Gut 2003;**52**:1655–1658

# **PostScript**

# **LETTERS**

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# Scintigraphic assessment of SO dysfunction

As diagnosis of sphincter of Oddi (SO) dysfunction may require perendoscopic manometric assessment of the sphincter, which is an invasive technique carrying a significant risk of pancreatitis, non-invasive scintigraphy has been proposed as an alternative diagnostic method. Craig et al (Gut 2003;52:352-7) reported their experience in assessing SO dysfunction in post-cholecystectomy patients with scintigraphy using the hepatic hilum-duodenum transit time (HHDT) of Cicala and colleagues<sup>1</sup> and the scoring system of Sostre and colleagues.2 In the study of Craig et al, scintigraphic data after cholecystokinin octapeptide (CCK-OP) infusion were compared with SO basal pressure, the latter recorded at manometry in the absence of any stimulus.

Craig *et al* concluded that none of the above scintigraphic variables was sufficiently sensitive to diagnose SO dysfunction identified at SO manometry. Although it is evident that the scintigraphic method of Craig *et al* used in their study was indeed poorly sensitive, the conclusion of their study cannot be extended to interpret the validity of scintigraphy, as performed in other centres.

It is necessary to identify regions of interest (ROIs) that are repeatable. In the original description of the method it was pointed out that only HHDT performed with the correct ROIs and subtractions was repeatable, com-

pared with other scintigraphic variables related to hepatic uptake and clearance of radiolabelled bile.\(^1\) Noticeably in the original HHDT method, ROIs were the heart, right external liver parenchyma, hepatic hilum, and duodenum, whereas in Craig's study ROIs were the right lobe of the liver and the common bile duct (CBD), which are not sufficient reference sites to construct a transit measurement from the hepatic hilum to the duodenum. In addition, an ROI placed on the CBD cannot correctly discriminate CBD activity from that of the major bile ducts at the hepatic hilum.

Furthermore, analysis of time threshold performed on visual assessment of three minute composite images implies a measurement error of several minutes. In addition, assessment of radiolabelled bile at different sites cannot be performed correctly with a visual method that is significantly delayed in comparison with assessment based on time activity curves (TAC), provided that frame timing is adequate. For example, this methodological error is clearly described and illustrated in figure 3 of the article by Cicala and colleagues, with the original description of the HHDT method where the time period assessed with static images at 2.5 minutes apart was delayed by 2.5 minutes in comparison with the assessment based on the TAC constructed on 15 second frame timing. Use of a cholecystokinetic stimulus to assess HHDT is also questionable as CCK is known to affect hepatic bile secretion and SO motor activity, either accelerating the transit of bile under normal conditions or slowing it in the case of SO paradoxical response. Madacsy and colleagues,3 comparing measurement of HHDT without any stimulus and after caerulein administration, showed that the 89% sensitivity of the test without the cholecystokinetic stimulus decreased to 0% after the cholecystokinetic stimulus. In addition, it is not acceptable to derive any conclusions on test sensitivity from a comparison between a scintigraphic assessment performed after a cholecystokinetic stimulus and manometric recordings performed in the absence of a stimulus. Craig et al's study refers to >9 minutes as an abnormal threshold of HHDT, as indicated in the study of Cicala and colleagues.1 Use of a reference threshold from another centre does not apply when a different technique is used. The technique of Craig et al should be validated with correct

reference standards defined in a control group, which was lacking in their study.

Several studies have used similar but not comparable scintigraphic techniques to assess SO dysfunction by means of the hepatic duodenum transit time or a score (see table 1).

All but one of the studies in table 1 have compared scintigraphy with manometry and have shown a high specificity of the test and, with the exception of Craig *et al*, have also shown a satisfactory sensitivity in the absence of a cholecystokinetic stimulus. Reliability of the HHDT test is supported by the following studies:

- (1) it is reproducible in asymptomatic controls (Cicala and colleagues¹) and in patients with SO dysfunction (Cicala and colleagues⁴); and
- (2) it discriminates asymptomatic controls from SO dysfunction patients (Corazziari and colleagues<sup>5</sup>).

