1 Cameron AJ. Incidence of iron deficiency anemia in patients with large diaphragmatic hernia. A controlled study. *Mayo Clin Proc* 1976; **51:** 757–9.
2 Higgins JA, Cameron AJ. Linear gastric erosion. A lesion associated with large diaphragmatic hernia and chronic blood loss anemia. *Gastroenterology* 1986; **91:** 338–42.
3 Holt JM, Mayet FGH, Warner GT, Callender ST, Gunning AJ. Iron absorption and blood loss in patients with hiatus hernia. *BMJ* 1968; **3:** 22–5.

Reply

EDITOR,—We are grateful to Dr Cameron for his interesting comments. The finding of a hiatus hernia is a very common one and he is commenting on patients with particularly large hernias. We believe that they have shown an association but would like to see more direct evidence for the lesions causing bleeding and thus iron deficiency anaemia. Many patients with a hiatus hernia do not have oesophagitis or gastritis within the sac. It is possible that aspirin or non-steroidal anti-inflammatory drugs may have more potential to cause local damage in hiatus hernias but the case is unproved. The presence of non-haemorrhagic gastritis or oesophagitis may not necessarily be a source of sufficient blood loss to explain anaemia. More evidence is required for us to accept hiatus hernias as a significant cause of gastrointestinal bleeding.

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Chemotherapy *v* symptomatic treatment for hepatoma

EDITOR,—It is with considerable interest that we read the paper by Madden *et al* on their randomised trial of chemotherapy *v* symptomatic treatment in hepatocellular carcinoma (HCC) (*Gut* 1993; **34:** 1598–600). This is actually the second paper reporting an unsuccessful outcome of lipiodol mediated local chemotherapy in hepatocellular carcinoma, on the basis of a randomised trial (the first being a study by a French group).[1]

As lipiodol mediated transcatheter arterial chemoembolisation (TACE) has been reported by a number of authors as a useful treatment for hepatocellular carcinoma,[2–4] it is natural to wonder about the possible explanations for such an unexpected result.

We suggest that the results presented by Madden *et al* may be explained by a number of drawbacks in the design of their study.

The authors show the number of patients joining the study as 25 for each arm, but only 18 patients were actually treated.

There may be a bias, apart from the racial one suggested by the author, as more than half of the selected patients were excluded from the study; the reasons for exclusion vary considerably, but patients living too far away, undergoing surgery or refusing to take part might well have had a better prognosis, for a variety of reasons.

The very low median survival (apparently similar to the survival rate reported by Okuda in patients with extremely advanced disease[5]) in both treated and untreated patients suggests that despite the good median Eastern Cooperative Oncology Group (ECOG) performance rating and Okuda stage reported, the patients included in the study all had extremely advanced disease, which may have been underestimated. In addition, nothing is said about liver function. On the other hand, it may be, as the authors suggest, that hepatocellular carcinoma has a worse prognosis in South Africans. But we know that, although TACE was originally proposed for all hepatocellular carcinoma patients ineligible for surgery or percutaneous ethanol injection, this treatment is only indicated in patients with a comparatively good functional state (Child-Pugh A and B). As the authors mention, this may also represent an important bias.

This possibility is further emphasised by the fact that only three patients were still eligible for a second course of treatment; moreover, it must be remembered that TACE is only useful when repeated courses are given to a patient.[6]

It has also been established that the most useful step in TACE is final embolisation, without which it is much less effective,[7] but it would seem that none of Dr Madden's patients had this procedure.

As we do not believe that a randomised trial of TACE *v* no treatment is ethically acceptable in hepatocellular carcinoma patients, our own experience is based on prospective data collection on 48 patients given an average of three courses of TACE since 1991. The Table gives the patients' age, male/female ratio, and Child-Pugh and Okuda staging. Most of our patients were in Okuda's stage I and fitted in the 0 or 1 ECOG performance rating. Their survival rates at 1 and 2 years were respectively 74% and 50%, with a median survival of 390 days and a treatment related mortality of 2%. This survival rate is actually higher than Okuda describes in stage I patients (345 days).

