interpretation of conclusions from this methodology, which have not been extensively analysed by others, are discussed.

METHODS

We investigated the cancer stage and the survival of all patients with histologically confirmed ulcerative colitis and colorectal cancer seen at The Johns Hopkins Hospital from 1956 to 1991. Cases were identified by searching the Johns Hopkins Inflammatory Bowel Disease Registry, surgical pathology files, and the Oncology Center Cancer Registry from 1956 to 1991. The findings leading to a diagnosis of ulcerative colitis, dysplasia, and colorectal cancer and information needed for the staging of cancers were obtained from the surgical pathology records. Original case findings were reviewed to verify questionable cases (JHY). Forty patients were identified. Each patient's medical records were evaluated and telephone contact with the individual or surviving family members was made if historical data was not current. Follow-up was 100%.

Patients were separated into 2 groups depending upon whether they had undergone colorectal cancer prevention measures or not. Patients in the Prevention Group (PG) were asymptomatic individuals with ulcerative colitis in whom colorectal cancer was diagnosed as a result of a diagnostic test administered as a screening procedure. These procedures included colonoscopy (n=14), flexible sigmoidoscopy (n=1), barium contrast studies (n=2) or colectomy (as part of a colorectal cancer prevention strategy) (n=1).

Patients in the Nonprevention Group (NPG) were known to have ulcerative colitis and had not received either diagnostic procedures directed at finding dysplasia or colorectal cancer nor elective surgery. They were found to have colorectal cancer after presenting with intially referred to The Johns Hopkins Hospital for ulcerative colitis.

Colorectal cancer stage was determined by histopathologic examination and clinical observation at the time of surgery and post operatively. Colorectal cancer was staged according to the TNM system of the American Joint Committee on Cancer (29) as follows :

I: Invasion of submucosa or muscularis propria.

II: Invasion through muscularis propria into subserosa or nonperitonealized pericolic or perirectal tissues or perforates visceral peritoneum or directly invades other organs or structures.

III. Metastasis to pericolic or perirectal lymph nodes.

IV. Distant metastasis.

Stage I, II, and III are equivalent to stages A, B, C, under the original Dukes' classification (30). Finer gradations of the TNM system were not considered because of the relatively small number of cases and limitations of available retrospective information.

Survival and cause of death was assessed by review of medical records, death certificates, cancer registry data, and telephone contact with the patient or surviving family members. Three living patients were operated upon less than 5 years ago (1 patient in PG, and 2 in NPG, all cancer stage III) and were included in the analysis.

Statistical differences in cancer stage between the Prevention and Nonprevention groups was calculated by Wilcoxon test. Survival analysis was done using the Kaplan-Meier method (31,32). Survival time was determined from date of colorectal cancer diagnosis to date of death or last contact. The two groups were compared using Peto's logrank test.

RESULTS

Forty patients with ulcerative colitis and colorectal cancer were included in this consecutive case review. The mean age at colorectal cancer diagnosis was 47.25 ± 2.32 years and the mean duration of ulcerative colitis at the time of cancer diagnosis was 20.60 ± 1.59 years. Nineteen of 37 patients died from colorectal cancer in the 5 year follow-up period. Death occurred at a mean of 0.87 ± 0.71 years from the colorectal cancer diagnosis (range 1 month to 3 years).

The Prevention Group (PG) was composed of 18 patients and there were 22 patients in the Nonprevention Group (NPG). There were no statistically significant differences in demographics, clinical characteristics (Table 1), or calender time of cancer diagnosis between these 2 groups. All 40 patients were white.

Colorectal cancer was diagnosed at a statistically significantly earlier cancer stage in the patients in the Prevention Group than in those in the Nonprevention Group (Table 2). The tumors in 12 of 18 PG patients (67%) were cancer stage I (Dukes A) or II (Dukes B) compared with 2/22 NPG patients (9%).

Table I: Characteristics of study population with ulcerative colitis and colorectal cancer.

