

## Policy Forum

# The management of hepatocellular carcinoma in Asia: A guideline combining quantitative and qualitative evaluation

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### Summary

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths around the world; Asian countries account for nearly 78% of the roughly 600,000 cases of HCC reported globally each year. Europe, the US, Asian-Pacific nations, South Korea, and Japan have published evidence-based guidelines for the management of HCC. The management of HCC in Japan has achieved remarkable results, which are attributed to a combination of quantitative and qualitative evaluation incorporated in the Japanese guidelines. However, many of the control methods and interventions in current HCC guidelines cannot be implemented in some Asian countries. The majority of HCC patients in Asia still present with advanced HCC and long-term outcomes following treatment are unsatisfactory because of a lack of effective adjuvant and systemic therapies. Asian countries should formulate evidence-based clinical practice guidelines and pay particularly close attention to combining quantitative and qualitative evaluation when drafting and implementing HCC guidelines. The guidelines should also be updated by incorporating new evidence.

**Keywords:** Hepatocellular carcinoma, guideline, evidence-based, qualitative indicator

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths around the world (1). Many countries have studied clinical practice guidelines for HCC in recent years (Table 1). The US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines) (2), the British Society of Gastroenterology Guidelines (BSG Guidelines) (3), and the American Society of Clinical Oncology Consensus (ASCO Consensus) (4) have been acknowledged and cited around the world in the treatment of liver cancer. The European Association for the Study of the Liver published clinical practice guidelines for HCC (EASL Guidelines) in 2001 (5),

the Korean Liver Cancer Study Group (KLCSG) and National Cancer Center (NCC) jointly published clinical practice guidelines for HCC (Korea Guidelines) in 2003 (6), the Japanese Ministry of Health, Labor, and Welfare published clinical practice guidelines for HCC (J-HCC Guidelines) in February 2005 (7), the American Association for the Study of Liver Disease published clinical practice guidelines for HCC (AASLD Guidelines) in November 2005 (8), and the Asian-Pacific Association for the Study of the Liver released the consensus recommendations for the treatment of HCC (APASL Guidelines) in 2008 (9). All of these guidelines provide an evidence-based approach to prevention, surveillance, diagnosis, staging, and treatment of HCC.

Asian countries account for at least two-thirds of the roughly 650,000 cases of HCC reported globally each year (10). HCC is prevalent in males, the incidence rates for men of the following countries and districts in Asia are > 25 per 100,000 persons: mainland China (58/100,000), Taiwan (53/100,000), South Korea

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**Table 1. Current standards for the management of hepatocellular carcinoma around the world**

Area	Series of standards	Publishing	Reference
Europe	BSG Guidelines	British Society of Gastroenterology	(3)
	EASL Guidelines	European Association for the Study of the Liver	(5)
America	ASCO Consensus	American Society of Clinical Oncology	(4)
	AASLD Guidelines	American Association for the Study of Liver Disease	(8)
Asia	Korean Guidelines	Korean Liver Cancer Study Group and the National Cancer Center	(6,13)
	J-HCC Guidelines	Japanese Ministry of Health, Labor, and Welfare	(7,14,18-20)
	APASL Guidelines	Asian-Pacific Association for the Study of the Liver	(9)
	Chinese Consensus	Chinese Anti-Cancer Association Society of Liver Cancer, Chinese Society of Clinical Oncology, Chinese Society of Hepatology Liver Cancer Study Group	(28)

(45/100,000), Thailand (33.4/100,000), and Hong Kong (29.9/100,000) (11). Of particular note is the fact that China alone accounts for 55% of cases of HCC worldwide (12). In Asia, only the Korean Guidelines and J-HCC Guidelines have been published and widely adopted; other countries are still in the research stage and have not formulated a nationwide evidence-based clinical practice guideline for HCC.

**Korean Guidelines for HCC:** Korean Guidelines for HCC were published by the KLCSG and NCC in 2003 and were based on scientific evidence and forty-five experts who formed a special committee to develop strategies to diagnose and treat HCC (6). The KLCSG and NCC revised the Korean Guidelines in 2009 (13). About forty specialists in the fields of hepatology, general surgery, radiology, and radiation oncology participated in the revision, domestic and foreign literatures were meticulously reviewed, and opinions were solicited from advisory committee conferences. The revision summarized diagnosis, surgical resection, liver transplantation, local treatments, transcatheter arterial chemoembolization (TACE), radiation therapy, chemotherapy, preemptive antiviral treatments, and evaluation of response to HCC treatment. In South Korea, a nationwide surveillance program was launched in 2003, and patients over 40 years or who had hepatitis B virus (HBV)/hepatitis C virus (HCV) or liver cirrhosis were screened by the program.

