Surveillance of patients with chronic ulcerative colitis

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In chronic ulcerative colitis, the object of surveillance is prevention of cancer or at least prevention of death from cancer by diagnosis at an early curable stage or by detection at a pre-malignant phase. Patients must be informed about their cancer risk as well as the limitations of endoscopic surveillance and the availability of surgical alternatives. Physicians must bear in mind the risks, benefits and costs of surveillance procedures.

Patients at greatest risk of cancer for whom endoscopic surveillance is warranted are those with extensive colitis of greater than 8 years duration. Colonoscopy should be performed every 1 to 2 years at which time multiple biopsies are obtained from every 10–12 cm of normal-appearing mucosa. Targeted biopsies should also be obtained from areas where the surface appears raised as a broad-based polyyp, low irregular plaque or villiform elevation, or from an unusual ulcer, particularly one with raised edges, or from a stricture. Typical inflammatory polyps need not be sampled. Colectomy is recommended in the presence of multifocal high-grade dysplasia if confirmed by an experienced pathologist. The identification of a mass lesion associated with any degree of overlying dysplasia is also a generally accepted indication for colectomy, while persistent low-grade dysplasia without a mass is somewhat more controversial. Recently introduced biomarkers may replace or supplement dysplasia in surveillance programmes as well as provide new information about malignant transformation.

Introduction

Among all the patients diagnosed as having a large bowel adenocarcinoma only about 1% give an antecedent history of inflammatory bowel disease. In many Western countries inflammatory bowel disease is only a small part of the cancer problem although cancer represents a larger part of the management of inflammatory bowel disease. This paper discusses colonoscopic surveillance of patients with ulcerative colitis who are in a high-risk category for the development of adenocarcinoma of the colon. Carcinoma of the colon also occurs in patients with long-standing Crohn’s colitis although the absolute risk is probably somewhat less (1). Dysplasia may be less common and at present regular surveillance is not recommended.

Carcinoma of the colon occurs more commonly in persons with ulcerative colitis than in the general population. There is some disagreement among investigators about the magnitude of the risk, but it is agreed that the cancers occur in colitis patients at a younger age than in the population at large. The reported incidence varies from approximately 2% (2) to over 4% (3) of all patients with ulcerative colitis, the incidence being directly related to the duration of symptoms. Development of carcinoma is very unusual within 10 years of onset; thereafter, most recent estimates give a cumulative incidence of about 5% at 20 years and 12% at 25 years (4–8). The extent to which genetic predisposition and environmental factors such as diet modify the risk is as yet unknown in patients with inflammatory bowel disease. As reported by Lennard-Jones (9), there are a number of issues which must be taken into account when analysing studies that describe the magnitude of risk. They include the following.

(a) The duration of follow-up; the proportion of patients followed for less than 10 years will affect the results.

(b) The population studied, with regard to:

—extent of the disease; patients with proctitis have no increase in risk of cancer (10). The risk for patients with left-sided colitis may be delayed until approximately 10 years later than in those patients whose entire colon is involved (11). The extent to which the risk is increased is still controversial as studies utilizing colonoscopy and biopsies to define the extent of colonic involvement have not been
performed. Studies which relied on radiological assessment of the extent of colitis may have overestimated the number of cases of left-sided colitis if some of the patients with radiologically determined left-sided disease, who had not been examined colonoscopically, actually had universal disease. It is likely that such “potential overestimation of the size of the population with left-sided colitis could produce only an underestimation of the cancer incidence in this group since only the denominator of the incidence ratio would have been overestimated” (11).

—referral bias; many series in the past included a majority of patients with the most severe disease who had been referred to large tertiary care hospitals. Patients from private practices may reflect a different group with lower risks of developing cancer (5).

(c) Treatment policy; in some centres about 20% of all patients with cancer undergo proctocolectomy within the first 10 years of their disease because of acute or chronic symptoms (9, 12). Improvements in surgical technique and newer procedures have favoured more aggressive surgical treatment, thus removing from the pool of patients those who would later be at risk for the development of a malignancy (5).

Risk assessment

Methods of data analysis

Often risk cannot be assessed since the incidence cannot be accurately expressed without knowledge of the size of the population at risk. The life-table method estimates the proportion of the population likely to develop cancer as if that were the only factor leading to withdrawal over the period of follow-up. This method tends to overestimate the number of patients who develop carcinoma in older age groups because the mortality rate from other causes is higher. It also overestimates the risk when many patients among an inception cohort are treated by proctocolectomy.

Despite these methodological difficulties it is well recognized that persons in the highest risk category are those in whom the entire colon is affected with colitis and who have had their disease for more than 8 years. Prior studies assessed the extent of risk based on the roentgenographic appearance of the colon. However, radiological changes are less sensitive than an assessment of extent judged by colonoscopic biopsies.

