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 colorectal 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 recommendations 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 were 70% and 41%, respectively. The overall five year survival rate of patients with colorectal cancer in HNPCC is approximately 55%. Multidimensional analyses has not shown HNPCC to be an independent parameter when comparing five year survival rates of HNPCC with sporadic colorectal cancer.2,3

Although these data strongly demonstrate a need for surveillance in HNPCC patients, they underscore the fact that if the decision for an extended prophylactic resection is made before the exact pathological staging of the tumour is known, 45% of patients will sustain a substantial decrease in quality of life with no counterpart in quantity (that is, life expectancy). de Vos tot Nederveen Cappel et al (Gut 2003;52:1752–5) calculated life expectancy for a hypothetical 27 year old patient with colorectal cancer whereas in our experience only 6% of MMR gene carriers belong to that very early onset group. The median age of patients with colorectal cancer under surveillance program for HNPCC is 44 years and the corrected mean estimation of increased life expectancy after extended resection for a 47 year old affected person is only one year. Different indications should be made in men and women because of their significantly different relative risks for metachronous cancer as well as for the competing risk of endometrial cancer (unless there is also a “recommendation” for “incidental” prophylactic hysterectomy). Last, but not least, the negative impact on life expectancy related to other tumours from the spectrum as well as to the prophylactic resections themselves are not taken into consideration. For young patients between the ages of 27 and 47 years with colorectal cancer, the choice between prophylactic surgery or segmental colectomy is a complex decision. One should ask honestly if these same patients who on one hand have to face the anxiety generating information that they have cancer are also ready or capable of making any reasonable decisions about a 2–3 year increase in life expectancy versus a potential decrease in their quality of life. Let us assume that the first expectation for these patients is to be alive with no recurrent disease 5–10 years later. An increased life expectancy is a somewhat theoretical conception which entails additional years at the end of one’s life while the negative impact on quality of life of extended operations will start from the first postoperative day.

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 2001;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.

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References

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 colocalised 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 25). 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 (CRI). All 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 patient. 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 haemochromatosis only 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.
Clearly future clinical studies in this field hold much promise.

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References

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 endoscopy assistants. We agree that this is certainly 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 endoscopy assistant 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 would 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 necessary. We have shown that the concentration of 5-ASA in the infant of a woman using 5-ASA therapy is low. It is therefore interesting to speculate whether the low levels of 5-ASA may, in part, for some difference in their rate of absorption.

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 risk of 5-ASA on the infant’s gut may be considered clinically unimportant. However, our finding of high levels of metabolite (N-Ac-5-ASA) in breast milk suggests that the metabolite is greatly enriched in breast milk. Differences in the physical properties of 5-ASA and N-Ac-5-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-Ac-5-ASA by breast tissue as a

Is mesalazine really safe for use in breastfeeding mothers?
Mesalazine containing preparations are commonly used for the treatment and maintenance of remission 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 sample the breast milk at the drug levels present in her breasts, and given the limited evidence in this area we designed a study to measure levels of mesalazine (5-ASA) and its metabolite (N-Ac-5-ASA) in breast milk from other mothers.

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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 specific findings relating to 5-ASA, the discovery of active drug metabolism in the breast has potentially wider implications. Based on 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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References


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 concern with regards to 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 staining 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 study which reveals side effects of 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 adenomas” (that is, Spigelman stage 3 with high grade dysplasia or stage 4). 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, so the range 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 polyectomy 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 but feel that this would have a negligible impact on their analysis. In the present era of selective COX-2 inhibition, our current clinical practice is to consider celecoxib treatment in those with stage 3 or 4 disease as well as those who have undergone surgical intervention. If this practice were followed using sulindac in the centres involved in this trial, then up to 91 (24%) patients in this cohort could have been exposed to non-steroidal anti-inflammatory drugs.

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References


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 platelet frozen plasma, factor VIII cryoprecipitated vWF concentrates, or preparations that contain vWF and factor VIII. Desmopressin, beta blocking drugs, and hormonal therapy with oestrogen with or without progesterone have also been used.

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 melaena, 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 1 vWD. His niece was also diagnosed with type 1 vWD whereas his father, brother and grandmother suffered from bleeding diathesis which had been investigated by our department. Laboratory investigation was compatible with the diagnosis of vWD, with prolonged bleeding time (15 minutes), moderate prolongation of activated partial thromboplastin time (41 seconds), mild deficiency of factor VIII (42%; normal range 50–160%), and a moderate decrease in vWF antigen (33%; normal range 50–160%). Platelet count and prothrombin time were within normal limits and the extensive laboratory investigation excluded the presence of concomitant disorders.

