exist. It is, therefore, likely that not only rats, but every species, including humans, exposed to long-term hypergastrinaemia is at risk of developing ECL cell carcinoids.

3. *Role of the ECL cell in gastric cancer*. Kuipers does not discuss the role of the ECL cell in gastric carcinogenesis. It is now apparent that a higher proportion of gastric carcinomas than previously realised are probably neuroendocrine carcinomas.[1 5] Moreover, most of these neuroendocrine carcinomas develop from the predominant neuroendocrine cell in the stomach, the ECL cell.[1] In addition, gastric ECL cell carcinoids secondary to hypergastrinaemia may progress to neuroendocrine carcinomas.[1] The gastric carcinomas developing in patients with pernicious anaemia most often originate in the oxyntic area, indicating that the lack of acidity is not the most important factor in gastric carcinogenesis in these patients, and that the ECL cell is probably the cell of origin in these carcinomas.[1] It should also be recalled that the carcinogenic effect of *Helicobacter pylori* infection may be related to hypergastrinaemia.[1]

To conclude, PPI treatment induces hypergastrinaemia. Long-term hypergastrinaemia predisposes to ECL cell tumours, such as ECL cell carcinoids and ECL cell neuroendocrine carcinomas. Long-term PPI treatment might, therefore, increase the risk of gastric cancer. It should be remembered that carcinogenesis is a long-term process often taking decades.

Helge L Waldum, Gunnar Qvigstad
Department of Gastroenterology and Hepatology, St Olavs Hospital, Trondheim University Hospital, Trondheim, Norway

Correspondence to: Professor H L Waldum, Department of Gastroenterology and Hepatology, St Olavs Hospital, Trondheim University Hospital, Olav Kyrres gt., N-7006 Trondheim, Norway; helge.waldum@ntnu.no

Competing interests: None.

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Author's response

In theory, profound acid suppression can promote the development of gastric neoplasia via various pathways, including the trophic effect of hypergastrinaemia on the epithelial lining, stimulation of enterochromaffin-like (ECL) cells leading to formation of carcinoids and neuroendocrine carcinomas, promotion of bacterial overgrowth and induction of a chronic active *Helicobacter pylori* pan-gastritis pattern. Waldum *et al* focus on the theoretical implications of hypergastrinaemia and ECL cell stimulation, a relevant hypothesis that has often been discussed but remains speculative. Indeed, as Waldum points out, data suggest that the incidence of gastric carcinoids has been rising. This has been noted over the past 50 years, in particular since the early 1970s. This primarily correlates with the increase in gastric diagnostic procedures, firstly using *x* rays and later endoscopy with biopsy sampling, rather than the more recent introduction of proton pump inhibitors (PPIs).[1] Nevertheless, gastric carcinoids remain rare, with an incidence of 0.1–0.2 per 100 000 population per year,[2] without an obvious association with PPI use. I mentioned previously that carcinoids have never been described in long-term PPI users, but I was mistaken. Dr Manson from the UK had reported a patient who was diagnosed with a primary gastric carcinoid after having taken 40 mg omeprazole for 4 years for reflux disease.[3] Waldum refers to another case; this was, however, not a long-term PPI user, but a patient with recurrent peptic ulcer who was diagnosed with a gastric carcinoid after intermittently having been treated with famotidine, omeprazole and lansoprazole for a total of 5 months over a 5-year period (ie, <10% of the time).[4]

ECL cells may also play a role in the formation of gastric adenocarcinoma. In fact, it has been suggested that about 10% of gastric adenocarcinomas, in particular of the diffuse type, may have a neuroendocrine component.[5] In the US, a rise in the incidence of the diffuse type of gastric cancer between 1973 and 2000 has been noted, from 0.3 to 1.8 per 100 000 per annum.[6] It is unknown whether acid-suppressive drugs have made any contribution to this process. As pointed out previously, data on gastric cancer formation in long-term PPI users have not shown any increased incidence of gastric cancer (diffuse and intestinal) at all within the first 18 years after the introduction of PPI.[7]

In conclusion, in contrast with the statement of Waldum *et al*, there is, at present, no evidence that promotion of ECL cell growth is a clinically important issue in long-term PPI users, for the formation of either gastric carcinoids or neuroendocrine adenocarcinomas. I fully agree though with the implicit proposition that monitoring of large cohorts of long-term PPI users as well as reporting of any specific cases such as that by Dawson *et al*[3] remains relevant, because only in that way can we eventually settle issues such as raised in this discussion.