Finally, in common with the validation process used for SO manometry, validity of a scintigraphic diagnostic test for SO dysfunction is proved if the tested variable (that is, HHDT or a score) normalises after, and predicts the outcome of, treatment of the abnormality that the test is designed to detect. Both of the above demonstrations for HHDT have been presented in the study by Cicala and colleagues.<sup>4</sup>

We are aware that information concerning reliability and outcome prediction of HHDT derive from a single group of investigators and confirmation studies with comparable techniques performed in other centres would be welcome. However, we would caution against making comparisons and drawing conclusions with techniques that are not comparable and have not been submitted to proper validation studies to ascertain their reliability.

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# References

1 **Cicala M**, Corazziari E, Scopinaro F, *et al.* Quantitative cholescintigraphy in the assessment

Table 1	Scintigraphic tests for sphincter of Oddi (SO) dystunction	1

CRL, caerulein; CCK-OP, cholecystokinin octapeptide; TAC, time activity curve; Rel, reliable; Pts, patients.

	Stimulus			Reproducibility (controls/ pts)	Versus manometry (no stimulus)		Versus sphincterotomy
Reference No		Frame/t	Analysis		Sensitivity (%)	Specificity (%)	(sensitivity)
Scintigraphic HI	HDTT (choledo	choscintigraphy	<i>(</i> )				
1, 4, 5	None	15 s ' ′	TAC	Rel/rel	83	100	93
3	None	1 min	TAC	Not assessed	89	100	Not assessed
3	CRL	1 min	TAC	Not assessed	0	100	Not assessed
6	None	1 min	Static	Not assessed	Not assessed		Not assessed
Craig et al	CCK-OP	1 min	Static	Not assessed	13	95	Not assessed
Scintigraphic sc	ore						
2	CCK-OP	1 min	Static +TAC	Not assessed	100	100	Not assessed
Craig et al	CCK-OP	1 min	Static +TAC	Not assessed	38	90	Not assessed

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- of choledochoduodenal bile flow. Gastroenterology 1991;100:1106-13.
- 2 Sostre S, Kalloo AN, Spiegler EJ, et al. A non invasive test of sphincter of Oddi dysfunction in postcholecystectomy patients: the scintigraphic score. J Nucl Med 1992;33:1216–22.
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- 4 Cicala M, Habib FI, Vavassori P, et al. Outcome of endoscopic sphincterotomy in post cholecystectomy patients with spincter of Oddi dysfunction as predicted by manometry and quantitative choledochoscintigraphy. Gut 2002;50:665–668.
- 5 Corazziari E, Cicala M, Habib FI, et al. Hepatoduodenal bile transit in cholecystectomized subjects. Relatioship with sphincter of Oddi function and diagnostic value Dig Dis Sci 1994;39:1985–93.
- 6 Sand JA, Turjanmaa VM, Koskinen MO, et al. Variables affecting quantitative biliary scintigraphy in asymptomatic cholecystectomized volunteers. Hepatogastroenterology 1999;46:130–5.

# Proposal for a new histological grading system for posttreatment evaluation of gastric MALT lymphoma

Gastric MALT lymphoma (GML) development is closely associated with Helicobacter pylori infection cases.1 The majority of stage IE GML regress following H pylori eradication but assessing cure of the disease requires prolonged follow up. Residual lymphoid infiltrate in post-treatment gastric biopsies can be very difficult to interpret and histological criteria for the diagnosis of minimal residual disease or complete remission are not clearly defined. Molecular follow up by polymerase chain reaction (PCR) for the rearranged immunoglobulin heavy chain variable region shows that persistent monoclonal bands is observed in 44% of cases showing apparent complete histological remission.<sup>2</sup> The significance of ongoing PCR monoclonality in the absence of histological disease is still under investigation.

Thus histological evaluation of gastric biopsies remains the cornerstone to assess lymphoma response to therapy. In 1993, Wotherspoon *et al* proposed a histological scoring system that was initially designated to express the degree of confidence of a diagnosis of GML on gastric biopsies.<sup>3</sup> This

histological scoring has been used to evaluate the response to therapy in a number of subsequent trials but many investigators have found the system difficult to apply and of low interobserver reproducibility. Other studies have used the criteria of partial and complete remission defined by Neubauer and colleagues.<sup>4</sup> Criteria of lymphoma response to therapy need to be standardised using a system that can be easily applied so that results of future clinical trials can be compared.

