

## Standardizing management of hepatocellular carcinoma in China: Devising evidence-based clinical practice guidelines

Peipei Song\*

Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan.

### Summary

Evidence-based clinical practice guidelines (CPGs) have been used in many countries around the world to promote standardized management of hepatocellular carcinoma (HCC). Guidelines implemented in Japan provide a good example of "translating the best current research evidence into clinical practice and obtaining new evidence in the course of influencing practitioners' attitudes and clinical decision-making". The Japanese guidelines have achieved remarkable results in terms of HCC management in Japan. The first Japanese evidence-based CPGs for HCC (J-HCC Guidelines) were published in 2005 and then revised in 2009. A second updated version that incorporates new evidence was just published on October 15, 2013. China accounts for 55% of HCC cases worldwide. Although the Government devised a series of directives on the management of HCC and Chinese Guidelines on HCC were published in 2009, neither were based on systematic review and evaluation of the literature and neither included recommendations supported by data. The novel concept of "precision surgery" was recently proposed in China. This concept is based on surgeons' clinical experience and should encourage the standardized management of HCC in China. However, recommendations supported by data are still urgently needed to guide clinical decision-making in order to facilitate standardized management of HCC in China.

**Keywords:** Liver cancer, clinical guideline, evidence-based medicine (EBM), precision surgery, evaluation

In recent years, the concept of "standardized management of care" has garnered substantial attention worldwide. Drafting of disease management guidelines that specify appropriate diagnosis and treatment based on scientific evidence and collaborations between medical professionals involved in the treatment of a given condition is the key to standardized management of care (1,2). The purpose of evidence-based clinical practice guidelines (CPGs) is to "translate the best current research evidence into clinical practice and obtain new evidence in the course of influencing practitioners' attitude and clinical decision-making".

CPGs have been used for the standardized management of hepatocellular carcinoma (HCC) in many countries worldwide, as exemplified by guidelines implemented in Japan and South Korea. China accounts for 55% of HCC cases worldwide (3). However, such evidence-based CPGs have not yet to be drafted, hampering the standardized management of HCC in China.

In Japan, HCC management has achieved remarkable results that are attributed to a combination of quantitative and qualitative evaluations incorporated in the Japanese guidelines (4). Since the first Japanese evidence-based CPGs for HCC (J-HCC Guidelines) were published in 2005, the CPGs have been included a process of systematic evaluation in accordance with evidence-based medicine (EBM) (5,6). Updated J-HCC Guidelines incorporating new evidence were published in 2009 (7), and the third version of J-HCC Guidelines (2013 version) were just published on October 15, 2013 (8). The systematic J-HCC Guidelines should further

\*Address correspondence to:

Dr. Peipei Song, Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan.  
E-mail: ppsong-tky@umin.ac.jp

promote the standardized management of HCC in Japan.

To draft the 2013 version of J-HCC Guidelines, literature consisting of 6,750 papers was systematically reviewed to obtain the best current evidence. After a second round of review, 596 articles were ultimately selected to form 57 pairs of clinical questions and recommendations with different levels of evidence to guide clinical decision-making. A multi-disciplinary expert panel consisting of surgeons, internists, radiologists, statisticians, and health care economists supervised their individual specialties. The guidelines cover aspects including prevention, diagnosis and surveillance, surgery, local treatment, transcatheter arterial chemoembolization (TACE), chemotherapy, radiotherapy, follow-up, prevention and treatment of recurrence. The guidelines also take the Japanese health insurance system into account to make surveillance, diagnosis, and treatment of HCC feasible. In order to adequately reflect disparate views, an internal evaluation and an external evaluation were conducted prior to publication and then the draft guidelines were modified. Moreover, plans are to revise the current guideline yet again. An updated vision of the J-HCC Guidelines will be published in the coming 3-4 years and incorporate new evidence (8).

In China, HCC is the second most common cancer in urban areas and the most common in rural areas; it ranks as the second leading cause of cancer-related deaths in males, with a total mortality rate of 26.26/100,000 (9,10). Over the past decades, the Government has devised a series of directives on the management of HCC in order to reduce incidence and mortality and to improve healthcare quality overall for patients. For instance, "Treatment Standards for Common Malignant Tumors in China (Vol. 2, Hepatocellular Carcinoma)" was published in 1989, "Guiding Principles for Clinical Research on Treatment of Hepatocellular Carcinoma Involving New Drugs/Traditional Chinese Medicines" was published in 1990, and "Choices for Hepatocellular Carcinoma Treatment Therapies" was published in 2000. However, none of these directives was based on a systematic review and evaluation of the literature. Cognizant of the concept of "standardized management of care", the Chinese Guidelines on HCC — Expert Consensus on the Treatment Standards for Hepatic Carcinoma — was published in 2009 (11). However, the guidelines were based on expert consensus, so they provided recommendations regarding the management of HCC based on the experience of those experts instead of recommendations supported by data provided by a systematic review and evaluation of the literature (12).