	Prevention Group n=18	Nonprevention Group n=22
No. (%) males	11 (61%)	14 (64%)
Mean (SEM) age at onset of ulcerative colitis	29.4 ± 3.4*	24.5 ± 3.4
(Range)	(8-45)	(4-73)
Mean (SEM) age at dx of colorectal cancer	48.5 ± 3.1	46.3 ± 3.4
(Range)	(29-81)	(13-74)
Mean (SEM) time from onset of ulcerative colitis to dx of colorectal cancer	19.2 ± 1.6	21.7 ± 2.6
(Range)	(1-29)	(1-52)
No. (%) with pancolitis	14/14 (100%)	10/14 (71%)

* Age of onset unknown in 1 patient.

Kaplan-Meier survival analysis with groups compared by the Peto's logrank method is shown in Figure 1. The Kaplan-Meier 5 year survival probablities are : Prevention Group 89% (CL, 61-97%) Nonprevention Group 19% (CL 6-39%).

The time from onset of ulcerative colitis symptoms to diagnosis of colorectal cancer was 19.17 ± 1.55 years in the Prevention Group and 21.70 ± 2.57 years in the Nonprevention Group (not statistically significant).

DISCUSSION

In this study, ulcerative colitis patients with colorectal cancer discovered as part of a cancer prevention strategy by diagnostic testing with colonoscopy, barium enema, or prophylactic colectomy had statistically significantly less invasive malignancies than patients not undergoing colon cancer prevention measures. Finding cancer at an earlier pathologic stage was accompanied by a significant improvement in survival

Table II: TNM stages of colorectal cancer in patients with ulcerative colitis classified by Prevention and Nonprevention groups.

Cancer Stage (V)	Prevention Group	Nonprevention Group
I	5	0
II	7	2
III	4	9
IV	2	11

Differences in TNM stage between Prevention and Nonprevention groups by Wilcoxon test $x^2 = 14.00$, $p < 0.01$.

at 5 years for those in the prevention group (89% vs. 19% respectively; $p < 0.001$).

These results strongly support the work of Choi (27) and Bozdeck (28). The above findings are necessary but alone not sufficient to prove the benefit of surveillance. Investigations of cancer surveillance are subject to a variety of potential biases which can produce inprovement in survival of surveillance cases, when, in fact, there would be no decrease in mortality in a surveyed population. Our study design did not eliminate some of these biases, but the possible impact of each can be assessed and discussed.

One explanation for the low mortality in the screened group could be overdiagnosis such that lesions detected on colonoscopy might never have come to clinical presentation (33). This bias can not be discounted, because we do not know how many patients were screened, and therefore cannot estimate the expected frequency of cancer in an entire prevention population. An elevated incidence of colorectal cancer would suggest an excess detection of benign lesions due to the screening. However, we believe substantial overdiagnosis to be unlikely based on several considerations. The yield of dysplasia and cancer in several "surveillance" programs does not exceed the frequency of cancer in the population of ulcerative colitis patients controlled for age of onset of colitis, duration, and extent of disease. Importantly, since 17 of the cancers in the Prevention Group were found on the first prevention test, they should not be considered a result of "surveillance" a term which is probably best utilized for studies in which an initial negative colonoscopy has established the absence of dysplasia or cancer. All colorectal cancer occurring in patients with inflammatory bowel disease at The Johns Hopkins Hospital from 1956 to 1991 have been included in our registry making it unlikely that a large number of patients in our patient population have had undetected colorectal cancer. Also, the natural history of colorectal cancer is generally one of progressive disease which eventually reaches clinical presentation (33). Furthermore, in ulcerative colitis patients, high grade dysplasia, a premalignant marker for risk of colorectal malignancy, usually progresses to cancer of the colon. Moreover, a recent study finds that even low grade dysplasia found on initial colonscopy eventually progresses to carcinoma in most patients (34).

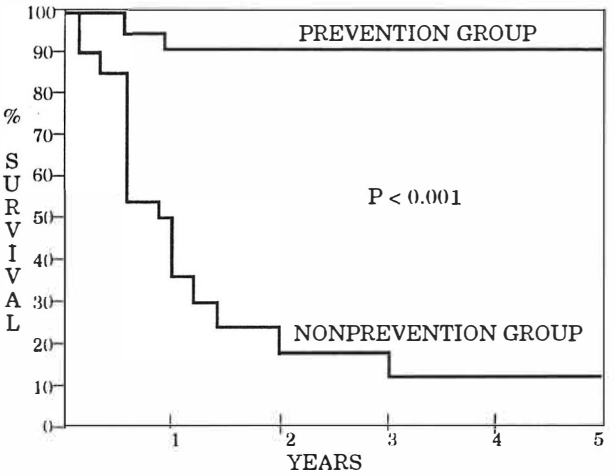

Fig. 1: Survival curves for Prevention group and Nonprevention groups. There is a significant difference between groups for mortality by Peto's logrank method ($p < 0.001$).