**J-HCC Guidelines:** The management of HCC in Japan is characteristic of such management in Asian countries. Supported by the Japanese Ministry of Health, Labor, and Welfare, the J-HCC Guidelines were published in February 2005 and then widely adopted in HCC treatment in Japan. The set of guidelines covers six clinically important fields for HCC treatment, including prevention, diagnosis and surveillance, surgery, chemotherapy, TACE, and ablation therapy. For users' convenience, practical algorithms for the surveillance and treatment of HCC were also created (14).

In March 2006, approximately a year after publication

of the J-HCC Guidelines, a questionnaire survey was conducted to investigate the level of awareness and influence of the guidelines among 2,279 members of the Liver Cancer Study Group of Japan and 689 primary care physicians in Osaka and Hyogo prefectures (15). Of the 1,175 respondents, 71.9% of hepatologists, 75.6% of liver surgeons, and 61.0% of primary care physicians have acknowledged the J-HCC Guidelines. After the introduction of the guidelines, 19-21% of hepatologists or liver surgeons changed their practices, 50-52% did not change but were convinced that their choice of treatment was similar to that recommended in the guidelines; 43% of primary care physicians changed their practices to follow the recommendations in the guidelines or paid closer attention to patient preferences.

Based on the surveillance algorithm and the diagnostic algorithm for HCC, patients with hepatitis HBV/HCV or liver cirrhosis in Japan have been closely followed with ultrasound, enhanced computed tomography (CT) scans, or enhanced magnetic resonance imaging (MRI) scans every 3-6 months before HCC develops; HCC nodules have been detected in the early stage in more than 60% of patients (16), and clinical diagnosis of HCC by diagnostic imaging is replacing pathological confirmation of the diagnosis (17). The treatment algorithm for HCC is based on three factors: degree of liver damage, number of tumors, and tumor diameter. The algorithm is easy to understand and can assist both physicians and patients in their decision-making regarding the treatment of HCC (16).

The management of HCC in Japan has achieved remarkable results, which are attributed to a combination of quantitative and qualitative evaluation incorporated in the J-HCC Guidelines:

(1) Quantitative evaluation was incorporated in the J-HCC Guidelines as the first evidence-based clinical practical guidelines for the treatment of HCC in Japan: (i) Medical literature on HCC in English was systematically reviewed. In total, 7,192 publications

on HCC were identified mainly from MEDLINE (1966-2002), and 334 articles were selected upon secondary selection. Of the selected articles, 44.2% were from Japan, 13.2% from elsewhere in Asia, and 42.6% from outside Asia (mainly from Europe) (18). (ii) With the incorporation of new evidence, a revised version of the J-HCC Guidelines was published in 2009 (19). A total of 2,950 articles were identified from MEDLINE (2002-2007). After the evaluation of evidence levels and content, 532 articles were ultimately selected. The next revision will be made in 2-3 years, and evidence reported after 2007 will be included in the new review. (iii) The algorithms in guidelines were established according to the current status of medical practices in Japan, where liver resection for HCC is regarded as safe with a mortality rate of less than 1% and cadaveric donors for liver transplantation are seldom available (20).

(II) The J-HCC Guidelines paid close attention to qualitative evaluation when the guidelines were formulated and implemented: (i) J-HCC Guidelines were compiled by an expert panel consisting of five surgeons, four internists, three radiologists, and one statistician. Most of the members were executive board members of the Liver Cancer Study Group of Japan. In order to assist in evidence collection and evaluation, a total of 26 physicians specializing in HCC also served as members of a task force for the establishment of the guidelines (20). (ii) The J-HCC Guidelines emphasized the evaluation of qualitative indicators. The 2005 J-HCC Guidelines incorporated 334 articles to form 58 pairs of research questions and recommendations; in the 2009 version, the 58 pairs of research questions were re-evaluated and 51 clinical questions were formulated. With these questions, physicians can better understand the guidelines and make the suitable clinical decisions for individual patients. (iii) Prior to publication, a draft of J-HCC Guidelines was submitted for internal evaluation (the 2005 guidelines were evaluated by 101 councilors of the Liver Cancer Study Group of Japan and the 2009 revision was evaluated by the 45th Japan Society of HCC) and external evaluation (the 2005 guidelines were evaluated by an external review board and the 2009 revision was available on the Web to seek public comments). In addition, a questionnaire survey was conducted to investigate the level of awareness and influence of the guidelines in 2006. (iv) While the guidelines are being followed, experts are researching problems encountered in actual clinical practice. For example, speakers at the 45th Annual Meeting of the Japan Society of Hepatology (2009) raised clinical questions regarding the remaining problems that needed to be clarified by the present guidelines, and HCC specialists (a total of 200 physicians) answered these questions using a question-and-answer analyzer system. Recommendations were approved when at least 67% of the HCC experts reached a consensus (21). This

will greatly contribute to future improvement of the guidelines.