Patients' characteristics

Mean age (y)		61·0 (range 37–81)
Male/female ratio		3·8/1
Child-Pugh grade	A	63%
	B	27%
	C	10%
Okuda grade	I	63%
	II	37%
	III	0%

Survival: median 390 days–1 year 74%, 2 years 50%

In conclusion, the authors correctly suggest that their data may not apply to hepatocellular carcinoma patients from other geographical areas, but we think it would also have been more suitable to emphasise that their study differs from other reports possibly in terms of the tumours treated, probably as regards patient enrolment, and certainly as concerns the lack of embolisation in the treatment protocol and the non-repetition of the TACE treatment. Despite this and the other study we quoted previously (the authors of which have recently claimed that chemoembolisation is effective in patients with Okuda I hepatocellular carcinoma[8]), unresectable patients with hepatocellular carcinoma clearly benefit from TACE and this has been shown in several studies from Japan and Europe and also in our own experience. To what extent randomised trials of TACE *v* symptomatic treatment are still ethically acceptable is open to debate.

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1 Pellettier G, Roche A, Ink O, Anciaux ML, Derhy S, Rougier P, *et al.* A randomized trial of hepatic arterial chemoembolisation in patients with unresectable hepatocellular carcinoma. *J Hepatol* 1990; **11:** 181–4.
2 Yamada R, Sato M, Kawabato M. Hepatic artery embolization in 120 patients with unresectable hepatoma. *Radiology* 1983; **148:** 397–401.
3 Kanematsu T, Furuta T, Takemata K. A 5 years experience of lipiodolization: selective regional chemotherapy for 200 patients with hepatocellular carcinoma. *Hepatology* 1989; **10:** 98–102.
4 Bismuth H, Morino M, Sherlock D, Castaing D, Miglietta C, Cauquil P, *et al.* Primary treatment of hepatocellular carcinoma by arterial chemoembolization. *Am J Surg* 1992; **163:** 387–94.
5 Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa, *et al.* Natural history of hepatocellular carcinoma and prognosis in relation to treatment. *Cancer* 1985; **56:** 918–28.
6 Ikeda K, Kumada H, Saitoh S, Arase Y, Chayama K. Effect of repeated transcatheter arterial embolization on the survival time in patients with hepatocellular carcinoma. *Cancer* 1991; **68:** 2150–4.
7 Takaysu K, Shima Y, Muramutsu Y, Moriyama N, Yamada T. Hepatocellular carcinoma treatment with intraarterial iodized oil with or without chemotherapeutic agent. *Radiology* 1987; **162:** 345–51.
8 Rougier P, Roche A, Pellettier G, Ducreux M, Pignon JP, Etienne JP. Efficacy of chemoembolization for hepatocellular carcinomas: experience from the Gustave Roussy Institute and the Bicêtre Hospital. *J Surg Oncol Suppl* 1993; **3:** 94–6.

Reply

EDITOR,—Dr Farinati *et al* feel that our random control trial may have underestimated the value of chemotherapy with lipiodol and 5-epidoxorubicin for hepatoma. We offer the following comments on the three points that they make.

They suggest that the outcome should be analysed by treatment received, not treatment intended. We published the results according to treatment intended because in both trials and clinical practice some patients cannot receive the treatment after it has been chosen. We also analysed the results according to treatment received. This did not change the conclusions.

They propose that the patients who were ineligible for the trial may have had a better prognosis than those randomised. We think that ineligible patients probably had a worse prognosis, although we did not follow them up until death. Sixty per cent were ineligible because of conditions that confer a bad prognosis. They were bedridden (33%), aged over 70 years (13%), had extrahepatic tumour (9%) or serious heart disease (6%).

Thirdly, they suggest that final embolisation makes the treatment more effective. The study that Dr Farinati says proves this statement was not a random control trial. We are cautious about accepting its claim.

Finally, Pelletier's trial used doxorubicin but not lipiodol, so this combination has not previously been tested in a random control trial.

We share Dr Farinati's concern that our findings may not apply to all cases of hepatoma because our patients had a short median survival time. We hope that workers who treat cases with a better prognosis will also perform random control trials. It is important to know if the treatment increases morbidity (which we found) or helps such patients.

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