As part of multicentre clinical trials on GML, GELA (Groupe d'Etude des Lymphomes de l'Adulte) pathologists and one of the authors (ACW) established a posttreatment histological grading system based on evaluation on haematoxylin-eosin (H&E) stained sections of three essential diagnostic features: the lymphoid infiltrate, presence of lymphoepithelial lesions (LEL), and stromal changes. We classified the morphological features observed in post-treatment gastric biopsies as follows: "complete histological response" (CR), "probable minimal residual disease" (pMRD), "responding/residual disease" (rRD), and "no change" (NC) (table 1). These groups give clinically relevant information to the clinician. In particular, the category responding/residual disease (rRD) implies that overt lymphoma is present in association with features that suggest a degree of regression. This would imply to the clinician an ongoing response that does not require immediate use of alternative therapies.

To assess the reproducibility of this histological grading system, we selected at random 10 patients with GML enrolled in the GELA clinical trial (seven men and three women: median age 60 years (range 35-74)).5 A total of 45 sets of gastric biopsies stained with H&E were evaluated separately by each histopathologist blind to the clinical follow up data using the new follow up system. Three to six sequential gastric biopsies were analysed for all patients with a mean follow up of 19 months after H pylori eradication therapy. Interobserver agreement evaluated by the weighted kappa value gave excellent results, with values over 0.84, indicating very good agreement among the seven observers.

Assessing the lymphoma remission status is of great importance for clinical practice. Developing tools to evaluate residual disease are needed, not only for clinical practice but also to conduct clinical trials that aim to define therapeutic guidelines. We propose in this study a histological grading system for

the evaluation of post-treatment gastric biopsies. Testing of this scheme in a small number of cases within the group developing this scheme has shown it to be highly reproducible. These results encourage further evaluation of this scheme on larger series, as well as investigation of its clinical significance and impact on clinical guidelines. In combination with molecular studies, this scheme could provide an interesting tool for the evaluation of residual disease in prospective studies on GML.

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- 2 Bertoni F, Conconi A, Capella C, et al. Molecular follow-up in gastric mucosa-associated lymphoid tissue lymphomas: early analysis of the LYO3 cooperative trial. Blood 2002;99:2541-4.
- 3 Wotherspoon AC, Doglioni C, Diss TC, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue type after eradication of Helicobacter pylori. Lancet 1993;342:575-7.
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# Remarkable resemblance in the mode of transmission of HCV infection among haemodialysis patients and IVDAs

Hepatitis C virus (HCV) infection is widespread among patients on long term haemodialysis (HD) and among intravenous drug abusers (IVDAs). However, there appear to be striking similarities in the mode of

**Table 1** GELA histological grading system for post-treatment evaluation of gastric MALT lymphoma

Score	Lymphoid infiltrate	LEL	Stromal changes
CR (complete histological remission)	Absent or scattered plasma cells and small lymphoid cells in the LP	Absent	Normal or empty LP and/or fibrosis
pMRD (probable minimal residual disease)	Aggregates of lymphoid cells or lymphoid nodules in the LP/MM and/or SM	Absent	Empty LP and/or fibrosis
rRD (responding residual disease)	Dense, diffuse, or nodular extending around glands in the LP	Focal LEL or absent	Focal empty LP and/o fibrosis
NC (no change)	Dense, diffuse, or nodular	Present, "may be absent"	No changes

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transmission between the two groups as both are at high risk for parenterally transmitted HCV infection.

The indispensable requirement of having a vascular access site possibly adds to the risk of acquiring HCV infection among patients on long term HD through nosocomial transmission, especially in high HCV prevalence units. Preliminary data suggest that among various types of vascular access used for HD, arteriovenous fistula and polytetrafluoroethylene grafts which require extra skilful handling, perhaps play a more significant role in the transmission of HCV than permanent or temporary central venous catheters.1 Sharing of contaminated dialysis equipment, dialyser reuse, and the physical proximity of an infected patient during HD are additional important factors incriminated in the transmission of HCV in the busy HD unit.2 Gilli et al reported an outbreak of HCV in an Italian HD unit due to sharing of multidose heparin vials.3 Another recent study from the USA reported an outbreak of HCV occurring when a multidose saline vial was contaminated with blood from a HCV infected patient in a Florida hospital.4 Breakdown in the implementation of standard infection control safety measures recommended by the CDC is essentially responsible for the rapid rise in HCV infection among HD patients worldwide.

