An alternative to prophylactic colectomy for colon cancer prevention in HNPCC syndrome

The French Ad-Hoc Committee on Hereditary Non-polyposis Colon Cancer (HNPCC) management meeting on behalf of the French Health Minister has recently released its statement. The report on prophylactic colectomy resections for HNPCC related adenocarcinomas (Gut 2003;52:1752–5) is in contrast with ours and we would like to discuss this point.

Use of decision analysis models is a smart approach in dealing with such complex situations. However, life expectancy related to the occurrence of metachronous colorectal carcinoma should be balanced against the negative impact on quality of life in the case of prophylactic extensive colorectal resections. Thus quality adjusted life expectancy, integrating the individual patient’s choice, might be a more accurate approach. Comprehensive, fair, and loyal information of what the patient can hope for is mandatory to fulfill the requirements of patient autonomy in such a shared decision. From the data reported by de Vos tot Nederveen Cappel et al (Gut 2003;52:1752–5) as well as from other data not mentioned in their paper, we derived somewhat different, if not totally opposite, conclusions. Five year survival rates for colorectal cancer considered in their model seem at the least optimistic. Five year survival rates reported for Dukes’ B and C colorectal cancers in HNPCC patients by Bertario and colleagues (2003;52:1752–5) is in contrast with ours and we would like to discuss this point.

The patient’s individual choice is pivotal in decisions for prophylactic extended resections and fully unbiased information may be more valuable than any doctor’s “recommendation”. The results of the study of de Vos tot Nederveen Cappel et al (Gut 2003;52:1752–5) should therefore be part of the information offered to patients. For these reasons, the conclusions of the French Ad-Hoc Committee are that not only are routine extended prophylactic resections not recommended but, on the contrary, given the efficacy of screening programmes, extended surgery is also not indicated. Controversial conclusions derived from the same scientific “evidence” in different cultural background have already been reported.1

Serum pro-hepcidin: measuring active hepcidin or a non-functional precursor?

We read with great interest the paper “Pro-hepcidin: expression and cell specific localisation in the liver and its regulation in hereditary haemochromatosis, chronic renal insufficiency, and renal anaemia” (Gut 2004;53:735–43).

We have two observations. Firstly it was shown that pro-hepcidin and hepcidin were co-localised within the liver and in Hep-G2 cells. However, it was not possible, using serum ELISA, to identify the C terminus of hepcidin (the mature form of hepcidin 29). Is it possible that the functional N terminal antibody used for serum analyses represents non-functional precursor amino acids and not the active molecule? This might explain the lack of correlation between iron parameters and hepcidin seen from the patient data.

Furthermore, the authors comment on the paradoxically elevated levels of pro-hepcidin in patients with chronic renal insufficiency (CKD) (EPO) (All of these patients were reported to have normal haemoglobin levels. Previous studies have shown that EPO inhibits hepatic hepcidin expression.1 The authors speculate that the elevated circulating hepcidin levels may reflect reduced renal clearance of the molecule in these patients. However, other studies have suggested chronic inflammatory diseases are associated with elevated serum hepcidin (in animal models)2 and urine hepcidin in humans.3 Another possibility, therefore, is that patients have elevated iron stores, in relation to chronic disease, and this may have a direct effect on hepcidin release. It would be interesting to know the iron metabolic parameters in these patients, as obviously haemoglobin in isolation is not an accurate measure of iron stores. It is unclear from the paper whether fig 8 represents data from patients with hereditary haemochromatosis (10 patients) or all patients studied (as implied in the last paragraph of the results). If the latter is the case it would be very interesting to separate the renal patient data from that of the haemochromatosis patients, in whom hepcidin expression is likely to be dysregulated due to direct effects of the HFE gene product.

References


Clearly future clinical studies in this field hold much promise.

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Use of oesophageal dilatation in clinical practice

Drs Riley and Attwood are to be commended for their recent publication (Gut 2004;53:1–6). We share their difficulty with one recommendation related to dilatation. Under 6.1, it is stated that during oesophageal dilatation the endoscopist should be supported by at least two endoscopists. We agree that this certainly is desirable when the complication structures are dilated or if one is dealing with an achalasia patient. However, for dilatation of Schatzki’s rings or simple peptic strictures, one endoscopist assistant generally is sufficient. At our institution, over the years numerous dilatations have been done with only one assistant and without any adverse consequences.

As written, your guidelines seem to indicate that the standard of care should be to have two endoscopy assistants present and I think this is both unrealistic and unwarranted.

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Variant Creutzfeldt-Jakob disease: update

Two years ago we reported current thinking on the potential for gastrointestinal endoscopy to act as a vector for patient to patient transmission of variant Creutzfeldt-Jakob disease (vCJD). In that article we stressed that the advice would be updated if new evidence became available. Gastroenterologists may be aware of a recently published article in the Lancet4 discrribing that the tissue distribution of abnormal prion protein (PrPsc) in monkeys that have been inoculated with brain homogenate from first passage animals with bovine spongiform encephalopathy (BSE) via the oral route, which is the route by which the vast majority of patients developing vCJD will have become infected. As the prion protein responsible for vCJD is found in all lymphoid tissue, our advice was to reduce “random” biopsies to an absolute minimum and ensure that re-useable biopsy forces were meticulously cleaned and decontaminated according to the strict British Society of Gastroenterology (BSG) guidelines. We also advised on the use of disposable biopsy forceps, particularly in the ileum, as it was felt that biopsies from vCJD is found in all lymphoid tissue, our disease: implications for gastroenterology. Gut 2002;50:821–2.