Over a period of 17 months, the patient had been admitted 14 times for recurrent episodes of melaena with an overall hospitalisation time of 98 days and consequent sick leave from his job. On admission, the haemoglobin concentration on admission was 6 g/dl. He required 40 red cell transfusions and 22 000 IU of purified vWF. During this period, upper endoscopy was performed five times, to small bowel three times, colonoscopy twice, and colonoscopy three times; computed tomography of the abdomen, radionuclide scanning with 99m-Tc pertechnetate labelled autologous red blood cells, angiography of the superior mesenteric artery, and exploratory surgery with intraoperative enteroscopy were also performed, but the source of bleeding could not be localised. He had received intranasal desmopressin for three months with no effect on bleeding. He was subsequently treated with octreotide LAR 20 mg (Sandostatin LAR; Novartis, Athens, Greece) intramuscularly once a month, along with propranolol 20 mg orally three times a day. With this therapeutic regimen the bleeding stopped completely, haemoglobin values stabilised at normal levels (13·8 g/dl), and no treatment related side effects were observed. During a follow up period of eight months, bleeding did not recur and the patient has returned to his work. Repeated evaluation of vWF revealed that vWF levels did not rise (28%), but nistocin induced platelet aggregation, moderate decrease in vWF antigen (33%; normal range 50–160%). Platelet count and prothrombin time were within normal limits and the extensive laboratory investigation excluded the presence of concomitant disorders.

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References


Antiviral treatment initiation costs in chronic hepatitis C

We thank Dr Poynard for his comments highlighting the role of pretreatment evaluation costs prior to antiviral treatment of patients with chronic hepatitis C (Gut 2003;52:1352). The rate of fibrosis progression varies in patients with chronic hepatitis C, so liver biopsy can identify those with advanced disease who are at greatest risk for progressing to decompensated cirrhosis when therapeutic options are limited. Other testing, such as genotyping and viral load, can help estimate the likelihood of antiviral response or determine the duration of therapy, and still others are obtained for baseline values to monitor for potential side effects from therapy.

In our cost effectiveness analyses of antiviral treatment strategies for chronic hepatitis C, treatment initiation costs included those related to procedures performed before the beginning of antiviral therapy: pregnancy test, quantitative hepatitis C virus (HCV)-RNA testing, HCV genotyping, thyroid stimulating hormone, thyroxine, and liver biopsy, as well as partial inpatient costs for initiation of antiviral medical treatment. Previously published cost effectiveness studies have applied different biopsy costs depending on the country and health care system.1,2 The costs in our study are based on the German Hepatitis C Database and reflect the German health care system. However, there are different options for defining these costs. Liver biopsy can be performed as an inpatient or outpatient procedure. The German Uniform Assessment Standard (Einheilicher Bewertungsmaßstab, EMB), which is the fee for service coding system in social health insurance for outpatient care in Germany, assigns a total of 1450–1630 score points to the performance of outpatient liver biopsy. This includes ultrasound guidance (350 points), biopsy (700 points), and histology (220–400 points), and translates to a cost between €49 and €55. The German Hepatitis C Model Clinical Expert Panel (n = 16) estimated that impatient liver biopsy requires an average hospital stay of one day or less. Based on administrative per diem costs, a one day hospital stay in Germany costs €234.3 To bias our analysis against antiviral treatment, we performed sensitivity analyses to obtain a conservative estimate of the cost effectiveness of antiviral treatment, we applied a full hospital day for all patients undergoing liver biopsy in our base case analysis.

When we performed sensitivity analyses on all cost parameters, we found little variation in the incremental cost effectiveness ratios of antiviral treatment compared with no antiviral treatment. When comparing combination therapy with peginterferon plus ribavirin versus interferon alfa-2b alone or with ribavirin as initial treatment for chronic hepatitis C, we discounted the expected long term clinical benefits and cost savings from antiviral treatment initiation prevention of future advanced liver disease, and still others are obtained for baseline values to monitor for potential side effects from therapy.

References
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 procedures (if a policy of no follow up for low risk polyps was adopted), 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

Correction
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In the Editor’s quiz: GI snapshot entitled “An unusual treatment for a colonic polyp” (Gut 2004;53(7):1000, 1019) the last two authors were listed incorrectly. The correct order is M Crobu and then MG Porpora.