Despite the aforementioned sources of variability, however, it is well worth noting that uniform methods of data analysis yield a rather striking uniformity of estimates of cancer risk in most populations of patients with ulcerative colitis, namely about 0.5–1% per year after the first 10 years of disease (13, 14).

Pathogenesis of cancer in ulcerative colitis

In the non-colitic population, most, if not all adenocarcinomas arise from a pre-existing adenoma (14). Adenomas are characterized by a cytological change (dysplasia) and a proliferative change which results in a polyoid or villous projection into the lumen. In chronic ulcerative colitis the mucosa undergoes analogous changes with development of cytological or architectural abnormalities. Dysplasia is defined as an unequivocal neoplastic alteration of the colonic epithelium. Dysplastic epithelium not only may be a marker or precursor of carcinoma but may itself overlie an area of malignancy associated with direct invasion into the underlying submucosa (14). It is important to recognize that all adenomas are dysplastic but in ulcerative colitis dysplasia may not take the form of an adenomatous polyp. In ulcerative colitis, adenomatous polyoid or villous lesions may occur but more commonly dysplastic cytological changes occur in flat mucosa (15).

Multiple areas of dysplasia may occur in the colon of an affected patient. Indeed, colitis-associated cancers are more often multifocal than are cancers in the general population (16, 17). Unfortunately an invasive neoplasm (carcinoma) may develop without passing through the stage of a precursor mass and thus those lesions may be extremely difficult to recognize endoscopically or by double-contrast radiography. However, the dysplasia may occasionally be proliferative, producing a slightly elevated velvety area or mucosal plaque on the mucosal surface. The likelihood of carcinoma rises significantly in the presence of a dysplasia-associated lesion or mass (DALM) (18, 19).

Patient management

The management possibilities for patients at high risk for cancer include periodic surveillance, prophylactic proctocolectomy, or no specific action. The decision to recommend prophylactic proctocolectomy after 7 to 10 years of colitis must be based on a number of considerations in the individual patient (18). These include intractability of symptoms, age, psychological make-up, availability of newer surgical procedures, etc. The patient who acquires extensive ulcerative colitis at a young age and faces a lifelong programme of surveillance may be better served by a prophylactic colectomy (13), but this has to be balanced against the morbidity of a Brooke ileostomy or newer procedures such as the Kock pouch or the ileal pouch–anal anastomosis. If the patient is unwilling to accept the surgical procedure, regular surveillance is a
reasonable alternative. Cancer surveillance may not be warranted in patients with the onset of colitis after the sixth decade of life because the increased risk of colitis does not then begin until the seventh decade at an age when the additional risk from colitis approximates to the average risk in the general population.

**Screening (surveillance) methods**

The aim of a screening programme is primarily to detect a premalignant phase or malignancy at an early curable stage. Ideally, in patients with ulcerative colitis, the aim is to identify patients in the high-risk group who appear especially likely to develop cancer by detection of high-grade dysplasia and thus prevent mortality from cancer by advising colectomy. Once cancer develops, it had previously been reported that the prognosis was worse than for non-colitic cancer; but more recent data (22, 23) suggest that the prognosis is similar in both groups, provided equivalent stages are compared.

Colonoscopic biopsies are used to obtain tissues from the entire colon. However, because of the vast surface area of the colon, it is clear that only a tiny fraction of the mucosa can be sampled and dysplasia may be overlooked. Clearly, the number of biopsy sites is arbitrary but many clinicians obtain biopsies at 10–12-cm intervals throughout the colon. The areas to be sampled are the caecum, ascending colon, hepatic flexure, transverse colon, splenic flexures, descending colon, sigmoid and rectum. The highest yield will be achieved by biopsying areas of mucosal irregularity. Biopsies from each area should be placed in separate containers and labelled separately. Areas of suspected abnormality can then be resampled if dysplasia is identified by the pathologist (24). Obvious inflammatory polyps (“pseudopolyps”) should not be biopsied since they may show inflammation that tends to make the diagnosis more difficult. However, if any mass lesions including inflammatory polyps are over 1 cm in diameter or differ in coloration from the usual inflammatory polyps, multiple biopsies should be taken (24).

Multiple biopsies and brushings from cytology should be obtained from strictures since a malignancy may be present in over one-third of the cases (9). If doubt exists about the extent of disease in patients with ulcerative proctitis or apparent left-sided colitis, a colonoscopic examination with biopsies is indicated to determine the extent of the disease. In patients with strictly left-sided ulcerative colitis, it is likely that the surveillance programme could begin at a later stage, possibly after 12–15 years of disease, although data are insufficient to support this viewpoint with any degree of certainty.

**Pathological interpretation**

A recent classification of dysplasia based on the extensive discussions of an expert panel of pathologists has helped to reduce some of the confusion that has plagued both clinicians and pathologists faced with the management of patients with chronic ulcerative colitis (24). This classification consists of three major categories: negative, indefinite, and positive for dysplasia.

