Leading article

Colonoscopic surveillance in ulcerative colitis – dysplasia through the looking glass

Reflection

Carcinoma was first described as a complication of ulcerative colitis (UC) by Crohn and Rosenberg in 1925. Since then many workers have attempted to quantify the degree of increased cancer risk associated with UC. Most early studies tended to overestimate the degree of risk, calculating cumulative cancer rates ranging from 16% to 43% depending on the duration of disease. In contrast, Hendricksen (in Denmark) and Maratka (Czechoslovakia) have produced figures for cumulative risk of 1.4% and 5% at 18 and 20 years from onset respectively. The reasons for such wide discrepancies in the assessment of cancer risk have been well reviewed by Whelan and Lennard-Jones. They relate to inadequate follow up, differences in study populations, treatment policy and methods of analysis. More recently, in a retrospective cohort study which took these criticisms into account, Gyde et al report cumulative risks for cancer in extensive colitis of 7.2% at 20 years and 16.5% at 30 years, while in a population based study in Israel, Gilat et al found an incidence of 9.3% and 13.8% at 15 and 20 years respectively for total colitis.

Based on such studies two factors have emerged as being of major importance in determining cancer risk, duration and extent of disease. There is a low risk of cancer at less than 10 years duration with increasing risk thereafter. There is a much greater cancer risk in patients with total colitis than in those with left sided disease, whose risk is at or around that of the general population. Onset of UC in childhood may be an additional risk factor but this has not been borne out by recent studies and cancer incidence standardised for duration of disease is higher in older patients.

In the past prophylactic colectomy or proctocolectomy was advocated in patients with total UC of greater than 10 years duration. Advances in surgical technique now mean that a permanent stoma can be avoided. Most patients with UC (more than 80%), however, do not develop colorectal cancer and many patients even with long standing UC are relatively young and have minimal symptoms. The alternative of endoscopic surveillance is therefore an attractive option.

Dysplasia through the endoscope

Precancerous changes occurring in UC were described by Dawson and Pryse-Davies in 1959 but it was Morson and Pang who reported that dysplasia was often widespread, could occur in flat mucosa and was detectable on rectal biopsy, thereby identifying patients who had entered a
'precancerous' phase. Sigmoidoscopy and rectal biopsy was recommended as a valuable method of follow up for patients at risk of developing carcinoma, and the finding of dysplastic change was an indication for prophylactic surgery. Further studies provided clinical support for this concept, confirming the association of dysplasia and carcinoma.11,15

Other workers, however, have highlighted the limitations of this approach. Extensive dysplasia is not always present in association with carcinoma and the rectum may not show these changes and thus not necessarily reflect the state of the colonic mucosa elsewhere. The fibreoptic colonoscopy can visualise the entire colorectal mucosa from which biopsies can be taken, but other difficulties remain. In assessing the value of colonoscopic surveillance, Ransohoff16 asserts that two conditions should be satisfied. First, dysplasia should regularly precede cancer. Second, dysplasia should be readily identified.

About 30% of cancers in UC show no associated dysplasia.17 Even when dysplasia is present it is frequently patchy17,18 and sampling error might overlook changes. Multiple random biopsies, currently taken at 10 cm intervals, can reduce the sampling errors together with brush cytology,19 which samples cells from a wider area than a biopsy. Cytopathological expertise is, however, not widely available. Fortunately, dysplasia often occurs in association with a macroscopic lesion visible as a raised irregular plaque or sessile polyp20,21 and target biopsies from such lesions will improve the detection of dysplasia and concurrent carcinoma.20 Dysplasia is by no means always accompanied by carcinoma. In the St Mark's series,22 18 of 28 patients with a preoperative diagnosis of dysplasia had no carcinoma in the resection specimen, and in five of them no dysplasia was detected either. Conversely, in a study of colectomy specimens from patients with long standing UC, Ransohoff et al17 diagnosed dysplasia in 27% of non-cancer cases. It may be that in those cases with dysplasia in the resection specimens colectomy has interrupted the natural history of the dysplasia carcinoma sequence and the main objective of surveillance has been achieved. In those cases where a preoperative diagnosis of dysplasia is not confirmed, and where patients develop advanced cancer despite being under surveillance, the accuracy of the histological interpretation is in doubt.

The true success of dysplasia-based surveillance has been exaggerated. Many dysplasia associated cancers are found at the first colonoscopic examination20 and cannot be claimed as cancers detected by 'surveillance'. Dysplasia and carcinoma may be found concurrently yet detection of dysplasia is claimed as pointing to the presence of the cancer. Some biopsies designated high grade dysplasia are, in our opinion, areas of well differentiated adenocarcinoma and not 'associated' dysplasia.