Correspondence to: Professor E J Kuipers, Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center, PO Box 2040, 3000 CA Rotterdam, The Netherlands; e.j.kuipers@erasmusmc.nl

Competing interests: In the past 5 years, EJK has received research funding from Altana Pharma, AstraZeneca and Janssen Pharmaceutics, and consulting fees from AstraZeneca.

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Dissemination of evidence-based clinical practice guidelines for hepatocellular carcinoma among Japanese hepatologists, liver surgeons and primary care physicians

Supported by the Japanese Ministry of Health, Labour and Welfare, the first *Clinical practice guidelines for hepatocellular carcinoma* (the *JHCC guidelines*) were compiled in Japan, using an evidence-based methodology. Covering six major research fields for hepatocellular carcinoma (HCC), this set of guidelines consists of 58 pairs of research questions and recommendations, and practical algorithms for the surveillance and treatment of HCC (fig 1).[1 2] A complete English translation of the main body of the guidelines has recently been uploaded on the website of The Japanese Society of Hepatology (http://www.jsh.or.jp/). The *JHCC guidelines* are primarily intended to support both physicians and patients in their decision making on the management of HCC.

In March 2006, approximately a year after the publication of the *JHCC guidelines* book, a questionnaire survey was conducted to investigate the level of awareness and influence of the guidelines among 2279 members of the Liver Cancer Study Group of Japan. Of the 843 (37.0%) responders, 467 (55.4%) were hepatologists and 320 (38.0%) were liver surgeons. More than 70% were working at university hospitals or designated teaching hospitals. Over the previous 3 months, 533 (63.2%) and 357 (42.3%) of the responders had treated ⩾10 HCC patients at outpatient and inpatient bases, respectively.

The same questionnaire was sent out to 689 primary care physicians in Osaka and Hyogo prefectures, and 332 (48.2%) responded; 159 (48%) were internists, 146 (44%) were surgeons and 209 (63%) were working at clinics. The majority (86.4%) had treated <10 patients with HCC in the previous 3 months.

The *JHCC guidelines* have been acknowledged by 71.9% of hepatologists, 75.6% of liver surgeons and 61.0% of primary care physicians. Answers obtained regarding the possible actions taken for clinical questions on HCC are shown in fig 2A. Medical magazines, literature search, the *JHCC guidelines* and colleagues' opinions were the main sources of information, both for hepatologists and for liver surgeons, whereas specialists' or colleagues' opinions were the major sources of information for primary care physicians. After the introduction of the *JHCC guidelines*, only 19–21% of hepatologists or liver surgeons changed their practice pattern (fig 2B); 50–52% did not change their practise pattern, and were convinced that their choice of treatment was similar to the recommendations in the guidelines. In total, 43% of primary care physicians changed their practice pattern as per the recommendations in the guidelines, or by paying more attention to patients' preferences.

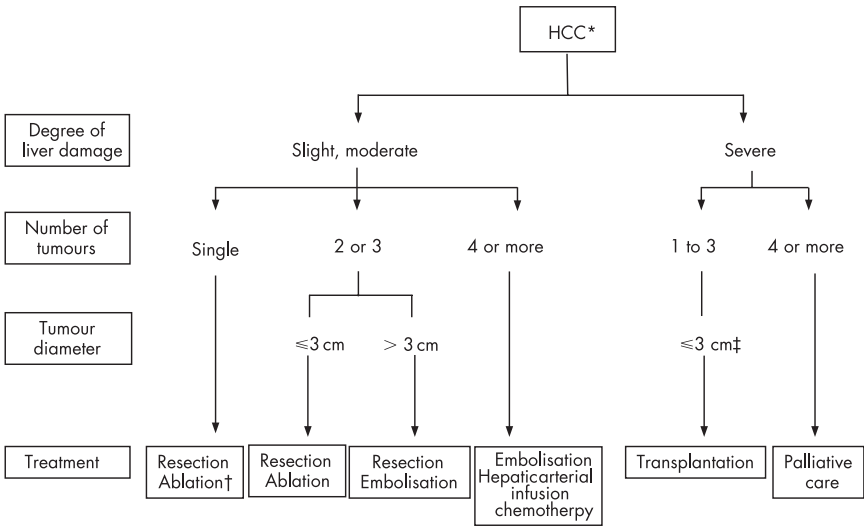

Figure 1 Treatment algorithm for hepatocellular carcinoma (HCC) (cited with permission from the Group formed to establish ''Guidelines for evidence-based clinical practice for the treatment of liver cancer''[1]).
*The presence of vascular invasion or extrahepatic metastasis is indicated separately. †Selected when the severity of liver damage is moderate and the tumour diameter is ⩽2 cm. ‡Tumour diameter ⩽5 cm, when there is only one tumour.

