

## "Knowledge into action" – Exploration of an appropriate approach for constructing evidence-based clinical practice guidelines for hepatocellular carcinoma

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### Summary

With the development of evidence-based medicine (EBM), the concept of "transfer of current best evidence into clinical decision-making" has garnered substantial attention worldwide. As such a good tool, many clinical practice guidelines (CPGs) for hepatocellular carcinoma (HCC) have been published worldwide under the guide of current best evidence. Our study did a systematic evaluation of the current 17 guidelines for HCC worldwide, which found that the appropriate constructing approach is the most important factor that influences guidelines implementation. Three factors of organizations or bodies drafting the guideline, exploration for achieving current best evidence, and purpose of constructing evidence-based CPGs for HCC should be paid close attention to. In order to achieve the current best evidence and promote evidence-based CPGs to be widely accepted and fully implemented, we recommend to conduct a systematic approach with 4 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.

**Keywords:** Hepatocellular carcinoma (HCC), clinical practice guidelines (CPGs), standardized management of care, evaluation

### 1. Introduction

Evidence-based medicine (EBM), which was defined as "the integration of current best evidence with clinical expertise and patient values", could go back to mid-19th century Paris and earlier, remains a hot topic for clinicians, public health practitioners, purchasers, planners, and the public worldwide (1). The core of EBM is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients (2). About how to

get "current best evidence", there have been many explorations in clinical practice during the past decades, such as, Team Oncology Medicine (3), and international registration of clinical trials (4). In recent years, the concept of "standardized management of care" has garnered substantial attention and has been fully implemented in several countries worldwide. Construction of a disease management guideline that specifies appropriate diagnoses and treatments based on scientific research evidence and collaborations between medical professionals involved in the treatment of a given condition is the key to standardized management of care (5,6). Clinical practice guidelines (CPGs) as a management model, have been used for many cancers worldwide. CPGs are a good tool for transferring research evidence into clinical practice as well as getting new evidence in the course of influencing practitioners' attitude and clinical decision-making. The evidence-based CPGs are expected to achieve the

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following goals with full implementation: a) assisting practitioners in appropriate clinical decision-making; b) improving quality of healthcare and outcomes for patients; and c) supporting and influencing regional or national policies for efficient resources allocation and better delivery systems (7).

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer-related deaths in men. The incidence of HCC is highest in Middle Africa (15.8%), followed by Eastern Asia (14.1%) and Western Africa (10.6%) (8). In the past decade, several remarkable advances have been made in the management of HCC. More importantly, many CPGs for HCC have been published worldwide with the purpose of reducing incidence and mortality as well as improving healthcare quality for patients. Our study group did an English language literature search on the topic of guidelines or consensus for HCC published in the PubMed database during the period of 2001 to 2011. After a second screening, 46 articles were adopted from 3,008 hits to form 17 current guidelines for HCC around the world according to the selection criteria of credibility, influence, and being multi-faceted (9), including 5 guidelines from America, 7 from Asia, and 5 from Europe (Table 1). We did a systematic evaluation on 17 current guidelines for HCC, which found that these guidelines have both similarities and differences in terms of what organizations or bodies drafted the guidelines and the approach, applicability, content, and recent updates of the guidelines as well as in terms of diagnostic and treatment algorithms. The comparative analysis of projected goals and implementation of guidelines for HCC showed that evidence-based CPGs for HCC is urgently needed and the appropriate constructing approach is the most important factor that influences guideline implementation.

## 2. "3 W" – Factors influence implementation of CPGs for HCC

### 2.1. "Who": Organizations or bodies drafting the guideline

Of the current 17 guidelines, only the J-HCC Guideline (10) in Japan was constructed with the support of government, the other 16 guidelines were constructed by national academic societies. Of the guidelines drafted by an expert panel that consisted mainly of hepatologists, only the J-HCC Guideline and the APASL Guideline (11) specified an expert panel consisting of radiologists, statisticians, and other experts besides hepatologists. The absence of governmental support and lack of public health experts may lead to gaps in information on the management of HCC, especially with regard to appropriate prevention and surveillance measures, domestic health systems, health resources, income levels, and so on. The absence of the above important information may hamper patients from getting adequate information on prevention and early detection, as well as hamper health policy-makers from making optimal health resource distributions, such as establishing nationwide programs for prevention, screening and surveillance. Our study recommends that constructing evidence-based CPGs for HCC require the early participation of all related bodies, including health policy-makers. For a guideline to achieve wide acceptance and full implementation, health policy-makers need to be given clear messages about its potential impact in order to help them in efficient resource allocation and better delivery systems. The expert panel drafting CPGs should consist of not only clinicians, but also experts from health statistics, epidemiology, health policy, health economics, and so on.

