Dysplasia in ulcerative colitis

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ABSTRACT: Patients at highest risk for developing cancer in ulcerative colitis are those with 'extensive' or total involvement of the large bowel who have had the disease for at least seven years. Dysplasia is used as a marker but has many problems including those of sampling, reproducibility and management. The risk in patients with colitis is unclear particularly in those with left-sided or distal ulcerative colitis. In countries at high risk from colorectal cancer about 4 to 6% of the population can be expected to develop this disease. It is assumed that surveillance will reduce the mortality from colorectal cancer, although the evidence that this is happening is very limited. Cancers which are resected but from which the patient survives are an acceptable outcome, although less so in theory, as survival is to a certain extent fortuitous. Many surveillance studies include patients who have both developed and died from carcinoma. Surveillance also assumes that cancers can be detected before they have become lethal, or that a marker such as the presence of dysplasia precedes all carcinomas for a long enough period of time to be detectable. Considerable question has been raised as to whether dysplasia is both endoscopically detectable and morphologically identifiable. Surveillance is based on the principle that carcinoma arises from a cancerous lesion, and that the identification of dysplasia and excision of the large bowel in these patients prevents subsequent death from disseminated carcinoma. Conversely, patients with quiescent disease and no dysplasia could be followed and not subjected to unnecessary colectomy. There is currently no 'best' way of managing patients with colitis who are at risk for developing carcinoma. Routine follow-up of patients relies heavily on colonoscopy with multiple biopsies. Controversy continues regarding the management of dysplastic biopsies because there are relatively few data regarding the likelihood of an underlying invasive carcinoma on which to base a rational decision. The notion that all patients must be managed on an individual basis, guarantees that data remain difficult to obtain. The presence of a dysplasia-associated lesion or mass are high risk factors for carcinoma. Dysplasia is frequently confined to small areas of the mucosa causing major sampling problems for the endoscopist both in detection and if confirmation by re-endoscopy is proposed. The finding of aneuploidy as a marker for both dysplasia and carcinoma may prove useful in the detection of patients at greatest risk. **Can J Gastroenterol 1990;4(7):378-383** *(pour résumé, voir page 379)*

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IN ULCERATIVE COLITIS THE SUBgroup of patients at highest risk for colorectal carcinoma are those with extensive or total involvement of the large bowel, who have had the disease for at least seven years; patients in this group are at a lifetime risk of the order of 25 to 50%. The use of dysplasia as a marker in ulcerative colitis has many problems including those of sampling, reproducibility and management.

WHICH PATIENTS ARE IN THE HIGH RISK GROUP?

There is no argument that patients with total involvement of the large bowel diagnosed radiologically are at risk. What is much less clear is the nature of risk in patients with colitis that is other than total, colitis that is total microscopically but not by other criteria, colitis that extended to total colitis from distal disease, or even Crohn's colitis (unless colectomy has been carried out Crohn's ileitis may not be easily amenable to endoscopic examination and biopsy). Inevitably, case reports are published of carcinoma coexisting with left-sided or distal ulcerative colitis. However, it must be remembered that in countries at high risk from colorectal cancer, about 4 to 6% of the population will develop this disease, and that in three-quarters of these (3 to 5% of the population) this will occur in the left colon, the rectosigmoid in particular. Carefully controlled studies are therefore essential to demonstrate whether there really is an