Likewise, sharing of contaminated equipment (needles and syringes) among IVDAs is also the primary concern attributed to the continuous increase in HCV infection. However, in a recent report from Kolkata, India,5 dissemination of HCV accelerated, paradoxically from a baseline prevalence rate of 17% in 1996 to 66% in 2002 and to 80% during the next year, regardless of the supply of fresh needles and syringes on a daily basis, under the supervision of trained field workers, with the equipment being taken away from IVDAs on the next day after use. Most of the IVDAs did not share their syringes or needles; none the less, they shared the multidose vials of the drugs. Indirectly sharing of the drug ampoules suggested contaminated body fluids/blood being the means of transmission of HCV through direct access to the blood circulation. Transmission of virus was also suspected to occur from sharing of a small pot containing water that some IVDAs used to clean the syringes and needles before using them again.

With strict implementation of standard infection control precautions and probably isolation of anti-HCV positive patients, it may be possible to effectively control the spread of HCV infection among patients on long term HD.<sup>6</sup> However, promiscuous sexual behaviour, lack of personal and community hygiene, and absolute disregard for life, prevalent among IVDAs, are the major practical problems preventing implementation of interventional measures for the control of the spread of HCV in this high risk group.

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#### Physician-technician

I have every sympathy with Dr Neale's opinion and feel he is entirely correct in worrying about the apparently overwhelming tendency for technological investigation and expertise instead of a more considered diagnostic and management approach (*Gut* 2003;**52**:770–1). I would also agree with his view of the aspirations of many gastroenterological specialist registrars, apparent from talking to many of them. He has highlighted the potential problems of such a technical dictum and not even mentioned what might happen when further advances in imaging obviate the need particularly for diagnostic colonoscopy.

#### What will all the technicians do?

However, Dr Neale has perhaps been a little over cautious in condemning colonoscopy in case No 1. I would agree that colonoscopy in case No 2 with a macrocytic anaemia and possible haematemesis must be regarded as a very doubtful indication. However, in case No. 1, with a marked microcytic anaemia and recurrent melaena without a definite cause in the upper gastrointestinal tract, many would regard visualisation of the colon by whatever means prudent, although given the likely comorbidity a non-invasive test might have been better, depending on resources. It is clear that in both of these typical cases appropriate thought had not gone into the diagnostic approach but also interestingly that in these days of great service pressures it was possible to perform oesophagogastroduodenoscopy and colonoscopy before haematinic estimations. In both cases the colonoscopist must share the blame for taking an overly technical view; bowel preparation may be rather unpleasant but that is no reason to continue and perform an unnecessary investigation if the patient turns up on a list. I would echo Dr Neale's thoughtful suggestion that we need to concentrate more on efficacy and safety of care.

# I Beales

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# Author's reply

I thank Dr Beales for his comments. Clearly, it is always easy to be wise in retrospect. However, we teach students to make a

diagnosis by listing the positive findings and linking these to build a coherent diagnosis.

In case No 1, the house officer noted aspirin ingestion, melaena, a hard liver edge, and thrombocytopenia. He suggested cancer of the gut with hepatic metastases. This was reasonable enough even though it did not include thrombocytopenia.

The next logical step might have been scanning of the upper abdomen in which case splenomegaly would have been added to the list and from there it was only a short step to hepatic cirrhosis and possible reinterpretation of the erythematous/exudative gastritis.

We also teach that patients be told the riskbenefit ratio of any procedure. Frank melaena is a rare presentation of cancer of the colon and the risk of colonoscopy is perhaps 0.2%.

I leave the reader to decide if the present day gastroenterologist should concentrate on honing specialist technical skills to gather information or should develop as a consultant who weighs the evidence as it unfolds.

#### G Neale

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#### Reference

1 Neale G. Informed consent. Gut 2000;46:5-6.

### **CORRECTION**

In the paper by Nikolaus et al (Gut 2002;**52**:1286-90, "Interferon ß-1a in ulcerative colitis: a placebo controlled, randomised, dose escalating study") an exploratory study in 17 patients is reported. In the paper a p value for the comparison between remission in the IFN group (3/10) and the placebo group (0/7) is quoted with 0.023. This is an error and should be 0.23. The conclusions ("Patients treated with escalating doses of IFN-ß-1a tended to show higher clinical response and remission rates than those receiving placebo, although the differences between the groups did not reach statistical significance") remain correct, as they were not based on any statistical significance.