Fortunately, a high level of liver surgery is currently practiced at leading medical facilities in China (13). A team in Beijing led by Dr. Jiahong Dong put forth the novel concept of "precision surgery". This concept

represents a new surgical paradigm that includes preoperative evaluation, clinical decision-making, surgical planning, surgical technique, and perioperative management, and this concept should encourage the standardized management of HCC in China (14). "Precision surgery" involves certainty-based practices to ensure the best result for each patient with multi-objective optimization of therapeutic effectiveness, surgical safety, and minimal invasiveness. However, this paradigm is based on the clinical experience of surgeons who perform over 700 hepatic resections each year. Recommendations supported by data are still urgently needed to guide clinical decision-making.

In conclusion, the practice of systematic evidence-based CPGs in Japan provides a good example of standardized management of HCC. Such guidelines need to be promptly drafted in China through systematic review and evaluation of the literature by a multi-disciplinary expert panel in order to provide recommendations supported by data to guide clinical decision-making.

## References

1. Gao JJ, Song PP, Tamura S, Hasegawa K, Sugawara Y, Kokudo N, Uchida K, Orii R, Qi FH, Dong JH, Tang W. Standardization of perioperative management on hepatobiliary-pancreatic surgery. *Drug Discov Ther.* 2012; 6:108-111.
2. Song PP, Gao JJ, Kokudo N, Tang W. New opportunity for orphan drug development in Japan: Early exploratory clinical trial bases promote drug translation from basic studies to clinical application. *Intractable Rare Dis Res.* 2012; 1:95-97.
3. International Agency for Research on Cancer. Cancer incidence and mortality worldwide in 2008 (GLOBOCAN 2008). <http://globocan.iarc.fr/factsheets/cancers/liver.asp> (accessed October 16, 2013)
4. Song PP, Tang W, Tamura S, Hasegawa K, Sugawara Y, Dong J, Kokudo N. The management of hepatocellular carcinoma in Asia: A guideline combining quantitative and qualitative evaluation. *Biosci Trends.* 2010; 4:283-287.
5. Makuuchi M, Kokudo N, Arii S, Futagawa S, Kaneko S, Kawasaki S, Matsuyama Y, Okazaki M, Okita K, Omata M, Saida Y, Takayama T, Yamaoka Y. Development of evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan. *Hepatol Res.* 2008; 38:37-51.
6. Song PP, Tobe RG, Inagaki Y, Kokudo N, Hasegawa K, Sugawara Y, Tang W. The management of hepatocellular carcinoma around the world: A comparison of guidelines from 2001 to 2011. *Liver Int.* 2012; 32:1053-1063.
7. Makuuchi M, Kokudo N. Clinical practice guidelines for hepatocellular carcinoma – The Japan Society of Hepatology 2009 update. *Hepatol Res.* 2010; 40(Suppl. 1):2-144.
8. Japan Society of Hepatology. Clinical practice guidelines for hepatocellular carcinoma (2013 version). Kanehara, Tokyo, Japan, 2013. (in Japanese)
9. Song P, Feng X, Zhang K, Song T, Ma K, Kokudo

- N, Dong J, Tang W. Perspectives on using des- $\gamma$ -carboxyprothrombin (DCP) as a serum biomarker: Facilitating early detection of hepatocellular carcinoma in China. *Hepatobiliary Surg Nutr.* 2013; 2: 227-231.
10. Song P, Feng X, Zhang K, Song T, Ma K, Kokudo N, Dong J, Yao L, Tang W. Screening for and surveillance of high-risk patients with HBV-related chronic liver disease: Promoting the early detection of hepatocellular carcinoma in China. *BioScience Trends.* 2013; 7:1-6.
  11. Chinese HCC Chinese Anti-Cancer Association Society of Liver Cancer, Chinese Society of Clinical Oncology, Chinese Society of Hepatology Liver Cancer Study Group. The expert consensus on the treatment standards for hepatocellular carcinoma. *Digestive Disease and Endoscopy.* 2009; 3:40-51. (in Chinese)
  12. Song PP, Gao JJ, Kokudo N, Dong JH, Tang W. "Knowledge into action" Exploration of an appropriate approach for constructing evidence-based clinical practice guidelines for hepatocellular carcinoma. *Biosci Trends.* 2012; 6:147-152.
  13. Emond JC, Kluger MD. International perspectives on advanced liver surgery. *Semin Liver Dis.* 2013; 33:187-188.
  14. Dong J, Yang S, Zeng J, *et al.* Precision in liver surgery. *Semin Liver Dis.* 2013; 33:189-203.

(Received October 19, 2013; Accepted October 26, 2013)