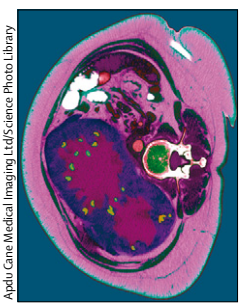
Apdu Cane Medical Imaging Ltd/Science Photo Library

of HCC in patients with chronic hepatitis B. Although other groups, such as Yuen and colleagues,[4] have reported risk scores for the development of this disease, this is the first group to provide validation of their risk score. The study analysed data from 3584 patients from a community-based Taiwanese cohort who were not receiving antiviral therapy and did not have cirrhosis, and validated their risk score in hospital-based cohorts from Hong Kong and South Korea.[3] Variables associated with an increased risk of HCC included patient factors (male sex, increasing age), disease factors (raised concentrations of serum alanine aminotransferase), and virological factors (HBeAg positivity and increased levels of serum HBV DNA). The risk score accurately estimated the risk of development of HCC at 3, 5, and 10 years. The investigators have contributed to the evolving work into risk scores for HCC by providing validation in a large, independent multicentre cohort. They conclude that this score could allow evidenced-based decisions for clinical management of hepatitis B carriers at variable risk of HCC.

The key question for clinicians is whether or not this risk score can lead to tailored decisions in the management of patients with chronic hepatitis B, such as no surveillance in patients with a low score or a change to more frequent surveillance or use of more sensitive imaging techniques in those with a high score. Prospective studies of surveillance every 3–4 months versus 6 months, or use of CT or MRI rather than ultrasound in high-risk patients with chronic hepatitis B would be needed before a clinician could with confidence change from the standard recommendation of ultrasonography every 6 months, usually with α-fetoprotein.[2] The population that was the basis of the Yang and colleagues' risk score did not include patients with cirrhosis, which is known to be the major risk factor for HCC and is present in up to three-quarters of HBV-related HCC.[5] Moreover, cirrhosis was the most important independent risk score for development of HCC in Yuen and colleagues' risk score.[4]

Many Asian–American patients who are undergoing antiviral therapy have undetectable HBV DNA, normal alanine aminotransferase concentrations, and are HBeAg negative; they would have a low risk score but yet fit the criteria for surveillance recommended in the AASLD guidelines on the basis of their age or other factors (eg, presence of cirrhosis or a family history of HCC). How to resolve the different advice provided by a risk score versus a society guideline is a dilemma for the clinician. Risk scores might be most helpful in identification of patients with a very low risk of HCC who do not need surveillance, rather than leading to a change in surveillance practices in patients with a high score. Additionally, the incidence of HCC differs according to the geographical distribution of risk factors, and surveillance strategies derived from a Taiwanese or Asian populations might not apply globally. Finally, scoring systems should include known risk factors such as the presence of cirrhosis, use of alcohol, and family history of HCC, and should be validated in white and African patients who are often infected in adulthood and whose risks for HCC differ substantially from those in Asian patients with chronic HBV infection dating from birth or early childhood. Thus, risk scores for the development of HCC are in the preliminary stages of development and not yet ready for widespread use in practice.

Emmet B Keeffe
Division of Gastroenterology and Hepatology, Department of Medicine, Stanford University Medical Center, Stanford, CA, USA
ekeeffe@stanford.edu

I have no conflicts of interest.

1 Zhang BH, Yan BH, Tang ZY. Randomized controlled trial of screening for hepatocellular carcinoma. *J Cancer Res Clin Oncol* 2004; **130:** 417–22.
2 Bruix J, Sherman M. Management of hepatocellular carcinoma: an update. *Hepatology* 2001; **53:** 1020–22.
3 Yang H-I, Yuen M-F, Chan HL-Y, et al, for the REACH-B Working Group. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* 2011; published online April 15. DOI:10.1016/S1470-2045(11)70077-8.
4 Yuen MF, Tanaka Y, Fong DY, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol* 2009; **50:** 80–88.
5 Yuen MF, Yuan HJ, Wong DK, et al. Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. *Gut* 2005; **54:** 1610–14.