Is mesalazine really safe for use in breastfeeding mothers?

Mesalazine containing preparations are commonly used for the treatment and management of inflammatory bowel disease. The young age of many inflammatory bowel disease sufferers means that the issue of whether to continue therapy in nursing mothers often arises.

We report a small study that was instigated after a nursing mother with Crohn’s disease approached us concerned about the safety of continuing to breastfeed while taking mesalazine. She had a cracked bleeding nipple and was worried about the dose of the drug that her baby would be receiving. We agreed to measure the drug level in the milk and the limiting evidence in this area we designed a study to measure levels of mesalazine (5-ASA) and its metabolite (N-acetyl-ASA) in breast milk from mothers on 5-ASA therapy.

It is thought that maternal use of 5-ASA medication is safe for the breastfed infant although bloody diarrhoea in an infant being breast fed by a woman taking sulphalazine has been reported,1 as has watery diarrhoea in the infant of a woman using 5-ASA suppositories.2 There has in fact been little research into excretion of 5-ASA and N-acetyl-ASA in breast milk.

We obtained breast milk samples from four breastfeeding mothers with inflammatory bowel disease who were taking a 5-ASA preparation. Ethics approval for the study was obtained from the local ethics committee. Breast milk analysis was performed using high performance liquid chromatography. Concentrations of 5-ASA in the breast milk of 5-ASA treated patients were 4–40 ng/ml while those of N-acetyl-ASA were 5.0–14.9 ng/ml (some 1000 times higher). These results are similar to levels found by other investigators.3,4

Based on an average intake of a breastfeeding infant of 150 ml of milk/kg of body weight/day, concentrations of 5-ASA found in breast milk samples equate to a dosage of 0.0006–0.006 mg/kg. This falls well below 10% of the standardised therapeutic dose, and therefore by this conventional criteria the safety of 5-ASA on the infant is considered clinically unimportant. However, our finding of high levels of metabolite (N-acetyl-ASA) in breast milk suggests that the metabolite is greatly enriched in breast milk. Differences in the physical properties of 5-ASA and N-acetyl-ASA may well account in part for some difference in their rate of transfer into breast milk. But it is more likely that the findings reflect the result of active metabolism of 5-ASA taking place within the glandular cells of the breast.

We have shown that the concentration of 5-ASA in the breast milk of patients receiving 5-ASA therapy is low. It is therefore interesting to speculate whether the low levels of 5-ASA may, in part, be due to metabolism of 5-ASA to N-acetyl-ASA by breast tissue as a
mechanism to prevent high levels of active 5-ASA from accumulating in milk. N-Ac-5-ASA is a relatively inactive metabolite and is therefore unlikely to have a toxic effect on the infant, although to our knowledge the effect of N-Ac-5-ASA on infants has not been studied. We therefore cautiously support the view that 5-ASA containing medication is safe for breastfeeding mothers with inflammatory bowel disease. In addition to our findings we would recommend that future studies looking at breast milk drug levels explore the possible effects of metabolism by breast tissue and the potential toxic effects of any metabolites produced.

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Duodenal adenoma and cancer in FAP

We congratulate the authors (Gut 2004; 53:381–6) on gathering this large cohort of patients in this important area in familial adenomatous polyposis (FAP) but would like to express some concerns regarding the study. Our first concern relates to the means of endoscopic assessment. Standard forward viewing endoscopy was used, whereas in clinical practice side viewing endoscopy is recommended as duodenal polyposis in FAP is more severe in the periampullary region and this is likely to be missed with standard endoscopy. This will therefore underestimate both adenoma staging and frequency. This matter is raised in their discussion where they describe side viewing endoscopy as unrealistic. We however feel this is unreasonable in an era where ERCP services are available in most hospitals, at least in the UK.

Furthermore, the need for appropriate endoscopy technique and biopsy protocols has been highlighted in a recent study1 which review the relative side effects duodenal disease when comparing biopsy specimens and resected specimens, in addition to the finding of invasive cancer in a number of specimens resected for “severe duodenal adenomatosis” (that is, Spigelman stage 3 with high grade dysplasia or stage A). The need to operate before biopsy proven carcinoma is demonstrated by the high mortality rates from metastatic disease in those with duodenal carcinoma. Accurate staging and assessment for endoscopic or surgical intervention is, in our opinion, not possible by standard forward viewing endoscopy.

Our other concern relates to the quoted cancer incidence, which we feel must be biased. The cohort was not followed up from a young age, therefore, of the cohort at first endoscopy was 20–81 years. Both the authors’ own data and others have shown that there is an increased risk of stage 4 disease and cancer with increasing age. As such, those older patients in this group we would expect to be self selected and to have less severe disease. Those who were destined to develop severe duodenal disease or cancer may well have developed it prior to screening. Of note, the median age of those developing cancer was 52 years (range 26–58).

