Hepatocellular carcinoma: is surveillance cost effective?

The development of hepatocellular carcinoma (HCC) constitutes a frequent event during the evolution of patients with liver cirrhosis (3–5% annual incidence rate) and constitutes their main cause of death. Survival is related to tumour stage at diagnosis and to the degree of impairment of liver function. Recent data have shown that survival after diagnosis is not as poor as reported years ago. This is due both to advances in diagnosis even in the absence of effective treatment (lead time bias) and to the application of curative treatments (surgical resection, liver transplantation, and percutaneous ablation). These offer the only chance of cure but their applicability and long-term success with five year survival exceeding 50% require the detection of HCC at an early stage, including patients with solitary nodules ≤5 cm or up to three nodules each ≤3 cm. In contrast, large/multifocal tumours are less likely to benefit from curative approaches and here three factors are important: (1) detection of HCC at an early stage, including patients with solitary nodules ≤5 cm or up to three nodules each ≤3 cm; (2) a thorough diagnostic work-up to rule out liver cirrhosis in the presence of elevated serum alpha-fetoprotein levels; and (3) close follow-up of patients with liver cirrhosis or chronic hepatitis B or C.

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apparently subtle form of bacterial overgrowth. The definition NASH may also have been inadequate: it requires histological assessment because liver test abnormalities and hepatic imaging do not reliably discriminate between uncomplicated steatosis and NASH. In this study, three of the NASH patients (all of the controls) were not subjected to liver biopsy, leaving open the opportunity for misclassification of cases.

Despite the finding that TNF-α levels were increased in patients with NASH, Wigg et al were unable to demonstrate either a “leaky” infected small intestine (as measured by the lactulose-rhamnose sugar test) or endotoxaemia. At first glance, this seems counterintuitive for the proposal that bacterial overgrowth of the small intestine plays a pathogenic role in NASH. Some plausible explanations for the paradox were suggested: limitations of the limulus assay, binding of endotoxin to plasma proteins, and systemic levels may not reflect portal endotoxaemia. Furthermore, other bacterial products such as peptidoglycan-polysaccharide polymers rather than endotoxin could stimulate release of TNF-α.

The latter concept is particularly cogent because Bacteroides species rather than aerobic Gram negative bacteria such as Escherichia coli, the source of endotoxin, appear to be implicated in the pathogenesis of small intestinal bacterial overgrowth. Measurement of peptidoglycan-polysaccharide polymers in patients with NASH would be an interesting direction of investigation in the future. In the Adelaide study, there was no relationship between body mass index and serum TNF-α levels, but a link between obesity and raised serum TNF-α has been described by others. Yang and colleagues noted that after endotoxin administration in leptin deficient ob/ob mice, hepatic induction of IFN-γ is increased whereas IL-10 induction is inhibited. IFN-γ increases hepatocyte sensitivity to TNF-α while IL-10 appears to inhibit the tissue response to TNF-α. These findings were interpreted as indicating possible macrophage dysfunction in obesity in a way that could promote steatohepatitis by sensitising hepatocytes to endotoxin. Guebre-Xabier et al have also shown that ob/ob mice have a selective reduction of hepatic CD4+ NK T cells, and this is associated with and possibly mediated by upregulation of IL-18 and IL-12. Whether these abnormalities of lymphocyte populations and cytokine responses are due to obesity per se or to leptin deficiency (which is not a feature of human obesity) remains to be determined.

NASH can be regarded as the hepatic consequence of the metabolic syndrome (central obesity, insulin resistance, type II diabetes, arterial hypertension, hyperlipidaemia). Attention has shifted from the reasons for steatosis to the mechanisms for hepatocellular injury, inflammation, and fibrosis. The findings reported by Wigg et al, while not definitive, may provide a new clue to the importance of cytokines in mediating liver cell injury in NASH. Whether the release of TNF-α is a consequence of small intestinal bacterial overgrowth, obesity, or oxidative stress will require further study.