Dysplasie et colite ulcéreuse

RESUME: Le risque du cancer du côlon est majoré chez les patients porteurs de colite ulcéreuse depuis au moins sept ans et chez qui la majeure partie ou la totalité du côlon est atteinte. La dysplasie constitue un signe avant-coureur mais pose de nombreux problèmes concernant les prélèvements, la reproductibilité des résultats et le traitement notamment. Le risque auquel sont exposés les patients souffrant de colite n'est pas clair, surtout dans les atteintes à prédominance gauche et dans la colite ulcéreuse distale. Dans les pays où les risques du cancer du côlon sont élevés, on estime qu'environ 4 à 6 % de la population contractera la maladie. On suppose que les examens de surveillance réduiront la mortalité pour cancer colorectal bien que les preuves à cet effet soient très limitées. Les cancers réséqués mais auxquels le patient survit représentent un dénouement acceptable, bien que sur le plan théorique la notion de survie soit fortuite. De nombreuses études de surveillance incluent à la fois les patients qui sont atteints de cancer et ceux qui en sont décédés. La surveillance suppose également que les cancers sont repérables avant de devenir incurables, qu'une manifestation telle que la dysplasie précède tous les carcinomes, et cela suffisamment à l'avance pour être décelée. On s'interroge beaucoup pour déterminer si la dysplasie est identifiable tant sous endoscopie que morphologiquement. La surveillance adopte le principe décrétant que le cancer se développe à partir d'une lésion cancéreuse, et que la reconnaissance de la dysplasie et l'amputation du côlon chez les patients atteints prévient les décès résultant des cancers généralisés. Ainsi, les patients en phase de quiescence et sans signe de dysplasie pourraient être suivis sans subir de colectomie inutile. Il n'existe actuellement pas de façon "supérieure" de traiter les cas de colite risquant de dégénérer en cancer. Le suivi de routine s'appuie surtout sur la colonoscopie accompagnée du biopsies multiples. Le traitement qui fait suite aux biopsies dysplasiques continue à être controversé parce qu'il existe relativement peu de données autorisant une décision rationnelle et permettant d'évaluer la présence éventuelle d'un carcinome invasif sous-jacent. Le principe préconisant le traitement individuel des cas continue à compliquer l'accès aux données. La présence d'une lésion ou tumeur de type dysplasique constitue un risque élevé de cancer. La dysplasie ne se manifeste souvent qu'à quelques endroits limités de la muqueuse; cette caractéristique pose un problème majeur à l'endoscopiste chargé d'effectuer le prélèvement tant au niveau de la détection initiale que lorsqu'il s'agit de confirmer les résultats. La détection d'une hétéroploïdie indiquant à la fois une dysplasie et un cancer peut s'avérer utile à la détection des patients à risque élevé.

increased risk in patients with distal ulcerative colitis in whom the extent of disease has been accurately assessed by endoscopy and biopsy. This is probably best assessed following a relapse, preliminary evidence suggesting that the proximal extent of disease may regress endoscopically when the disease is in remission (1).

All of these factors combine to produce a clinical problem for which there is no easy solution, the only alternatives available being either to carry out proctocolectomy fairly indiscriminately after about 10 years of disease, or to observe the patient closely and try to detect precarcinomatous (dysplastic) changes or carcinoma as early as possible. Although proctocolectomy might still be the best mode of therapy in some patients such as those who appear unreliable, are easily lost to follow-up or in whom total colonoscopy and biopsy is technically difficult, a surgical approach is often resisted by both patients and their physicians. The possibility that dysplasia might be used as a method of screening to detect patients within the group that might be at greatest clinical risk has contributed further to the demise of 'routine' proctocolectomy as a method of cancer prevention when no other indications for the operation are present.

THE CONCEPT OF DYSPLASIA

Surveillance in ulcerative colitis has as its basic tenet the assumption that surveillance will reduce the mortality from colorectal cancer, although the evidence that this is happening is very limited (2). This would ideally have been proven in studies using a control arm with patients not in a surveillance program, but this is obviously difficult to carry out ethically. In the absence of a controlled study, data are required showing that surveillance prevents the development of lethal cancers. One study used as a 'control' patients that had been lost to follow-up, and indeed found two cancers in 1168 patient-years of patients followed but with no mortality, compared with five cancers, three of which were lethal in 315 patient-years of patients lost to follow-up (3). Theoretically then, cancers which are resected but from which the patient survives, are acceptable. Unfortunately, many surveillance studies include patients under surveillance who have both developed (4-7) and occasionally even died from carcinoma (8-10). Many colitic cancers are flat or plaque-like and readily escape endoscopic or radiologic detection (11), while even if found there are few data showing that they really are less advanced pathologically (3,10,12,13). Nevertheless, while several studies indicate that no lethal cancers developed, the number of patient-years of follow-up must be sufficiently high to allow determination of the number of cancers that might have been expected together with whether the program actually showed a significantly different figure from this.

A second major tenet of surveillance is either that cancers can be detected before they have become lethal, or that a marker such as dysplasia precedes all carcinomas for a long enough period of time to be detectable, analogous to the adenoma-carcinoma sequence in the noncolitic bowel (14). Also, if dysplasia is present it must be both endoscopically detectable and morphologically identifiable. Considerable question has been raised regarding all of these issues.

The concept of dysplasia in ulcerative colitis is based on the principle that carcinoma also arises from a precarcinomatous lesion, and that the identification of dysplasia and excision

TABLE 1
Modification of biopsy classification of dysplasia and its clinical implications

Biopsy classification	Clinical implications
Negative	Regular surveillance
Indefinite	Increased surveillance
Positive	
Low grade	Increased surveillance
High grade	Consider colectomy

of the large bowel in these patients prevents subsequent death from disseminated carcinoma. Conversely, patients with quiescent disease and no dysplasia could be followed and not subjected to unnecessary colectomy.