In addition, those 12 patients undergoing open duodenotomy and polypectomy are likely to be those with most advanced disease and a highest risk of malignant transformation, thus again biasing the likely natural incidence of duodenal carcinoma.

There are also few details with regard to medical intervention which may affect duodenal staging and disease progression. In the discussion, the authors mention that a few patients may have been on periodic sulindac which we feel must be biased. The cohort was not followed up from a young age, therefore, of the cohort at first endoscopy was 20–81 years. Both the authors’ own data and others have shown that there is an increased risk of stage 4 disease and cancer with increasing age. As such, those older patients in this group we would expect to be self selected and to have less severe disease. Those who were destined to develop severe duodenal disease or cancer may well have developed it prior to screening. Of note, the median age of those developing cancer was 52 years (range 26–58).

We report a patient with VWD who had suffered recurrent and life threatening bleeding from the gastrointestinal tract in whom, despite an extensive investigation, no apparent cause of haemorrhage was identified. He was successfully treated with combined administration of octreotide LAR (long active released) and propranolol. This is the first report on the use of octreotide LAR in a patient with VWD.

A 55 year old man presented to our department because of recurring episodes of melena, which first appeared five years previously. He had a history of epistaxis during his childhood. During investigation of his bleeding diathesis, he was found to have type I VWD. His niece was also diagnosed with type I VWD whereas his father, brother, and grandmother suffered from an unrelated bleeding diathesis. An investigation into the source of bleeding could not be localised.

Treatment of recurrent gastrointestinal haemorrhage in a patient with von Willebrand’s disease with octreotide LAR and propranolol

Von Willebrand’s disease (vWD) is the most common inherited bleeding disorder and is caused by quantitative deficiency or qualitative abnormalities of von Willebrand factor (vWF). Until recently, treatment of bleeding from the gastrointestinal tract in patients with vWD included administration of tranexamic acid or clotting factor products such as fresh frozen plasma, cryoprecipitated vWF concentrates, or preparations that contain vWF and factor VIII. Desmopressin, beta blocking drugs, and hormonal therapy with oestroogen with or without progesterone have also been used.

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Conflict of interest: None declared.

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References
Octreotide is mainly used in acromegaly and in gastrointestinal and pancreatic tumours. Nevertheless, it has also been proved to be effective in controlling bleeding from the gastrointestinal tract due to angiodysplasia and variceal bleeding. It is postulated that it exerts its actions through a reduction in splanchic and portal blood flow. Only one report on the effectiveness of octreotide therapy in two patients with VWD was found in the literature. In one of these patients, vWF was increased after administration of octreotide. In our patient, octreotide did not cause any increase in the synthesis or release of vWF. We can therefore assume that the combined administration of octreotide LAR and propranolol was effective in preventing bleeding in our patient through a direct effect on the splanchic circulation. Undoubtedly, more trials are required to clarify the mechanism of action of octreotide in this setting.

In conclusion, combined administration of octreotide and propranolol appears to be an attractive alternative treatment in patients with VWD and recurrent bleeding from the gastrointestinal tract, particularly when other therapeutic modalities have failed.  

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Adherence to BSG adenoma surveillance guidelines will reduce colonoscopic workload

There is an ever increasing demand for colonoscopy nationally which will increase further when colorectal cancer screening is rolled out nationally. To accommodate this, a marked improvement in the efficiency of endoscopy units is required. One simple way of reducing demand is to reduce the number of repeat procedures performed. We have found that by following the British Society of Gastroenterology (BSG) polyp follow up guidelines, our unit could prevent a significant number of unnecessary colonoscopies.

Our unit’s three-month retrospective audit found that 79 of 528 patients undergoing colonoscopy had colonic polyps; 130 polyps in total were detected of which 65 were histologically confirmed adenomas (45 tubular, 18 tubulovillous, and two villous). Over two thirds were in the rectum/sigmoid.

By classifying patients with polyps according to BSG guidelines:
- 32 were low risk, of which 16 had too short a follow up interval and 16 had correct follow up (of the 16 with too short a follow up, 10 had no follow up and six had a five year follow up);
- 13 were intermediate risk, with three having correct follow up, six too short a follow up interval, one too long a follow up, and three had no follow up;
- one patient was high risk and received too long a follow up interval;
- 11 had incomplete polyp removal of which four received appropriately rapid follow up, two had late follow up, and five received no follow up;
- of 22 patients with non-adenomatous polyps, only eight had an unnecessary repeat procedure arranged.

Strict adherence to the BSG guidelines would have added eight apparently overlooked procedures but could have saved up to 30 other surveillance procedures (if a policy of no follow up for low risk polyps was used), resulting in a net reduction of 22 procedures. This is equivalent to a 47% reduction in surveillance colonoscopies.

The simple measure of reviewing repeat requests for surveillance procedures to ensure they adhere to BSG guidelines should reduce the number of unnecessary procedures performed, creating additional capacity within our endoscopy unit and reducing the exposure of patients to unnecessary risk.

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Reference