G C FARRELL
Storr Liver Unit, Westmead Millennium Institute, University of Sydney at Westmead Hospital, Westmead, NSW 2145, Australia.
geoff.farrell@semi.usyd.edu.au

8 Weltman MD, Farrel GC, Liddle C. Increased hepatic CYP2E1 expression and its role in hepatic steatosis in obesity with insulin resistance. Gastroenterology 1996; 111:1645–53.
surveillance programmes for patients with cirrhosis. HCC has most requisites for such a policy: the population at risk is known, the disease is highly prevalent, it has a high mortality, and effective screening tests are available and acceptable. However, other conditions are not yet met: the recall policy on raising suspicion is not well defined and, unfortunately, there is no unequivocal proof that treatment improves survival. Radical therapies have never been evaluated in randomised controlled trials but are widely considered “effective” and assumed to improve survival.\(^1,3\)

In contrast, randomised controlled trials assessing palliative treatments (that is, chemoembolisation) have shown negative results.\(^7\) Accordingly, the usefulness of surveillance programmes in cirrhotics is still controversial, leading to the suggestion that they provide a minor benefit in terms of efficacy (years of life saved) and cost effectiveness. The only method to clarify this issue would be to design a randomised controlled trial comparing surveillance versus non-surveillance in a large series of cirrhotics who would be treated if diagnosed with HCC. Such an investigation would be ethically questionable and in addition, almost unfeasible. Ultrasound examination is commonly used for evaluation of cirrhotics, irrespective of the type of symptoms and this would “contaminate” the control arm.

In the absence of randomised controlled trials, how may we estimate the benefits of surveillance? Two approaches are proposed: to conduct follow up investigations or to perform decision-analytical studies using assumptions reported in clinical studies.\(^7\) Bolondi and colleagues\(^8\) conducted a follow up study, reported in this issue of Gut, recruiting a large series of cirrhotics and applying the most common surveillance policy: ultrasound and a fetoprotein determinations every six months (see page 251). On suspicion, they followed a predefined recall policy to determine the diagnosis and select the most suitable therapy aiming to offer all radical options to patients with early HCC. The outcome of patients under surveillance was compared with that of patients referred to hospital for HCC that was incidentally detected outside their programme. This comparison has allowed a rough estimation of the surveillance benefits but detection of patients with asymptomatic small solitary tumours outside surveillance suggests potential “contamination” of the control group by uncontrolled surveillance within the community physicians who thereafter refer patients with suspected HCC to the tertiary hospital for evaluation and treatment.

As surveillance is aimed at reducing disease specific mortality, comparison of long term survival between both cohorts is crucial. Unfortunately, the difference in survival was significant but not impressive (45% vs 33% at three years). This may reflect both a lead time phenomenon and a real impact of treatment on survival. Interestingly, the applicability of radical therapies was not significantly different between the two cohorts (60% vs 54%), although liver transplantation was more frequently applied in the surveillance cohort. Nevertheless, multivariate analysis identified liver function and tumour stage as survival predictors. Tumour stage may be a surrogate of surveillance and thus surveillance may prompt earlier HCC detection not allowing a better therapeutic approach, and this would prevent a marked impact on survival. In addition to this clinical output, Bolondi et al showed that the cost per year of life saved was above US$100 000, a value largely exceeding the cut off accepted for surveillance by policy makers and health providers.\(^9\)

Do these findings imply that the study is not relevant? The answer is no. Evaluation of surveillance for HCC requires several clinical studies with different designs in different settings. Bolondi and colleagues\(^8\) describe the outcome of a hospital based programme including all types of cirrhotics and it may be that the clinical impact would be higher in a community based programme. In the latter, the risk of HCC might be lower because of better liver function (the study confirms age, advanced liver disease, and increased a fetoprotein concentrations as the main HCC predictors within cirrhosis) but the applicability of liver resection or transplantation may be increased. Thus a relevant increase in survival could be attained. On the other hand, the cost of each detected HCC in low risk individuals may also rise, and perhaps the unacceptable cost effectiveness ratio would not be modified. Another approach is more intense surveillance (that is, every three months) or the use of different tools. The results of these awaited studies will provide the assumptions to be used for estimation of the benefits and cost effectiveness of surveillance in different scenarios by using statistical techniques such as the Markov model.

Until these data become available, the debate will persist and surveillance will be initiated in cirrhotics, even without evidenced based data. However, this approach does have positive benefits. The diagnosis of patients at a non-advanced stages prompts further refinement of treatments with progressive improvement in long term outcomes. In addition, in the era of genetic profiling, careful recruitment of both clinical and biological data within surveillance will surely introduce molecular concepts into clinical practice. Ultimately, this research will change our understanding of the disease and help us to identify new targets for both prevention and treatment.

J BRUIX

J M LLOVET

BCLC Group, Liver Unit, Hospital Clinic, IDIBAPS, University of Barcelona, Catalonia, Spain

Correspondence to: Dr J Bruix, BCLC Group, Liver Unit, Hospital Clinic, University of Barcelona, Villarroel 170, 08036-Barcelona, Catalonia, Spain. jbruix@clinic.ub.es

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*Gut* 2001 48: 149-150
doi: 10.1136/gut.48.2.149

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