Screening for Hepatocellular Carcinoma

MF Yuen, MD, PhD

Department of Medicine, The University of Hong Kong

After graduation from the University of Hong Kong in 1992, Dr MF Yuen has been working in the Department of Medicine, The University of Hong Kong. He started the specialty training of Gastroenterology and Hepatology in 1995. He obtained the degree of Doctor of Medicine (MD) with Sir Patrick Manson Gold Medal in 2001 and the degree of Doctor of Philosophy (PhD) in 2005. He is now the Associate Professor of Department of Medicine, The University of Hong Kong. He serves as a council member in different organizations including Asia Pacific Hepatitis B Management Advisory Board, Hong Kong Association for the Study of Liver Diseases, and The Hong Kong Society of Gastroenterology. He also serves as reviewer for many international journals including *Gastroenterology, Hepatology, Gut* and *Journal of Hepatology.*

Dr Yuen's research interests are on chronic hepatitis B infection with extensive studies on prevention, natural history, molecular virology and treatment of this disease including treatment of hepatocellular carcinoma. He has already published more than 13 research papers in various international journals. He was awarded the Outstanding Young Researcher Award by The University of Hong Kong in 2005.

Hepatocellular carcinoma (HCC) is the fourth most common cancer in the world. The median survival in symptomatic patients is only a few weeks. HCC fulfills most of the 10 criteria for cost-effective screening set up by WHO in 1968. The one issue that remains to be settled is whether the cost of diagnosis and treatment is economically balanced with the whole medical expenditure.

The two screening tests for HCC are ultrasonography and alpha fetoprotein (AFP) levels. Ultrasonography (US) can detect lesions down to 1-2 cm but often cannot distinguish HCC from haemangioma and cirrhotic nodules. In one study the false positive rate was 82.5% with a positive predictive value of 15.1% only[1]. AFP as a screening test is also problematic because it is often raised in acute exacerbation of chronic hepatitis[2]. In a case control study it had a sensitivity of 60% and positive predictive value of 25% only[3] though combining the US and AFP can increase the sensitivity. At present, they remain the main screening methods because they are convenient, non-invasive and easily assessable. Though earlier studies fail to show improvement in patient management and survival by screening, more recent studies demonstrate that screening can increase the chance of curative treatment and, more importantly, improve survival even after the adjustment of lead-time bias. This is probably due to the improvement in medical treatment and technology.

The interval of surveillance should be around 4-6 months based on the extrapolated growth rate of HCC from a study in Taiwan showing that the most rapid growing tumours take 4.6 months to grow to 3 cm in diameter[1].

The scene for the debate on usefulness/cost-effectiveness of screening for HCC has been set by an Italian study in 1991 which showed that operability of screened HCC (4 out of 29) was lower than that of HCC which were detected incidentally (13 out of 29; p=0.027)[5]. More recent studies are beset by the problem of lack of a prospective control group for ethical and practical reasons. This leads to lead-time bias and length bias. Bearing these biases in mind, four recent studies show that screening for HCC does lead to better chance of treatment and prolonged survival[6-9]. However while the study of Yuen et al calculated the annual cost to detect one HCC to be US$1,167, that of Bolondi et al found the cost per treatable HCC to be an unacceptably high US$17,934. The debate on cost-effectiveness continues. The ultimate answer may depend on the prevalence of the disease in different localities.

References

1. Sherman M, Peltekian K, Lee Cindy. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. Hepatology 1995; 22:432-438.

2. Lok ASF, Lai CL. α-fetoprotein monitoring in Chinese patients with chronic hepatitis B virus infection role in the early detection of hepatocellular carcinoma. Hepatology 1989; 9:110-115.

3. Trevisani F, D'Intino PE, Morselli-Labate AM, Mazzella G, Accogli E, Caraceni P, Domenicali M, De Notarüs S, Roda E, Bernardi M. Serum α-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver diseases: influence of HBsAg and anti-HCV status. J Hepatology 2001; 34-570-575.

4. Shen JC, Sung JL, Chan DS, Yang PM, Lai MY, Lee CS, Hau HC, Chuang CN, Yang PC, Wang TH, Lin JT, Lee CZ. Growth rate of asymptomatic hepatocellular carcinoma and its clinical implications. Gastroenterology 1985; 89:259-266.

5. Colombo M, de Franchis R, Del Ninno E, Sangiovanni A, De Fazio C, Tommasini M, Donato MF, Piva A, Di Carlo V, Dioguardi N. Hepatocellular carcinoma in Italian patients with cirrhosis. N Engl J Med. 1991; 325:675-680.

6. McMahon BJ, Bulkow L, Harpster A, Snowball M, Lanier A, Sacco F, Dunaway E, Williams J. Screening for hepatocellular carcinoma in Alaska natives infected with chronic hepatitis B: a 16-year population-based study. Hepatology 2000; 32:842-846.

7. Yuen MF, Cheng CC, Lauder IJ, Lam SK, Ooi CG, Lai CL. Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. Hepatology 2000; 31:330-335.

8. Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, Piscaglia F, Gramantieri L, Zanetti M, Sherman M. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. Gut 2001; 48:251-259.

9. Trevisani F, De NS, Rapaccini G, Farinati F, Benvegnu L, Zoli M, Grazi GL, Del PP, Di N, Bernardi M. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience). Am J Gastroenterol 2002; 9:734-744.