Another factor that can produce artifactual survival time benefit is lead-time bias : survival benefit is produced by an earlier time of diagnosis, with no change in ultimate age at death. This bias cannot be eliminated in this study, since the mechanism of survival benefit is disease detection and treatament at a time before it presents clinically. However, in this study there was a dramatic difference in stage distribution, as well as differential in 5 year mortality. Numerous other studies have shown a strong correlation between 5 year and long-term survival and the neoplastic invasion stage (35). Conversely, if an earlier or less invasive disease stage at

time of diagnosis had only a lead time effect, we would expect the survival curves of different cancer stages to be identical after adjustment for lead time effect. In our study, this was not the case.

The degree of diagnostic advancement produced by screening can be estimated biologically. A recent study approximates that the latent phase -the duration of time between the initial asymptomatic development of malignancy and subsequent occurrence of a clinical problem from more invasive stages of cancer- is about 5 years (33). In high risk colorectal cancer populations, investigators have estimated that it takes 10 to 15 years for flat normal colorectal mucosa to progress to colorectal cancer (36). In ulcerative colitis patients, there appears to be an approximately 7 year period between the initial detection of colorectal dysplasia and the development of invasive carcinoma (37). In our study, the 2.5 years difference between the two groups in duration of UC before cancer diagnosis would appear to be the best estimate of the lead time effect. Repeating the survival analysis with 2.5 years added to the non-prevention group survival time did not appreciably effect the results as is evident from Figure 1. It should be noted however, if there had been substantial over-diagnosis, (which we believe is unlikely) the effect of lead-time bias could not be accurately assessed.

Another distortion of survival benefit can occur with referral bias, wherein the prevention population is different in a way that would effect prognosis after diagnosis independently of screening. We do not believe that this unduly affected our results. All our subjects were cared for at The Johns Hopkins Hospital, had been referred for management of ulcerative colitis, and had similar demographic characteristics. Also, they all had cancer. Any characteristic associated with being screened would have to be associated with prognosis after diagnosis, and no such characteristic is currently known.

A difference between the two groups that could be related to prognosis and screening is calendar time. However, roughly equal proportions of patients from the prevention and nonprevention group were screened during each of three decades. Although screening for colon cancer in the general population has led to earlier diagnosis, there has been no major improvement in colon cancer survival, stage for stage, over the past 30 years. This is due in part to lack of effective chemotherapy for more invasive cancer stages.

The most subtle potential effect is length-time bias, whereby the timing of the screening selectively detects tumors that are slower growing i.e. have a longer pre-clinical phase, and therefore, might have a better prognosis independent of screening. Without repeated screening, this effect is difficult to assess. On close scrutiny, there is empirical evidence in these data both for and against this effect. The evidence in favor of a length-time bias is seen in the 2.3 year older age at the time of ulcerative colitis diagnosis in the prevention group. If screening was done partially because of the subjects advancing age, then any subject who had a faster growing tumor that presented before that age would not have a chance to enter into the screening group. The fact that one patient had a colectomy because of the "long duration of ulcerative colitis" lends anecdotal support for this possibility. Another clue to length-time bias might be differing prognoses between the two groups with in the same cancer stage. Unfortunately, the sample size was too small to assess this factor.

The shorter duration of UC at the time of cancer diagnosis in the prevention group is evidence against the lenght-time bias. Since duration of UC is one of the strongest clinical risk factors for colorectal cancer development, stronger than age at diagnosis of UC, it is reasonable to assume that screening started at a time before most cancers would have presented clinically in the prevention patients would have profited by colonoscopic biopsy or contrast X-ray screening. Since no patients in the prevention group presented with colorectal cancer after an earlier negative screening colonoscopy, it seems that most of these lesions were long-standing.