The large step from the pure concept of dysplasia to its applications in patient management implies three major points. One is that prophylactic proctocolectomy in all patients in the high risk clinical group is unacceptable. The second is that a laissez faire attitude is similarly not condoned. Third, there is no good method of easily anticipating which patients within the clinical high risk group will develop carcinoma. Dysplasia is therefore best regarded as an aid to predicting which patients are at greatest risk of developing carcinoma, so that prophylactic surgery would be offered only to this subgroup.

Many institutions have now attempted to use dysplasia as part of the long term follow-up of colitics at greatest risk for developing carcinoma. It seems logical that patients with these changes should be at greater risk for having or developing invasive carcinoma, compared with their fellow colitics who do not have dysplasia. This appears to have been established in view of the proportion of patients undergoing proctocolectomy for rectal dysplasia that are subsequently found to have an invasive adenocarcinoma (usually unsuspected) when the resected bowel is subjected to close pathologic examination. Fortunately, most of these carcinomas are detected early and have not infiltrated through the muscularis propria or into the adjacent lymph nodes. The cure rate for these early carcinomas is expected to be over 90%. However, some unexpected carcinomas do extend through the wall and into the lymphatics, and survival in this group will be less favorable.

STANDARDIZED DEFINITION AND CLASSIFICATION OF DYSPLASIA

Dysplasia is defined as an unequivocal neoplastic alteration of the colonic epithelium which not only may be a marker or precursor of carcinoma, but may itself be malignant and associated with direct invasion into underlying tissue (15). Because dysplastic mucosa of any grade may give rise directly to an invasive carcinoma (carcinoma infiltrating into the submucosa or beyond), a positive diagnosis of dysplasia cannot be taken lightly. This definition of dysplasia is analogous to that used when speaking of adenomas in the colon, the rest of the gastrointestinal tract, and other sites in patients who do not have IBD. The classification consists of three major categories (Table 1): negative, indefinite and positive for dysplasia. It is essential that the pathologist be aware of the wide range of inflammatory and reparative changes that may affect the colonic mucosa in chronic IBD (15), and that these be excluded before an unequivocal diagnosis of dysplasia is made. If the observer has any doubt at all regarding whether the changes are dysplasic/neoplastic, the diagnosis is changed to that of indefinite for dysplasia.

The morphological diagnosis of dysplasia has been clarified. The subjective categorization of biopsies into those negative, indefinite and positive for dysplasia, the description of the changes found in regeneration epithelium and criteria for subdivision of dysplasia into low grade and high grade have been defined (15). However, despite the best efforts of an international panel of pathologists there is still inter- and intra-observer variability, and even more clinical disagreement on criteria for the timing of colectomy between institutions and within them. However, these are relatively uncommon at both ends of the dysplasia spectrum (negative for dysplasia and high grade dysplasia), but like any spectrum arbitrarily and subjectively divided, areas of overlap inevitably occur in areas where the bell-shaped curve (for the reading of dysplasia when carried out by a series of pathologists for each biopsy) overlaps with those of its neighbours.

DYSPLASIA-ASSOCIATED LESIONS AND MASSES (DALMs)

A critical issue in the management of colitis is the finding that an endoscopic lesion may show only dysplasia on biopsy, either high or low grade, and yet be the superficial part of any invasive carcinoma (16). Indeed, that dysplasia has this potential is an integral part of the definition of dysplasia. Both the presence and usefulness of the concept of DALMs have been demonstrated (16-18).

ABSENCE OF DYSPLASIA WITH INVASIVE CARCINOMA

Although studies examining adjacent and distant mucosa in patients presenting with clinical carcinoma find dysplasia in only about three-quarters (19), it is easy to argue that the invasive component outgrew and destroyed pre- or coexisting dysplasia analogous to the lack of finding an adenomatous edge to a carcinoma in noncolitic cancers. Nevertheless in the stomach the preceding lesion for the diffuse variant of carcinoma remains poorly defined and virtually impossible to diagnose on biopsy. Because a proportion of colitic cancers are morphologically similar to this variant of gastric cancer, it may not be surprising if the same occasionally occurs in the large bowel. In addition, some carcinomas complicating ulcerative colitis have a very strong endocrine component and may be regarded as endocrine carcinomas, the preinvasive phase of which is again poorly defined irrespective of whether they occur in the setting of dysplasia or not. Finally, the precancerous phase may be very brief or dysplasia limited to the immediate vicinity of the carcinoma. Surveillance, therefore, now entails a deliberate search both for mucosal abnormalities which may prove on biopsy to be invasive carcinoma, or areas of

dysplasia with or without an underlying invasive element.