**Dysplasia through the microscope**

The term dysplasia has been defined as 'an unequivocal neoplastic epithelial proliferation'.21 As with all histological assessment, the recognition of dysplasia is subjective and in the presence of active inflammation the distinction between dysplasia and reactive or regenerative cytopathological abnormalities (atypia) can be extremely difficult. A 'standardised' classification of dysplasia has been described23 but although the definitions may be standard, their interpretation and application by individual pathologists is
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not. Thus there is considerable scope for interobserver disagreement. Two recent studies have underlined this problem by revealing wide disagreement in the diagnosis of dysplasia even among specialist pathologists.24 25 It would be prudent therefore to confirm the diagnosis of high grade dysplasia by taking further biopsies and by seeking a second histopathologist's opinion before proceeding to colectomy.

Low grade dysplasia is often diagnosed when the appearances actually represent inflammation or regeneration. For example, the incidence of dysplasia found in three colonoscopic surveillance series was 22% of 303 patients in the St Mark's study,22 32% of 112 patients in the Leeds study,26 and 35% (including 'probably dysplastic' cases) in a study from Stockholm.27 These incidence rates are greatly in excess of those found for cancer in non-surveillance populations indicating that many of the patients diagnosed as having dysplasia do not have a genuine premalignant change. Dysplasia is therefore over diagnosed, leading to unnecessary repetition of colonoscopy and even to 'negative' colectomies.

The histological recognition of dysplasia is far from ideal as a 'marker' of increased cancer risk. Some investigators have attempted to reduce the subjective element in its recognition by employing morphometric techniques,28 but although this approach might be of value in 'educating' pathologists in identifying the most important diagnostic criteria, it is unlikely to be used in routine diagnostic practice. Other tissue changes which might be more closely associated with cancer, or are less subjective in their interpretation have therefore been sought.

Looking for a marker

Quantitative and qualitative alterations in mucus production have been described in the development of colorectal cancer. Filipe30 originally introduced the concept of 'transitional' mucosa occurring adjacent to colorectal carcinoma where there was a reduction or absence of sulphomucin and a predominance of sialomucin, contrasting with the normal sulphomucin predominance. These findings suggested that sialomucin predominance may be a manifestation of preneoplastic change.

Sialomucin predominance may be significantly associated with cancer and dysplasia in UC.30 31 Our findings based on colonoscopic samples from cancer and non-cancer UC cases tend to support a role for mucin histochemistry in assessing cancer risk,32 but others deny its value.33 34 Allen et al.,34 however, also sought a variant of sialomucin using a modified Periodic acid-Schiff stain and claimed that this could be useful as a preneoplastic marker, a view endorsed by Agawa et al.35 Further evaluation of these techniques is needed before any recommendations for routine use can be made. The same caveat applies to recent claims that the detection of mucin antigens may be useful in cancer prediction.36

Changes in glycosubstances in cells can be investigated by identifying their carbohydrate moieties using lectin histochemistry. Alterations in lectin binding have been documented in colonic adenocarcinoma37 but of more interest abnormal staining patterns, particularly with peanut agglutinin (PNA), have been found in 'transitional' mucosa.38 A study of PNA staining in dysplasia associated with UC by Pihl et al.39 suggested that this technique
could be diagnostically useful. Unfortunately, subsequent studies have revealed a considerable lack of specificity for PNA positivity as a marker ofpreneoplastic change. \textsuperscript{22,40,41} Identical changes can be seen in colitis without dysplasia, particularly in the presence of active inflammation.

Other markers including immunohistological studies on carcino-embryonic antigen\textsuperscript{42} and products of c-myc\textsuperscript{34} and ras oncogenes\textsuperscript{43} have produced variable results. The major problem with these and other putative markers is that the alterations are largely quantitative, and the interpretation of staining patterns is therefore subjective.

Dysplasia is frequently used as an 'end-point' to determine whether or not a change is linked to neoplasia when, as noted previously, the recognition of dysplasia is highly subjective. None of the markers so far investigated approaches the degree of specificity required.

\textbf{Looking at the nucleus}

The initiation of some cancers is dependent on a chromosomal aberration, thereby altering the expression of certain genes, which results in a change in the cells' response to normal growth control mechanisms.\textsuperscript{44} Gains or losses of chromosomes may alter the amount of specific cell products necessary for the control of division and differentiation. Such genetic abnormalities may increase the rate of spontaneous mutation and allow progression to a malignant phenotype.\textsuperscript{45} An abnormal chromosome complement in colonic adenocarcinoma was first reported by Lubs and Clark in 1963.\textsuperscript{46} Since then numerous reports have confirmed the finding of cytogenetic abnormalities in colorectal carcinoma and there is limited evidence of such changes in UC.\textsuperscript{47} Chromosomal spreads are difficult to prepare, however, and the technique is not suitable for diagnostic application.

