Molecular biology. Setting the stage in colorectal cancer?

Over 18,000 people die each year in the UK from colorectal cancer. The mortality has remained largely unchanged over the decades despite greater public awareness and better diagnostic facilities. Improving the outlook for patients will require either diagnosing cancer at an asymptomatic and, presumably, earlier phase or offering more effective treatment for those with advanced disease. Recent studies have expressed cautious optimism both for screening and for the use of adjuvant therapy, yet closer examination raises as many doubts as hopes.

Faecal occult blood screening

Faecal occult blood testing is the only realistic method available today for periodic screening of people deemed to be at average risk of colorectal cancer. Results of well controlled studies offer considerable hope of an improvement in survival. Duke’s A and B lesions account for over 75% of cancers detected in asymptomatic individuals by initial faecal occult blood testing, yet while less than 50% of symptomatic patients are compared stages at diagnosis. Now a report from the Minnesota group seems to confirm these expectations with a 33% reduction in cancer related mortality over 13 years. There are, however, concerns still to be allayed. Thirty eight per cent of the annually screened population in the Minnesota study underwent colonoscopy because of the low specificity of the rehydrated guaiac slides. Despite this, only 50% of cancers in this group were actually detected by faecal occult blood testing, the remainder arose as asymptomatic cancers in the period between screenings. Clearly, only a percentage of lesions bleed at any one time and it may be that screening favours the detection of more slowly growing tumours (length or time bias). The lack of specificity of faecal occult blood testing also results in large numbers of unnecessary colonic evaluations, adding greatly to the cost of such programmes. The decrease in mortality in the Minnesota study may relate to the high percentage of colonoscopies performed rather than the faecal occult blood testing per se and, if so, lends support to the concept of endoscopic screening as proposed by Atkin et al.

Genetic screening

Until recently, research in molecular biology was limited by the expensive and technically demanding procedures needed to detect abnormalities within the genome. The polymerase chain reaction, which enables the millionfold amplification of short segments of DNA, has now brought genetic research within reach of small laboratories. Genetic mutations play a major, though complex, role in sporadic colorectal cancer and the detection of genetic changes rather than occult blood in stool might form the basis of screening tests in the future. There are theoretical advantages in searching for DNA mutations rather than occult blood in stool. DNA is extremely stable, whereas blood, especially from the right colon, may be degraded by bacteria and subsequently not detected by the guaiac method. This may explain the predominance of left sided cancers detected by faecal occult blood testing. The specificity of DNA mutations ensures that adenomas or carcinomas are present, thus eliminating the problem of a false positive result. Sidransky has reported the identification of tumour derived DNA in the stools of patients with colorectal cancer or adenomatous polyps and p53 mutations have been detected in the DNA of epithelial cells isolated from the stool of patients before colonoscopy. While these techniques are not sufficiently developed to use in other than a research capacity at present, they offer the hope that, in future, it will be possible to identify asymptomatic individuals by testing their stools against a panel of DNA probes.

Screening high risk individuals by colonoscopic methods is an established procedure, but identification is crude except for those few families with hereditary colorectal cancer. Currently, patients at risk of familial adenomatous polyposis (FAP) undergo the ordeal of regular colonoscopic evaluation from early adulthood to middle age before the diagnosis can be confidently excluded. Molecular biology will allow a scientific approach to identifying the population at risk. The FAP gene, thought to be crucial in the development of colorectal cancer in these patients has been localised to chromosome 5q and has been characterised. Identification of this gene provides an opportunity to screen for disease within polyposis families at birth.

The study of patients with FAP has led to a greater awareness of the importance of family history in apparently sporadic colorectal cancer. Houlston et al estimate the lifetime risk of developing colorectal cancer as 1 in 10 where the proband is aged under 45 at diagnosis, and 1 in 6 where two or more first degree relatives are affected. Colonoscopy, using these estimates, yields a sizeable number of adenomatous polyps; however, the point at which the potential benefits of intensive screening by endoscopic or radiological methods is outweighed by the risks involved is difficult to determine. Again, molecular biology may be of value in the identification of susceptible members within hereditary non-polyposis colorectal cancer families. The recent localisation of a hereditary non-polyposis colorectal cancer gene to chromosome 2 provides confirmation of a genetic predisposition to colorectal cancer within certain families and may allow the introduction of effective screening programmes for these people.