MUCOSA INDEFINITE FOR DYSPLASIA

Modification to the original classification of dysplasia: This group was originally subdivided into probably negative, unknown and probably positive subgroups. Increasingly, the regenerative and reparative changes originally classified here are being recognized for what they really are, so that the number of biopsies in this category (probably negative) has diminished over the past decade and its use is now relatively infrequent. Functionally, the inclusion of active reparative changes with 'negative for dysplasia' rather than with 'indefinite for dysplasia – probably negative' leaves only the other two categories of 'indefinite for dysplasia' ('unknown', and 'probably positive') in the 'indefinite for dysplasia' category. In practice, it is hardly worth vacillating between these two, as both have the same clinical implication of a need to gather more data by repeating endoscopy and biopsies. This results in a simpler classification and suggested management of biopsies (Table 1).

The subcategorization of 'probably positive' implies that the changes observed are most likely neoplastic but either fail to display sufficient nuclear changes to justify inclusion in that category or contain an overriding factor, usually active inflammation and regeneration, that results in caution on the grounds that they are unlikely to completely regress and may progress to unequivocal dysplasia. Also, as detection of aneuploidy becomes more frequent, there may be a trend to subdivide patients in the 'indefinite for dysplasia' group on this criterion rather than a subjective morphological interpretation.

IMPLICATIONS OF BIOPSY RESULTS FOR PATIENT MANAGEMENT

This section is included because there is no 'best' way of managing patients with colitis who are at risk for developing dysplasia, and because the pathologist's advice is invariably critical, particularly when the question of possible colectomy is raised. Routine follow-up of patients relies heavily on colonoscopy with multiple biopsies, and this is usually carried out at roughly annual intervals. Preliminary data indicated that double contrast barium enemas may have a place in the localization of suspicious lesions to be biopsied, but this is not generally used (20). Single contrast barium enemas are frequently worthless because only gross lesions are detected; if these prove to be neoplastic the prognosis is usually extremely poor. Given the current lack of objective data, colonoscopy with multiple biopsies appears to be the best method of following patients and detecting early neoplastic changes. Recommendations following colonoscopy are very limited, consisting only of follow-up colonoscopy about one year later, follow-up at a shorter interval (increased surveillance), or a recommendation for colectomy (usually proctocolectomy).

REPRODUCIBILITY

The system of classification rests on whether biopsy interpretations prove reasonably reproducible by the same pathologist and by other pathologists familiar with the system. As with all subjective assessments of a spectrum of changes that is somewhat arbitrarily divided and that depends to a certain extent on personal experience, reproducibility is not absolute. Nevertheless, given the relatively limited number of options available, false-negative and false-positive results will be relatively uncommon (15). However, as these will occasionally occur, some form of confirmation should be sought when biopsy changes are a major indication for considering surgical intervention, preferably by the aid of a second pathologist familiar with the system, or by repeated biopsies (15). The latter is fraught with hazard, primarily because the endoscopic appearances of dysplasia remain very poorly documented so that it may be virtually impossible to return to what may have been a very small patch of dysplasia.

MANAGEMENT OF DYSPLASTIC BIOPSIES

Controversy continues regarding the management of dysplastic biopsies. The immediate problem is that there remain relatively few data regarding the likelihood of an underlying invasive carcinoma being present on which to base a rational decision. The notion that all patients must be managed on an individual basis continues to guarantee that data remain difficult to obtain. This is often the case because the decision for colectomy is rarely made on the basis of dysplasia alone, but weighing both the risks and benefits of all courses of action. Numerous factors affect this decision, including the extent of disability from the disease, the attitude of both the patient and physician towards colectomy, age and life expectancy of the patient, operative risk, and availability of and confidence in both the pathologist and surgeon, the latter particularly if a pouch procedure is contemplated.

However, there are circumstances where there is relatively uniform agreement regarding a recommendation for colectomy. These include the presence of a DALM endoscopically which probably stands a greater than 50% risk of being an invasive cancer on resection, particularly if found on the first (diagnostic) rather than subsequent (surveillance) colonoscopy (16,18).

The reason is that at the first endoscopy the length of time that a lesion has been present is unknown, while if seen at surveillance colonoscopy it is unlikely to have been present for extended periods of time. The same also holds true for the presence of dysplasia of any grade if seen at the first colonoscopy; thus its presence at first colonoscopy should lead to much more serious consideration of dysplasia than if it develops at surveillance colonoscopy.

Confirmation of dysplasia: The question of whether confirmation of dysplasia is required, and if so how it is best confirmed has become contentious. Confirmation by a second pathologist clearly depends on the competence of both pathologists and the degree of confidence that the gastroenterologist has in each pathologist.