Negative biopsies include normal tissue and inactive and active colitis without any dysplasia. The indefinite category includes biopsies that cannot be classified as unequivocally positive or negative. The positive category includes all instances in which dysplasia is unequivocally present; these are further subdivided into low-grade and high-grade dysplasia.

Low-grade dysplasia corresponds to biopsies previously described as mild or moderate dysplasia. High-grade dysplasia refers to the severe cytological and architectural features of neoplasia previously called severe dysplasia.

**Clinical interpretation**

Based on the new pathological classification, an approach to patient management is suggested below (see “Recommendations for practice”) and in the algorithm (Fig. 1). This approach is followed by many but not all clinicians and pathologists. The recommendations place considerable emphasis on the finding of an endoscopic mass in the presence of dysplasia, but the management of a patient with low-grade dysplasia is not well defined in the absence of a mass. Obviously, when dysplasia is found, it does not necessarily mean that carcinoma is present. In the series of surveillance colonoscopies that were reported and summarized by Waye (25), 15% of the patients had dysplasia and 20% of these were subsequently found to have carcinoma of the colon. It is of interest to note that 1% of patients had the diagnosis of cancer made by a direct mucosal biopsy. Of concern is the finding that 10% of patients with cancer did not have dysplasia in any of the endoscopic biopsies. To further emphasize the fact that dysplasia may not be identifiable in all patients with cancer in colitis, distant dysplasia was found in only 73% of specimens in a retrospective survey of resected colons (26). All biopsies and especially any suggestion of dysplasia should be carefully reviewed by an experienced pathologist. The decision to recommend a colectomy on the basis of mucosal dysplasia is strengthened if the dysplasia is found in more than one location in the colon or on more than one occasion, but even the single finding of unequivocal high-grade dysplasia or any grade of dysplasia in association with a mass lesion is sufficient indication, provided that the pathologic diagnosis is
confirmed by a specialist in the field. Although the significance of low-grade dysplasia without a mass is unknown, its persistence over a period of months may be cause for concern; more prospective information is needed.

Management of adenomas

In the young patient an adenomatous polyp is more likely to be part of a dysplasia-associated mass. In the patient over 40 years of age, it is possible that a sporadic adenomatous polyp may occur as it frequently does in the general population. A sporadic adenoma is often stalked, which is not a feature of a dysplasia-associated mass. It is necessary to examine the stalk and the adjacent mucosa. If the stalk is part of a large patch of dysplasia, colectomy is probably indicated. An adenomatous polyp situated in normal mucosa proximal to distal colitis may be treated as a sporadic adenoma.

Frequency of screening

If a decision to place a patient under surveillance is made, it seems prudent in the absence of dysplasia to perform colonoscopy at 12–24-month intervals once the duration of colitis exceeds 8–10 years and if no dysplasia is found on the initial evaluation. It is important to emphasize the greater risk of cancer associated with dysplasia detected at the initial colonoscopy compared to those in whom it appears later. During the first 8–10 years of colitis, the risk of carcinoma is so low that regular colonoscopy is not needed. If colonoscopy is not available, regular rigid or flexible sigmoidoscopy with biopsy yields useful results because about half of the carcinomas in colitis occur in the rectosigmoid and dysplasia may also be found in this region.

New biomarkers

Recent efforts have focused on a search for intermediate biomarkers that could forecast the development of dysplasia or cancer before the phenotypic expression of cancer. These include changes in tumour antigens (27), aneuploidy detected by flow cytometry (28, 29), oncogene expression (30), and lectin binding (31, 32).

Cost-benefit analyses

Cancer surveillance in ulcerative colitis is expensive. Lennard-Jones and his colleagues have emphasized the significant efforts involved for medical staff and patients (6). They acknowledge that the “ideal result, the prevention of cancer and restriction of operation to patients with demonstrated precursor has not occurred as often as we had anticipated”. Nevertheless, their surveillance for carcinoma in over 400 patients may have prevented the development of carcinoma in 12 patients and permitted the diagnosis of carcinoma at a curable stage in another 12 (6).

Recommendations

The approach to the patient with chronic ulcerative colitis must be individualized. Not only is it based on an estimate of the individual’s personal risk for development of cancer but must also include an assessment of the local facilities for surveillance and management. Patients who are non-compliant or who enter the high-risk category when very young may be better advised to undergo prophylactic proctocolectomy.

Reduction to an absolute minimum of the risk for cancer is clearly an important goal but surveillance, however carefully performed, is not 100% reliable in achieving this end. Nevertheless, for many patients who do not wish to have a prophylactic colectomy, it provides a reasonable alternative.
Specific recommendations

(1) Assess the duration of symptoms and determine the extent of colonic involvement, preferably by colonoscopic biopsies.