The work of Lennard-Jones and colleagues (15,17,24), Bosdeck et al., (28) and Choi et al., (27) strongly reinforce our conclusions. All three support the concept that colorectal cancers found as the result of a dysplasia detection pro-

gram are at a less invasive cancer stage than those neoplasms found only as a result of cancer related symptoms. The Lahey Clinic Study also demonstrated an improved 5 year survival in the "surveillance group" (27). In view of these three studies mentioned above as well as the natural history of ulcerative colitis and colorectal cancer, we think it unlikely that various biases could have produced the dramatic survival difference observed in our study. A carefully done case-control or cohort study is needed to accurately determine the survival impact and cost-effectiveness of a cancer/dysplasia surveillance program in UC patients. It is doubtful that an untreated group of patients with dysplasia, especially high grade dysplasia could be followed without surgical intervention.

Presently, physicians caring for individuals with extensive ulcerative colitis are faced with several management options to prevent cancer in their patients. These options include : first, prophylactic colectomy before or after 8-10 years of pancolitis especially of individuals with onset of colitis before 20 years of age; second, colonoscopic biopsy surveillance at some regular frequency directed at persons with longstanding and extensive colitis, considering colectomy if dysplasia is found; or third, expectant management waiting for cancer-related symptoms before applying diagnostic testing. The last option has been shown in this mortality based retrospective cohort study to be unacceptable compared to some method of colorectal cancer screening and secondary prevention. In patients with extensive colitis deferring colectomy, our results represent an important confirmation from mortality data that colorectal cancer survival is improved by applying a strategy of early detection of dysplasia or cancer prevention rather than expectant management.

KAYNAKLAR

1. 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.
2. Ekbom A, Helmick C, Zack M, Adami HO. Ulcerative colitis and colorectal cancer : a population based study. N Engl J Med 1990; 323 : 1228-33.
3. Dawson IM, Pryse-Davies J. The development of carcinoma of the large intestine in ulcerative colitis. Br J Surg 1959; 47 : 113-128.
4. Devroede GJ, Taylor WF, Sauer WG, Jackman RJ, Stickler GB. Cancer risk and life expectancy of children with ulcerative colitis. N Engl J Med 1971; 285 : 17-21.
5. Devroede GJ, Taylor WF. On calculating cancer risk and survival of ulcerative colitis patients with the life table method. Gastroenterology 1976; 71:505-509.
6. MacDougal IP. The cancer risk in ulcerative colitis. Lancet 1964; 2 : 655-658.
7. Michener WM, Gage RP, Sauer WG, Strickler GB. The prognosis of chronic ulcerative colitis in children. N Engl J Med 1971; 265 : 1075-1079.
8. Prior P, Gyde SN, Macartney JC, Thompson H, Waterhouse JA, Allan RN. Cancer morbidity in ulcerative colitis. Gut 1982; 23 : 490-497.
9. Maratka Z, Nedbal J, Havelka J, Kudrmann J, Hendl J. Incidence of colorectal cancer in proctocolitis : a retrospective study of 959 cases over 40 years. Gut 1985; 26 : 43-9.
10. Gilat T., Fireman Z, Grossman A, et al. Colorectal cancer in patients with ulcerative colitis : a population study in central Israel. Gastroenterology 1988; 94 : 870-7.
11. Gyde SN, Prior P, Allan RN, et al. Colorectal cancer in ulcerative colitis : a cohort study of primary referral from 3 centres. Gut 1988; 29 : 206-17.
12. Katzka I, Brody RS, Morris E, Katz S. Assessment of colorectal cancer risk in patients with in ulcerative colitis; experience from a private practice. Gastroenterology 1983; 85 : 22-9.
13. Mir-Madjlessi SH, Farmer RG, Easley KA, Beck GJ. Colorectal and extracolonic malignancy in ulcerative colitis. Cancer 1986; 58 : 1569-74.
14. Rosenstock E, Farmer RG, Petras R, Sivak MV Jr, Rankin GB, Sullivan BH. Surveillance for colonic carcinoma in ulcerative colitis. Gastroenterology 1985; 89 : 1342-6.
15. Lennard-Jones JE, Morson BC, Ritchie JK, Williams CB. Cancer surveillance in ulcerative colitis : experience over 15 years. Lancet 1983; 2 : 149-52.
16. Blackstone MO, Riddell RH, Rogers BHG, Levin B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis : an indication for colectomy. Gastroenterology 1981; 80 : 366-74.
17. Lennard-Jones JE, Morson BC, Path FRC, Ritchie JK, Shove DC, Williams CB. Cancer in colitis : assessment of the individual risk by clinical and histological criteria. Gastroenterology 1977; 73 : 1280-9.
18. Nugent FW, Haggitt RC. Results of a longterm prospective surveillance program for dysplasia in ulcerative colitis. Gastroenterology 1984; 86 : 1197.
19. Nugent FW, Haggitt RC, Gilpin PA. Cancer surveillance

in ulcerative colitis. Gastroenterology 1991; 100 : 1241-8.

