Meet the Professor

Prof. Wei Tang—biomarkers: evaluation of early diagnosis and prognosis for patients with hepatocellular carcinoma

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Expert Introduction

Prof. Wei Tang, studying and working in The University of Tokyo Hospital since 1993, has published more than 200 English papers until now. His research interests include intrahepatic invasion and metastasis of HCC, gastroenterological cancer, HCC, clinical pathology, metastasis, invasion, angiogenesis, chemotherapy, cancer drug targets, glycoprotein and tumor maker. In the research field of tumor marker for HCC, he devotes to promoting the Japan-China joint research projects in recent years, and has published a number of papers in this field (*Figure 1*).

Figure 1 Prof. Wei Tang, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo.

Interview

HBSN: How is current clinical situation of applying biomarkers to diagnose hepatocellular carcinoma?

Prof. Tang: As we know, an ideal cancer biomarker should have an acceptable sensibility and specificity. Besides, the molecular heterogeneity of cancer and that for individual person are also obstacles. In order to maximize the detective capability, the combined information from multiple biomarker assay are recommended.

According to HCC Guideline in Japan, the combined testing of DCP and AFP is recommended to be performed every 3 to 4 months for very high-risk group—it means patients with cirrhosis type B or C, and every 6 months for high risk group—it means patients with HBV/HCV or cirrhosis. Since most high-risk patients were closely followed before developing HCC, HCC nodules could be detected in early stage in more than 60% of patients in Japan.

While in China, AFP is the serum biomarker most widely used and recommended by the HCC Guideline. However, most HCC cases were detected with advanced-stage diseases in China. The high-risk population in China are cases with HBV infection, accounting for about 85%, but in Japan, 70% of patients are cases with HCV infection. In order to investigate the clinical usefulness of DCP for Chinese patients with HCC, our research group launched a multi-center case-controlled study in China involving 1,153 cases between 2012 and 2013. For HCC diagnosis, results showed that the sensitivity of DCP with cut-off value of 86 mAu/mL was 71.5%, AFP with cut-off value of 21 ng/mL was 68.0%, the combined testing of DCP could achieve a higher sensitivity than either alone. DCP was approved to be used in China in 2014, as we know, now it has been used in many hospitals in China.

HBSN: What are the advantages of biomarkers in diagnosis of HCC compared to traditional imaging?

Prof. Tang: The diagnosis of HCC is generally based on a combination of clinical and laboratory features, as well as radiographic and histopathologic presentation. Generally speaking, imaging diagnostic tools are widely used in Western countries, the serum biomarkers are still regarded as useful tools in Asian countries.

Of course, the specificity of imaging tools is higher; however, as we know, the successful detection depends on the availability of imaging equipment, the expertise of

physician, and the echo texture of liver. In view of such condition, serum biomarkers are still regarded as useful tools for HCC early diagnosis in Asian countries, especially in some countries with imbalanced health resources distribution.

Many expert panels consider serum biomarker to be a good surveillance marker due to its wide utility in diagnostic settings, where it has been studied extensively, and its role in combination with US, which can significantly maximize early detection of HCC. In Japan, for high risk group, the combined testing of DCP/AFP and ultrasound are commended to be performed every 6 months. For very high-risk group, such examinations are recommended to be performed every 3–4 months.

HBSN: How do you use biomarkers to evaluate the prognosis for patients with HCC?

Prof. Tang: Many studies have showed that the clinical usefulness of DCP could be in three aspects: (I) HCC screening and diagnosis; (II) as preoperative predictor to assess HCC progression; and (III) post-treatment monitoring.

About the usefulness of DCP in HCC progress, in our study, the relation between DCP expression and the prognosis has also been confirmed. Results showed that the high level of DCP was significantly associated with larger tumor size, poorly differentiated tumor, presence of MVI, more advanced TNM stage, or presence of tumor recurrence. The survival for patients with high DCP level was significantly poorer than those with low DCP level.

DCP has also been used in post-treatment monitoring in Japan. In our department, within one year, the test of DCP, AFP, and ultrasound are performed every month, CT is tested every 4 months. After one year, the test of DCP, AFP, and ultrasound are performed every 2 months, CT is tested every 6 months.

HBSN: You have published a review article "The management of hepatocellular carcinoma around the world: a comparison of guidelines from 2001 to 2011" with high cites. In your opinions, what is the biggest difference between the HCC guidelines in 2001 and the guidelines in 2011?

Prof. Tang: Recently, our research group updated this review and published an article on representative guidelines published worldwide from 2001 to 2017 with a focus on the clinical management of HCC (The clinical management of hepatocellular carcinoma worldwide: A concise review and comparison of current guidelines from 2001 to 2017. BioScience Trends 2017;11:389-98.). Surveillance, diagnosis, and treatment in the characteristic guidelines were compared to provide the latest information to clinicians.

In this updated article, based on the inclusion criteria of credibility, influence, and multifaceted, 18 guidelines that were published between 2001 and 2017 were identified for analysis, including eight guidelines from Asia, five from Europe, and five from the United States of America.

Since the year 2001 when the European Association for the Study of the Liver (EASL) issued their HCC guideline, at least 20 guidelines have been published or updated thus far, and each has its own advantages. Nonetheless, gaps in knowledge and areas of controversy regarding certain aspects of HCC management are evident and cannot be ignored.

It cannot to say that which HCC guideline is better than other ones. "Knowledge into action", with the development of evidence-based medicine, the concept of "transfer of current best evidence into clinical decision-making" has garnered substantial attention worldwide, and evidence-based clinical practice guidelines (CPGs) for HCC are urgently needed. In order to achieve current best evidence and promote evidence-based clinical practice guidelines to be widely accepted and fully implemented, it requires the early participation of all stakeholders, including clinician, experts from health statistics, epidemiology, health policy, health economics, as well as health policy-makers; CPGs should be the integration of native information from evidence-based, resource-based and population-based situations; and systematic evaluation should also be conducted during the whole course of constructing and implementing CPGs for HCC.

Based on the comparative assessment of current guidelines for HCC worldwide, we recommend conducting a systematic approach with four steps of global guidelines assessment, systematic literature review, experts' consensus and draft implementation, as well as implementation evaluation and periodic update in constructing and implementing evidence-based CPGs for HCC.

HBSN: AFP is one of the most widely used serum marker in diagnosis of HCC. What are the controversial issues with AFP in diagnosis of HCC?

Prof. Tang: For early HCC detection, AFP has been widely

used in clinical practice. However, the low sensitivity, specificity, and limited accuracy in detecting small HCC limited its clinical usefulness. So, other reliable biomarkers need to be identified. And now, worldwide, many biomarkers for HCC detection are under investigation.

In 2012, a study published in *Lancet Oncology* indicated that DKK1 was highly accurate in diagnosing AFP-negative patients with HCC, the combined testing of DKK1 and AFP could improve the accuracy than test alone.

In 2013, a study published in *Clinical Cancer Research* indicated that MDK has a higher sensitivity than AFP in diagnosing very early-stage HCC, the sensitivity of MDK could be as high as 89% when diagnosing cases of AFP-negative HCC. Especially, worldwide, a number of studies have looked at DCP. The mechanism research in hepatic cells has been fully investigated. In our study, the combined testing of DCP with a cut-off of 86 mAU/mL and AFP with a cut-off of 21 ng/mL could achieve a better sensitivity, which was higher than DCP or AFP alone, even for tumor ≤2 cm.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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