(2) Begin surveillance colonoscopies in patients with 8 years of symptoms who have pancolitis (extending to at least the hepatic flexure) and in those with left-sided colitis (more distal involvement) after 12–15 years. The recommendation for surveillance in left-sided colitis is not yet based on firm evidence.

(3) Repeat surveillance colonoscopies every 1–2 years. Take biopsies from normal-appearing mucosa at 10–12-cm intervals throughout the colon.

(4) Take multiple biopsies from areas of mucosal irregularity and plaque-like lesions; do both biopsies and cytology brushings within strictures.

(5) Obtain expert pathological consultation.

(6) If the biopsies are classified as negative or indefinite, continue surveillance at 1–2-year intervals.

(7) If low-grade dysplasia is found, follow-up in three to six months is advisable. Colectomy is indicated (a) for a macroscopic lesion with overlying low-grade dysplasia, (b) for low-grade dysplasia in multiple foci, and (c) possibly for persistent unifocal low-grade dysplasia on repeated examinations even if the available data are insufficient to support this.

(8) If unequivocal high-grade dysplasia is found, colectomy is indicated.

Recommendations for research

The following specific research objectives might be useful in improving the clinical results of surveillance and in enhancing our understanding of the biology of cancer.

(1) Develop uniform criteria for identifying the high-risk group to be studied (e.g., age, duration of disease, and definition of the extent of the disease, preferably by colonoscopic biopsies).

(2) Standardize endoscopic and pathological reporting.

(3) Map abnormalities throughout the colon using techniques such as flow cytometry, mucin immunohistochemistry, and oncogene assay and correlate them with the distribution of histological dysplasia.

(4) Use molecular genetic techniques to study genetic abnormalities, e.g., genetic linkage, allelic deletion, and loss of heterozygosity.

(5) Assess newer endoscopic techniques, e.g., autofluorescence, laser-induced fluorescence, ultrasound, and magnification endoscopy.

(6) Evaluate possible metabolic abnormalities, such as abnormal bile salt metabolism which may play a role in carcinogenesis.

Résumé

Surveillance des malades atteints de rectocolite ulcéro-hémorragique

Dans la rectocolite ulcéro-hémorragique, l’objectif de la surveillance est de prévenir la mortalité par cancer, par détection de la phase pré-maligne ou par diagnostic du cancer à un stade où la guérison est possible. Les médecins doivent avoir à l’esprit les risques possibles de la maladie et connaître les techniques de surveillance. Les malades doivent être bien informés du risque de cancer et des limites certaines de la surveillance par endoscopie, et de l’existence de nouvelles opérations.

Les malades courant le risque le plus élevé de cancer, pour lesquels la surveillance endoscopique est tout à fait justifiée, sont ceux ayant une rectocolite étendue durant plus de huit ans. Une coloscopie devrait être effectuée tous les un à deux ans, et s’accompagner de biopsies multiples prélevées à une distance de 10–12 cm de la muqueuse d’apparence normale. Des biopsies focalisées devraient être également effectuées sur les régions villeuses de la muqueuse, les zones d’ulcération avec une bordure surveillée et les rétrécissements. Il n’est pas nécessaire de faire des prélèvements des polypes inflammatoires. La colectomie est recommandée quand il existe une dysplasie multifocale ou d’un stade avancé, confirmée par un anatomo-pathologiste expérimenté. L’identification d’une masse associée à un degré quelconque de dysplasie sous-jacente est également considérée de façon générale comme une indication de colectomie alors qu’une dysplasie persistante de faible gravité, non accompagnée d’une masse, est une indication discutée.

La prévention du cancer est un facteur important à envisager quand il faut conseiller des malades jeunes, ayant une rectocolite étendue, sur l’éventuelle nécessité d’un traitement chirurgical. L’existence de nouvelles techniques chirurgicales comme la poche iléale et l’anastomose iléo-anale peuvent offrir aux malades une qualité de vie améliorée, comparée à celle que donne une iléostomie permanente, ce qui influence également la décision concernant un traitement opératoire. La surveillance régulière est un choix raisonnable si le malade n’est pas prêt à accepter une opération majeure. La surveillance du cancer peut ne pas être justifiée chez les malades dont la rectocolite a commencé après la soixantaine car il n’y a pas d’augmentation du risque après l’âge de 70 ans, quand le risque supplémentaire dû à la colite est à peu près équivalent à celui du risque moyen de la population en général.
Des biomarqueurs récemment mis au point peuvent améliorer les résultats de la surveillance et aider à éclaircir la biologie de la transformation maligne. Ces nouveaux marqueurs comprennent l'expression d' oncogènes, les antigènes tumoraux, la liaison aux lectines et l'anéuploïdie décelée par cytométrie de flux.

References