Authors' reply

Although our predictive score for risk estimation of hepatocellular carcinoma in patients with chronic hepatitis B was externally validated,[1] we agree with Emmet Keeffe[2] that further validation is needed in patients of other ethnic origins and in those infected with hepatitis B virus later in life. Family history of hepatocellular carcinoma and alcohol consumption are also important factors, but present problems for clinicians in terms of data collection. Subsequent revisions to this risk calculator will depend on the wide

availability of additional tests, and physicians' ability to monitor patients. Although strong evidence suggests that cirrhosis is an important predictor for future development of hepatocellular carcinoma,[3] patients with existing cirrhosis by definition need close monitoring and initiation of antiviral therapy. Risk prediction in this group of patients or use of cirrhosis as a variable might therefore be redundant.

Keeffe suggests that risk calculation might be best suited to establish surveillance patterns in patients who are identified to be at low risk, rather than for increasing surveillance in high-risk patients. Although we acknowledge that further research might be necessary to validate changes in established surveillance techniques, we believe that this notion ignores a potentially more important use of this prediction score. Because antiviral therapy has the potential to improve histology,[4] timely identification of high-risk patients for whom antiviral therapy will be beneficial could provide these patients with the best opportunity to improve quality of life and prolong survival. We hope that a risk prediction score could complement clinical practice guidelines, allowing it to be refined and incorporated into future revisions.

Chien-Jen Chen, Hwai-I Yang, for the REACH-B Working Group
Genomics Research Centre, Academia Sinica, Nankang, Taipei, Taiwan (C-JC, H-IY); Graduate Institute of Epidemiology, School of Public Health, National Taiwan University, Taipei, Taiwan (C-JC); and Molecular and Genomic Epidemiology Center, China Medical University Hospital, Taichung, Taiwan (H-IY)
cjchen@ntu.edu.tw

H-IY and C-JC have received speakers' honoraria and travel expenses from Bristol-Myers Squibb in relation to the REACH-B working group meeting. C-JC has received research grant support from the Department of Health; Academia Sinica and National Health Research Institute, Taiwan; and Bristol-Myers Squibb.

1 Yang HI, Yuen MF, Chan HL, et al. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol* 2011; **12:** 568–74.
2 Keeffe EB. Risk score for development of HCC: ready for use in practice? *Lancet Oncol* 2011; **12:** 517–18.
3 Yuen MF, Tanaka Y, Fong DY, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol* 2009; **50:** 80–88.
4 Mommeja-Marin H, Mondou E, Blum MR, Rousseau F. Serum HBV DNA as a marker of efficacy during therapy for chronic HBV infection: analysis and review of the literature. *Hepatology* 2003; **37:** 1309–19.

...and a two-edged sword in their hands

Willem van Gijn and colleagues[1] report mature (10 year) results in terms of local recurrence and survival from the Dutch total mesorectal excision (TME) trial in rectal cancer. The trial had excellent quality assurance for surgery and pathology and, although many changes in staging and management have taken place since the original design, the results remain relevant today.

The 10-year cumulative incidence of local recurrence was 5% in the group assigned to short-course preoperative radiotherapy (SCPRT; 5×5 Gy) versus 11% in the surgery alone group (p<0·0001). Key messages are that this 50% relative reduction in local recurrence is maintained long-term, and in a subset of patients with a TNM stage III tumour and with a negative circumferential margin (CRM), preoperative radiotherapy improved 10-year survival from 40% to 50% (p=0·032).

However, the overall results of the Dutch trial do not show a difference in survival, which implies that some groups (maybe those who are node negative) are disadvantaged by radiotherapy in terms of survival. Deaths from second malignancy were more frequent in the radiotherapy group than in the TME-alone group (14% *vs* 9%). Because this finding is noted after only a median of 11·6 years of follow-up, this difference is highly likely to widen at 15–25 years. Mature results of the Swedish rectal cancer trial also suggest an increased risk of a second malignancy.[2]

SCPRT is also recognised to have long-term effects on bowel function, urinary incontinence, and sexual functioning. Whether these complications relate to the high fraction size unique to SCPRT or to more conventional variables such as the volume encompassed within the radiation field, the total dose, and dose inhomogeneity remains unclear. Further, because follow-up in these studies is generally short, and the median age within studies is higher than 60 years, the risks of late effects and second malignancies are likely to be underestimated for younger patients. As radiation oncologists, we might have failed to take these long-term effects sufficiently into account, and focused on the reduction of local recurrence. National Institute for Health and Clinical Excellence (NICE)


DannyGys/Reporters/Science Photo Library

Published **Online** May 18, 2011
DOI:10.1016/S1470-2045(11)70126-7

See **Articles** page 575

For more on **NICE guidance** see http://guidance.nice.org.uk/CG/Wave16/2/Consultation/Latest