### **NOTICES**

# Sir Francis Avery Jones British Society of Gastroenterology Research Award 2004

Applications are invited by the Education Committee of the British Society of Gastroenterology who will recommend to Council the recipient of the 2004 Award. Applications (TWENTY COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

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Entrants must be 40 years old or less on 31 December 2004 but need not be a member of the Society. The recipient will be required to deliver a 30 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TWENTY COPIES) should be made to the Honorary Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.

# British Society of Gastroenterology Hopkins Endoscopy Prize 2004

Applications are invited by the Endoscopy Committee of the British Society of Gastroenterology who will recommend to the Council the recipient of the 2004 Award. Applications (TEN COPIES) should include:

- A manuscript (2 A4 pages ONLY) describing the work conducted
- A bibliography of relevant personal publications
- An outline of the proposed content of the lecture, including title
- A written statement confirming that all or a substantial part of the work has been personally conducted in the UK or Eire.

An applicant need not be a member of the Society. The recipient will be required to deliver a 20 minute lecture at the Annual meeting of the Society in Glasgow in March 2004. Applications (TEN COPIES) should be made to the Endoscopy Section Secretary, British Society of Gastroenterology, 3 St Andrews Place, London NW1 4LB by 1 December 2003.

# British Society of Gastroenterology Paul Brown Travel Fellowships

The Paul Brown Travel Fellowships are awarded by the Endoscopy Committee of the BSG. They are intended to assist trainee gastroenterologists and established consultants in visits to units outside the United Kingdom for specialist experience and training in endoscopy.

Specialist registrars who have not achieved their CCST are expected to have the approval of their Postgraduate Dean and their Regional Training Director when they apply for a Travel Fellowship. Applicants are expected to provide confirmation that they have been accepted for training in the unit that they wish to visit.

Successful applicants will be expected to provide a brief written report to the Endoscopy Committee of the outcome of their visit.

Application forms are available from the British Society of Gastroenterology Office, 3 St Andrew's Place, London NW1 4LB. Email: bsg@mailbox.ulcc.ac.uk

# 3rd Congress of the European Chapter of the American College of Nutrition

This meeting will be held on 14-15 November 2003 in Göttingen, Germany. Abstract deadline: 01 October 2003. Main topics: Metabolic Syndrome. Plant-genomics. Treatment of Obesity, Hormonal Regulation of the Body Weight, Pediatric Nutrition, Malnutrition, Food-induced Diseases, Food and Allergy. Further details: G Schickedanz, Congress Secretary, Department of Gastroenterology and Endocrinology, University of Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany. Tel +49 551 396326: fax: +49 551 3919125; email: nutrition2003@ med.uni-goettingen.de; nutrition-europe.org

# European Course on Laparoscopic Endoscopy

This course will be held on 18–21 November 2003 in Brussels, Belgium. Further details: Secretary to Professor Cadière, Service de Chirurgie Digestive, Rue Haute 322, Brussels 1000, Belgium. Tel: +32 (0)2 648 07 60; fax: +32 (0)2 647 86 94; email: straeb.asmb@

proximedia.be; website: www.straeb-asmb.

# Hong Kong-Shanghai International Liver Congress 2004

This conference will be held on 14–17 February 2004 in Hong Kong. The topic of the conference is "Liver Diseases in the Post-Genomic Era". Further details: Ms Kristie Leung, Room 102–105 School of General Nursing, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong. Tel: +852 2818 4030; email: kristieleung@hepa2004.org; website: www.hepa2004.org

# PET/CT and SPECT/CT Imaging in Medical, Radiation, Surgical and Nuclear Oncology

This continuing medical education programme will take place on 19–20 March 2004 at Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. Further details: Office of Continuing Medical Education, Johns Hopkins University School of Medicine, Turner 20, 720 Rutland Avenue, Baltimore, Maryland 21205-2195. Tel: +1 410 955 2959; fax: +1 410 955 0807; email: cmenet@jhmi.edu; website: www.hopkinscme.org

# 39<sup>th</sup> Annual Meeting of the European Association for the Study of the Liver

This meeting will be held on 15–19 April 2004 in Berlin, Germany. Further details: Secretariat, c/o Kenes International, 17 rue du Cendrier, PO Box 1726, CH-1211 Geneva, Switzerland. Tel: +41 22 908 0488; fax: +41 22 732 2850; email: info@easl.ch; website: www.easl.ch/easl2004

- Deadline for receipt of abstracts: 16 November 2003
- Deadline for early registration 10 February 2004