**Table 1. Current characteristic guidelines for HCC worldwide**

Areas	No.	Years	Drafted by	Guidelines
America	1	2005	National Comprehensive Cancer Network	NCCN Guideline
	2	2005	American Association for the Study of Liver Disease	AASLD Guideline
	3	2007	American College of Surgeons	ACS Guideline
	4	2009	World Gastroenterology Organisation	WGO Guideline
	5	2010	United States National Cancer Institute	NCI (USA) Guideline
Asia	1	2003	Korean Liver Cancer Study Group and National Cancer Center	Korean Guideline
	2	2005	Japanese Ministry of Health, Labor, and Welfare	J-HCC Guideline
	3	2006	Saudi Gastroenterology Association	SGA Guideline
	4	2007	Japan Society of Hepatology	JSH Guideline
	5	2008	Asian-Pacific Association for the Study of the Liver	APASL Guideline
	6	2009	Asian Oncology Summit 2009	AOS Guideline
	7	2009	Chinese Society of Liver Cancer Chinese Society of Clinical Oncology Chinese Society of Hepatology Liver Cancer Study Group	Chinese Guideline
Europe	1	2001	European Association for the Study of the Liver	EASL Guideline
	2	2003	British Society of Gastroenterology	BSG Guideline
	3	2004	Belgian Association for the Study of the Liver	BASL Guideline
	4	2008	European Society for Medical Oncology	ESMO Guideline
	5	2008	Italian Southern Oncological Group	GOIM Guideline

## 2.2. "Way": Exploration for achieving current best evidence

Our study showed that CPGs should be the integration of the following three aspects in order to achieve current best evidence:

*Evidence-based information.* Of the current 17 guidelines, 5 guidelines were constructed by systematic literature analysis, which provided data-support recommendations on the management of HCC, and the other 12 guidelines were constructed by experts' consensus, which provided experts' experience-support recommendations on the management of HCC. According to levels of evidence (from level 1 to level 5, from high to low) from the Oxford Center for Evidence-Based Medicine (CEBM) (12), guidelines drafted based on a literature analysis have a different level of evidence (level 1 to level 4) than do guidelines drafted based on experts' consensus (level 5), but both are still in accordance with EBM. The management of HCC in Japan showed that consensus recommendations based on experts' experience could provide additional information for CPGs, which is especially helpful for up-to-date information (9). Our assessment of guidelines established by literature analysis or experts' consensus showed that both of them have advantages and disadvantages. Thus, we recommend that the best move is to construct evidence-based CPGs for HCC by combining a systematic literature review with experts' clinical experience.

*Resource-based information.* Of the current 17 guidelines, only the AOS Guideline (13) and the WGO Guideline (14) suggested providing different recommendations for countries with minimal resources, moderate resources, or extensive resources. It has been shown that although evidence-based CPGs constructed in resource-affluent countries define optimal goals and care, many measures could not be directly implemented in resource-constrained countries due to the lack of required fundamental infrastructure and resources (15). For example, many studies have proved that the combined testing of DCP and AFP or AFP-L3 could increase the sensitivity of HCC diagnosis, but DCP is currently approved just in Japan, Korea, and Indonesia (9). Thus, our study recommends that local resources in terms of health systems, medical technology, income levels, and other resources must be given full consideration in constructing evidence-based CPGs for HCC.