Most of the time the diagnosis of dysplasia is very straightforward, so that confirmation by a second pathologist is usually only necessary if either party is insecure. This assumes that there has been a distinct learning curve over the past decade, particularly in the distinction from reparative changes, which certainly appears to be the case. However, the likelihood of requesting a second opinion inevitably increases if colectomy is being considered primarily because of the biopsy diagnosis of dysplasia.

Focality of dysplasia and problems of sampling: In contrast to patients presenting clinically with invasive carcinoma in whom dysplasia may be relatively widespread and cancers multiple (19,21), in patients under surveillance both of these are uncommon. Dysplasia is frequently confined to small areas of the mucosa, causing major sampling problems for the endoscopist. Further, endoscopic dysplasia is very poorly defined in the literature which largely reiterates gross pathological descriptions. No good prospective study exists, and most accept that dysplasia (and sometimes invasive carcinoma) may occasionally be found on random biopsies in the absence of an endoscopic abnormality. Unless dysplasia is widespread or an area of dysplasia can be visualized endoscopically, confirmation of dysplasia by repeat endoscopy and biopsy is usually doomed to failure because it has repeatedly been shown that dysplasia is patchy (22-24). Current sampling methods of taking one to two biopsies every 10 cm of bowel assume that perhaps 5 mm^2 of biopsy is representative of 100x100 mm^2 of mucosa, that is, at best 1/2000th of the mucosa is being sampled. Given this intense sampling problem, if one is fortunate enough to detect dysplasia on biopsy it makes little sense to ignore it if the criterion for colectomy is the development of dysplasia. To accentuate the sampling problem further, a 2x2 cm^2 patch of dysplasia would require about 20 to 25 evenly spaced biopsies in a 10 cm length of bowel to reasonably guarantee its detection. In requesting an endoscopist to confirm the presence of dysplasia by repeating the endoscopy and the biopsies, we are clearly being incredibly optimistic and unrealistic, and should not be surprised if such missions fail.

Options for management: Options for patient management are regular surveillance, increased surveillance or resection. If resection is not recommended then the option is to repeat the endoscopy and biopsies; the only issues are when and how the results will affect the management algorithm. Some have criteria for consideration of colectomy which variously include the repeated demonstration of dysplasia on endoscopic biopsy, the development of high grade dysplasia, the repeated demonstration of low grade dysplasia, or the development of a DALM. All of these options are geared towards delaying colectomy, the assumption being that the risk of a potentially lethal cancer at this time is extremely low, a position for which there is little support, and which deliberately chooses to disregard that part of the definition of dysplasia stating that it may give rise directly to invasive carcinoma irrespective of the grade, and may also be the superficial part of an invasive carcinoma. It also ignores the fact that carcinomas may escape endoscopic detection, that it is impossible to time colectomy to the point of minimal invasion, and that strategies along these lines do not appear to have reduced mortality from colorectal cancer in surveillance programs.

Currently, 'surveillance' now implies looking for both colorectal cancer and dysplasia at the time of colonoscopy, which in these patients is usually carried out annually or bennially, but there is no predetermined 'best' time interval between colonoscopies. At colonoscopy a careful search is made of the large bowel for plaque-like lesions or mucosal irregularities which may be the endoscopic counterpart of either dysplasia or carcinoma (DALM). The presence of invasive carcinoma in these lesions may only be apparent following histological examination of the resected specimen. In the absence of such lesions multiple biopsies of the large bowel are taken – usually one to two biopsies every 10 cm in a random search for dysplasia.

The endpoint of surveillance in ulcerative colitis is therefore some grade of dysplasia or a reasonable suspicion of the presence of invasive carcinoma. The reason that dysplasia is a reasonable endpoint is that the operative mortality for colectomy in the age group under consideration (primarily well under 70 years) is of the order of 1%, and considerably less in patients younger than 45 years of age in whom elective colectomy is carried out.

Although there has been investigation into a variety of potential markers including changes in mucin, lectins and to a certain extent oncogenes and their products, the most exciting potential marker in both fields is the finding of aneuploidy as a marker for both dysplasia and carcinoma (25).

Important remaining problems: The extent of colitis has no standard method of definition, variously being established by barium enema (single or air contrast), endoscopy or biopsy, so that other than those in whom total disease has been defined radiologically, the precise population at risk is unknown.

Dysplasia may be very focal so that random biopsies have major sampling problems.

There has been no study on the endoscopic appearances of dysplasia or colitic carcinoma.

Dysplasia may not be an absolutely reliable marker of carcinoma, not being detected in up to one-third of patients under surveillance in whom invasive carcinoma subsequently develops.

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