**The management of HCC in China:** Since the 1970s, China has taken measures to prevent hepatitis. In Taiwan, HBV immunization of newborns was introduced in 1984 (22), and follow-up results from the program have indicated a significant reduction in the incidence of HCC in children. The average annual incidence of HCC in children 6-14 years of age declined from 0.70/100,000 (1981-1986) to 0.57/100,000 (1986-1990) and to 0.36/100,000 (1990-1994) ( $p < 0.01$ ) (23). Taiwan has a surveillance program in place but the program may not be widely available. There is no government-funded surveillance program for HCC in Hong Kong or other parts of China.

The national government and research institutes have researched the treatment of HCC in China. In 1989, the Medical Administration Department of the Ministry of Health of the People's Republic of China published "Treatment Standards for Common Malignant Tumors in China (Vol. 2, Hepatocellular Carcinoma)" (24). In 1990, the Drug Administration Department of the Ministry of Health of the People's Republic of China published "Guiding Principles for Clinical Research on Treatment of Hepatocellular Carcinoma Involving New Drugs/Traditional Chinese Medicines" (25). In 1999, the Chinese Anti-Cancer Association (CACA) published "New Treatment Standards for Common Malignant Tumors in China (Hepatocellular Carcinoma Section)" (26). In 2000, the 6th China Hepatic Surgery Academic Conference published "Choices for Hepatocellular Carcinoma Treatment Therapies" (27). In 2007 and 2008, the CACA Society of Liver Cancer (CSLC), Chinese Society of Clinical Oncology (CSCO), and Chinese Society of Hepatology (CMA) Liver Cancer Study Group jointly organized a consensus conference that met three times in Shanghai. More than sixty experts participated in the conference; they systematically reviewed the guidelines for and consensus opinion regarding the treatment of HCC around the world and they discussed the topics of diagnosis, surgery, interventional therapy, local ablation therapy, radiotherapy, biotherapy, molecularly targeted therapy, systemic chemotherapy, and combined treatments with traditional Chinese and western medicines. Based on the discussion, "The Expert Consensus on the Treatment Standards for Hepatocellular Carcinoma (the Chinese Consensus)" was published in 2009 (28) to promote the development of treatment standards for HCC. However, actual nationwide evidence-based clinical practice guidelines for HCC have yet to be formulated.

In conclusion, a greater number of Asian countries have paid close attention to the management of HCC and have achieved notable results over the past few years. South Korea and Japan have published and

widely adopted nationwide evidence-based clinical practice guidelines, but other Asian countries have not formulated a nationwide guideline until now. HCC prevention and surveillance in Asia have made some progress, but the majority of HCC patients in Asia still present with advanced HCC. Moreover, long-term outcomes following treatment of even early/intermediate or advanced disease are often unsatisfactory because of a lack of effective adjuvant and systemic therapies (17).

EASL Guidelines, AASLD Guidelines, APASL Guidelines, Korean Guidelines, and J-HCC Guidelines are all evidence-based guidelines that have outlined optimal approaches to managing HCC in resource-rich countries. However, many of the current HCC control methods and interventions can not be implemented in some Asian countries because these countries have limited resources. The current guidelines also fail to consider inconsistent resource distribution in areas with high overall standards of living and they fail to address inadequate infrastructure and resources in resource-poor Asian countries (29).

The practical effectiveness of J-HCC Guidelines have typically highlighted the importance of following clinical guidelines to treat HCC, and combination of quantitative and qualitative evaluation should be emphasized when drafting and implementing guidelines. In accordance with the current status of medical practices and medical methodologies, Asian countries should establish an expert panel with the support of government to formulate evidence-based clinical practice guidelines. Particularly close attention should be paid to combining quantitative and qualitative evaluation when drafting and implementing HCC guidelines. The guidelines should also be updated by incorporating new evidence.

### Acknowledgements

This project was supported by Grants-in-Aid from the Ministry of Education, Science, Sports, and Culture of Japan.

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(Received October 30, 2010; Revised November 22, 2010; Accepted November 29, 2010)