Another approach has been the microdensitometric measurement of total nuclear DNA content after Feulgen staining.\textsuperscript{48} This technique allows microscopy to be combined with DNA measurement enabling selected nuclei to be measured, but it is laborious and time consuming so that only small numbers of cells can be sampled. Automated measurement of DNA using flow cytometry permits the quantification of thousands of cells in a few minutes with comprehensive sampling and accurate DNA histograms.

We have tested the value of flow cytometric DNA measurements in the assessment of premalignancy in UC and found that the presence of DNA aneuploidy was linked to the duration of disease but that an identical prevalence was found in long standing disease with and without carcinoma. There was no significant association with histological dysplasia. We concluded that the detection of DNA aneuploidy was not useful as an independent predictor of the presence of concurrent carcinoma.\textsuperscript{49} Hammarberg \textit{et al}\textsuperscript{50} found DNA aneuploidy in a small proportion of histologically normal or inflamed biopsies but an increasing prevalence in dysplastic lesions; they and other authors claim it is of value as an adjunct to histology in the recognition of pre-malignancy.\textsuperscript{25,51} This claim has not been adequately investigated in a prospective study. While the finding of DNA aneuploidy might indicate an early preneoplastic change, its diagnostic usefulness is limited by its lack of specificity and absence in more than 40\% of non-cancerous samples from cancer cases.\textsuperscript{25,50}
Looking ahead

Cancer surveillance in UC is a costly business. Lennard-Jones and his colleagues have emphasised the effort involved for patients and staff and the strain on medical resources. They acknowledge that the ‘ideal result, the prevention of cancer and restriction of operation to patients with demonstrated precancer, has not occurred as often as we had anticipated’. Nevertheless their surveillance of 303 patients probably prevented the development of carcinoma in eight patients and permitted the diagnosis of carcinoma at a stage when cure was likely in 11. They have also highlighted the difficulties of patient compliance in such programmes which further detracts from the number of cancers prevented.

In view of the small number of cancers prevented or detected at an early stage by colonoscopic surveillance and the considerable costs involved, several commentators have questioned its value. In a provocative review, Collins, Feldman, and Fordtran concluded that it was not cost effective and that ‘some gastroenterologists and pathologists have oversold surveillance’. They estimated that about £200 000 would be spent for each cancer found or prevented, while in the setting of a UK District Hospital, Jones et al calculated that a surveillance programme necessitates 12 colonoscopies/100 000 population annually and that the cost for each carcinoma detected is approximately £6015.

The cost effectiveness of surveillance colonoscopy could be improved by ‘targeting’ higher risk patients and performing less frequent examinations on the remainder. Most centres have a policy of annual colonoscopy in patients with extensive disease of more than eight or 10 years duration. The rationale for annual colonoscopy and the importance of disease duration is still open to question. For instance, in the study by Gyde et al there was considerable variation in the intervals between onset of colitis to cancer but much less variation in the actual age patients developed cancer (most patients developing cancer around 50 years of age). If this observation is confirmed that the maximum risk of cancer in UC patients is around age 50 and not dependent on disease duration it would be more rational to base surveillance policy upon the age of the patient rather than screening after eight years from onset of colitis. Furthermore, surveillance based on duration is confounded by the inaccuracy of the historical record and the problem of ‘sub-clinical’ disease.

Lashner et al have proposed that to minimise the delay in detecting cancer, the interval should be governed by the ‘hazard rate’. Because the hazard rate increases over time, uniform screening intervals are not optimal. The application of their approach might therefore involve three yearly intervals in younger patients and annual or even six monthly intervals as the patient approaches 50 years of age.

The move away from surgical treatment advocated in the 1970's might need reappraisal. Given the choice between a prophylactic colectomy and enrolment into a life long surveillance programme, some young patients might choose the former. Most young people with few symptoms, however, remain resistant to surgery and this poses a considerable dilemma.

Cost effectiveness of surveillance colonoscopy may become paramount. The choice may lie between screening long standing colitics or other high risk groups like occult blood positive people over 50 years detected on
population screening. Colonoscopy in this group will yield at least 10 times the number of cancers found in the same number of examinations in UC patients. Recent developments in molecular biology which facilitate the detection of subtle genetic abnormalities in preneoplastic calls may eventually yield the ideal 'marker' which we are seeking.

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