In conclusion, 1 year after its publication, the *JHCC guidelines* have become well disseminated among both specialists and primary care physicians in Japan. As expected, these guidelines have begun to be applied at every level of clinical decision making for HCC.

Acknowledgements

We thank Mr Hiromichi Suzuki and the International Medical Information Center (Tokyo) for their clerical work for the questionnaire survey.

Norihiro Kokudo
Department of Surgery, Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, University of Tokyo, Tokyo, Japan

Yo Sasaki
Department of Gastrointestinal Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

Takeo Nakayama
Department of Health Informatics, Kyoto University School of Public Health, Kyoto, Japan

Masatoshi Makuuchi
Department of Surgery, Hepato-Biliary-Pancreatic Surgery Division, Artificial Organ and Transplantation Division, University of Tokyo, Tokyo, Japan

Correspondence to: Professor N Kokudo, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan; kokudo-2su@h.u-tokyo.ac.jp

doi: 10.1136/gut.2007.119362

Competing interests: None declared.

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One- or two-week triple therapy for *Helicobacter pylori*: questions of efficacy and inclusion of a dual therapy treatment arm

We read with interest the recent paper comparing 1 and 2 weeks of triple therapy for *Helicobacter pylori* infection in patients with duodenal ulcer disease. (*Gut* 2007;**56**:475–9) *H pylori* is an infectious disease and the goal of treatment is to cure the infection. In 2007, one would hope to be able to reliably cure ⩾95% of the treated patients (discussed by Graham *et al*).[1] In 1989, a successful treatment has been defined as one that cures >80% of the patients.[2] By 1995, it seemed that 90% was achievable.[3] The Maastricht consensus conferences defined a useful therapy as the one with an intention to treat (ITT) cure rate of >80%,

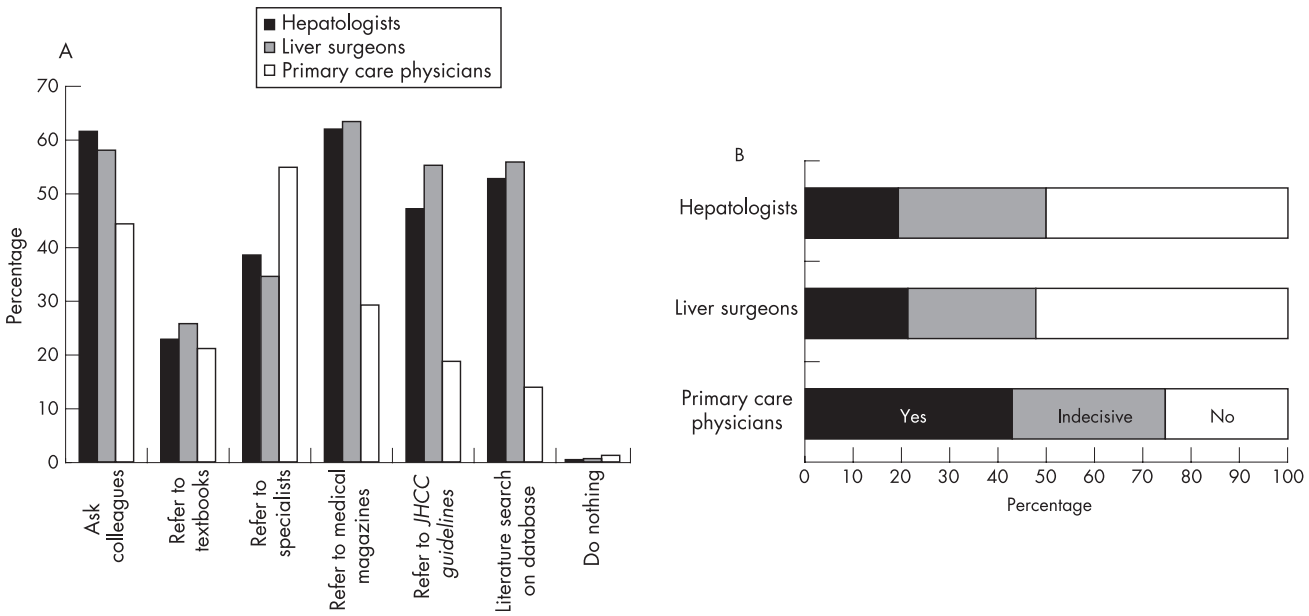

Figure 2 (A) What are your possible actions when you have clinical questions or problems in regard to the management of patients with hepatocellular carcinoma (HCC)? (a multiple-choice question). (B) Have you changed your practice pattern for HCC after reading the *JHCC guidelines*? (Responders who did not acknowledge the guidelines were excluded.)