Adjuvant therapy and staging

The value of an accurate, objective staging system cannot be overemphasised now that large studies have shown adjuvant therapies to be beneficial in selected groups. Patients with high risk rectal cancers who undergo curative surgery and receive adjuvant therapy with 5-fluorouracil and radiotherapy may expect an improvement in survival. Patients with Duke’s C cancer also represent a group with a poor prognosis – 65–75% die within five years of surgery – and benefit from combined therapy with 5-fluorouracil and levamisole. These studies show that if we can define a population with a high risk of recurrent disease then the outlook may be improved by medical treatment.

In terms of prognosis after curative surgery, Duke’s B colorectal cancer represents a therapeutic dilemma. More patients fall into this category than any other but despite the
relatively localised extent of disease the long term outcome is unpredictable, 35–40% dying as a result of metastatic spread. Trial II adjunction gene sequences have, to date, been in these patients.18,19 This may be partly explained by the large study population needed to show even a modest advantage; the statistical power of the study being proportional to the number of deaths within the population.17 The identification of factors within Dukes’s B colorectal cancer associated with recurrence would modify patient selection for trials of adjuvant therapies and help avoid unnecessary treatment of the 60–65% of those who remain disease free without their use.

The inference is that present histological systems such as those of Dukes, Jass, and the TNM classification fail to predict consistently a prognosis with confidence. Various non-histological features such as age, sex, symptom presentation, tumour size, site, ploidy status, and tumour marker levels may all be helpful when considering long term outcome; however, these indices still fail to predict disease recurrence with precision. In addition to providing possible screening tests for colorectal cancer, molecular biology will be extremely useful if an improved staging system can be constructed.

Genetic staging

Data is accruing which suggest that molecular biology may be of help in this staging process. A range of abnormalities has been identified in colorectal cancer including ras mutations and deletions on chromosomes 5, 7, and 18.20 Mutations may result in the activation of oncogenes or the inactivation of tumour suppressor genes, leading to abnormal or unregulated cell growth. Other mechanisms may also be at work. Recently, a hereditary non-polyposis colorectal cancer gene has been localised to chromosome 2.21 This gene seems to be neither an oncogene nor tumour suppressor gene, but could be responsible for an increase in genetic instability by way of multiple replication errors within the genome.

The FAP gene and ras mutations may be important initiating events in colorectal cancer, but seem to have little independent prognostic importance.20 In contrast, allelic losses on chromosomes 17 and 18 confer a poor prognosis independent of conventional staging20 as do a combination of c-ki-ras gene mutations and p53 overexpression, as measured immunohistochemically.22 Allelic losses, insertions, and point mutations have been detected on many other chromosomes23 but it has still to be established whether such changes function simply as markers for colorectal cancer, or as potential prognostic indicators.

The stepwise progression of colorectal cancer through a series of genetic alterations as proposed by Vogelstein24 is attractive in that it postulates an inter-relationship between the accumulation of genetic changes and tumour stage. It is therefore reasonable to suggest that a staging system might be devised which is based upon the type and number of genetic changes associated with conventional tumour stage and, more importantly, with survival. The present consensus is that the behaviour of colorectal cancer seems to be dependent on the total number of genetic changes present in tumour tissue rather than their order,25 and that patient survival is inversely proportional to the number of allelic losses found in tumours.18 While it is clear that specific genetic alterations serve as prognostic indicators, not all correlate with a poor prognosis. The presence of multiple replication errors or microsatellite instability within tumours is actually associated with increased survival.26 Future studies in this area will help to elucidate these relationships more precisely.

In the study of colorectal cancer we are fortunate that there exists both a familial form of the disease and a precursor lesion, namely the adenomaous polyp. These characteristics have been employed to great effect by geneticists, and advances to date have been remarkably swift. A haematological screening test for FAP is now possible and there is potential to design screening tests for hereditary non-polyposis colorectal cancer and asymptomatic sporadic disease in the future. A staging system for established cancer might also be based on genetic mutations. If the study of genetic aspects of colorectal cancer continues at its present pace, molecular biology may soon outgrow its immediate role as a research tool and take its place on the clinical stage.

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