20. Riddell RH, Goldman H, Ransohoff DF, Appleman HD, Fenoglio CM, Haggitt RC, Ahren C, Correa P, Hamilton SR, Morson BC, Sommers SC, Yardley JH. Dysplasia in inflammatory bowel disease : standardized classification with provisional clinical applications. Human Pathol 1983; 14 : 931-68.

21. Morson BC, and Pang LSC. Rectal biopsy as an aid to cancer control in ulcerative colitis. Gut 1967; 8 : 423-434.

22. Lashner BA. Recommendations for colorectal cancer screening in ulcerative colitis : a review of research from a single university-based surveillance program. American Journal of Gastroenterology 1992; 87 : 168-75.

23. Levin B, Lennard-Jones J, Riddell RH, Sachar D, Winawer SJ. Surveillance of patients with chronic ulcerative colitis. W.H.O. collaborating center for the prevention of colorectal cancer. Bull World Health Organ 1991; 69 : 121-6.

24. Lennard-Jones JE, Melville DM, Morson BC, Ritchie JK, Williams CB. Precancer and cancer in extensive ulcerative colitis : findings among 401 patients over 22 years. Gut 1990; 31 : 800-6.

25. Bozdech JM, Oakley JR, Farmer RG. Cancer surveillance in ulcerative colitis. Evidence for improved survival. Gastroenterology 1990; 98 : A471.

26. Axon ATR. Carcinogenesis in ulcerative colitis : Is surveillance worthwhile? Scan J Gastroenterol 1990; 4 : 397-399.

27. Choi PM, Nugent FW, Schoetz DJ, Silverman ML, Haggitt RC. Colonoscopic surveillance reduces mortality from colorectal cancer in ulcerative colitis. Gastroenterology 1993; 105 : 418-23.

28. Bozdech JM, Oakley JR, Farmer RG. Cancer surveillance in ulcerative colitis : Evidence for improved survival. Gastroenterology 1991; 100 : A199.

29. American Joint Committee on Cancer, Manual for staging of cancer. Beahrs, OH, ed. 3rd ed. Philadelphia : Lippincott, 1988.

30. Dukes CE. The classification of cancer of the rectum. J Pathol Bacteriol 1932; 35 : 323-332.

31. Cox DR. Regression models and life tables. J R Stat Soc B. 1972; 34 : 187-220.

32. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Assoc. 1958; 53 : 457-81.

33. Koretz RL. Malignant polyps : Are they sheep in wolves' clothing? Annals of Internal Medicine 1993; 118 : 63-68.

34. Woolrich AJ, DaSilva MD, Korelitz BI. Surveillance in the routine management of ulerative colitis : The predictive value of low grade dysplasia. Gastroenterology 1992; 103 : 431-8.

35. Moertel CG, Thynne GS. Large Bowel. In : Holland JF, Frei E, eds. Cancer Medicine. 2nd ed. Philidelphia : Lea and Febiger, 1982 : 1830-58.

36. Boland CR, Itzkowitz SH, Kim YS. Colonic polyps and the gastrointestinal polyposis syndromes. In : Sleisenger MH, Fordtran JS, eds. Gastrointestinal disease : pathophysiology, diagnosis, and management. 4th ed. Philadelphia : WB Saunders, 1989 : 1500-7.

37. Kewenter J, Hulten L, Ahren C. The occurrence of severe epithelial dysplasia and its bearing on treatment of longstanding ulcerative colitis. Ann Surg 1982; 195 : 209-13.

38. Gyde S. Screening for colorectal cancer in ulcerative colitis : dubious benefits and high costs. Gut 1990; 31 : 1089-1092.