*Population-based information.* There are many geographic variations in the prevalence of HBV-related and HCV-related HCC as well as other cancerogenic factors. For example, HCV infection is the primary etiological factor in Western countries but HBV infection is the primary etiological factor in Asian countries except Japan. More importantly, the wide acceptance and full implementation of evidence-based CPGs for HCC will also be critically influenced by the

understanding of the intended target population in the aspect of getting adequate information on prevention and early detection as well as keeping adequate cooperation with clinicians in clinical decision-making. Thus, from the perspective of cost-effectiveness analysis, our study recommends that population-based epidemiological information should be seriously taken into account in constructing evidence-based CPGs for HCC. It will be helpful in implementing CPGs, especially in the aspects of prevention, screening, surveillance, and appropriate selection of treatment modalities.

## 2.3. "What": Purpose of constructing evidence-based CPGs for HCC

The purpose of constructing evidence-based CPGs is to transfer current best evidence into clinical practice to improve medical treatment for patients with HCC. The establishment of evidence-based CPGs is just the beginning, not the end. How to promote CPGs to be widely accepted and fully implemented is one of the most important challenges. In the current 17 guidelines, only the J-HCC Guideline and the AASLD Guideline published their studies on awareness and influence of HCC guidelines, both of which showed that the HCC Guideline could benefit clinicians in clinical decision-making (16,17), but no other supporting data were found on the aspects of improving outcomes for patients and health policy-makers. 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 Guideline (18). The J-HCC Guideline was first published in 2005 using systematic literature analysis of 7,192 publications on HCC and then revised in 2009 with the incorporation of new evidence. Prior to publication, a draft of the J-HCC Guideline was submitted for internal evaluation (the 2005 version was 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 version was 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 in 2006 to investigate the level of awareness and influence of the J-HCC Guideline among 2,279 members of the Liver Cancer Study Group of Japan and 689 primary care physicians in Osaka and Hyogo prefectures (16), which showed that more than 70% of clinicians have acknowledged the guideline, and part of the clinicians have changed their practices to follow it. Thus, our study recommends to actively explore an appropriate approach to promote guidelines for use on the basis of absorbing advanced experience from current well implemented CPGs worldwide, especially the systematic evaluation from the whole course of constructing and implementing CPGs for HCC.

### 3. "4 S" – Constructing evidence-based CPGs for HCC

Our study concludes a systematic approach for constructing and implementing evidence-based CPGs according to our comparative assessment on the current 17 guidelines for HCC worldwide. It could be divided into 4 steps (Figure 1):

*Step 1: Global guidelines assessment to get advanced experience.* During the past decade, many guidelines for HCC have been published worldwide and some recommendations have been widely accepted and fully implemented, such as, liver resection is most beneficial for solitary tumors in patients without cirrhosis, with post-resection 5-year survival rates of 41-74%, and liver transplantation for patients meeting Milan criteria (a solitary tumor  $\leq$  5 cm or up to 3 tumors  $\leq$  3 cm each) could obtain 5-year survival rates of 70-80% (19,20). So global guidelines assessment is necessary and could help us get advanced experience worldwide, especially for current criteria of diagnosis and treatment for HCC.

*Step 2: Systematic literature review to get the native information for evidence-based, resource-based, and population-based situations.* According to EBM, systematic literature review and analysis is one of most important ways to get the current best evidence, but it also should be noted that evidence-based CPGs established in resource-affluent countries defining optimal care and services have limited use in resource-

constrained countries. In addition, there are many differences in the measures of prevention, screening, surveillance and appropriate selection of treatment modalities due to the variations of population-based epidemiology information and understanding of intended target populations. So systematic literature review as well as research on native health resources and population is necessary, it will be helpful in getting native information for evidence-based, resource-based and population-based situations, especially local resources in terms of health systems, medical technology, income levels, and so on, then benefit CPGs to be really widely accepted and fully implemented.

*Step 3: Experts' consensus and draft implementation to get the evaluation information.* Evidence-based CPGs constructed by systematic literature analysis could provide data-support recommendations, but some information, especially some of the most up-to-date information, is still lacking due to the factors of papers' publishing cycle, etc. The management of HCC in Japan has shown that experts' consensus-based recommendations could provide additional information for evidence-based CPGs, especially for some up-to-date information, so it is necessary to conduct internal evaluation among experts' in related areas before CPGs can be officially published. In addition, CPGs are a good tool for transferring research evidence into clinical practice, on the one hand, they are the scientific conclusion of current research evidence, and on the other hand, they could provide new evidence in the course

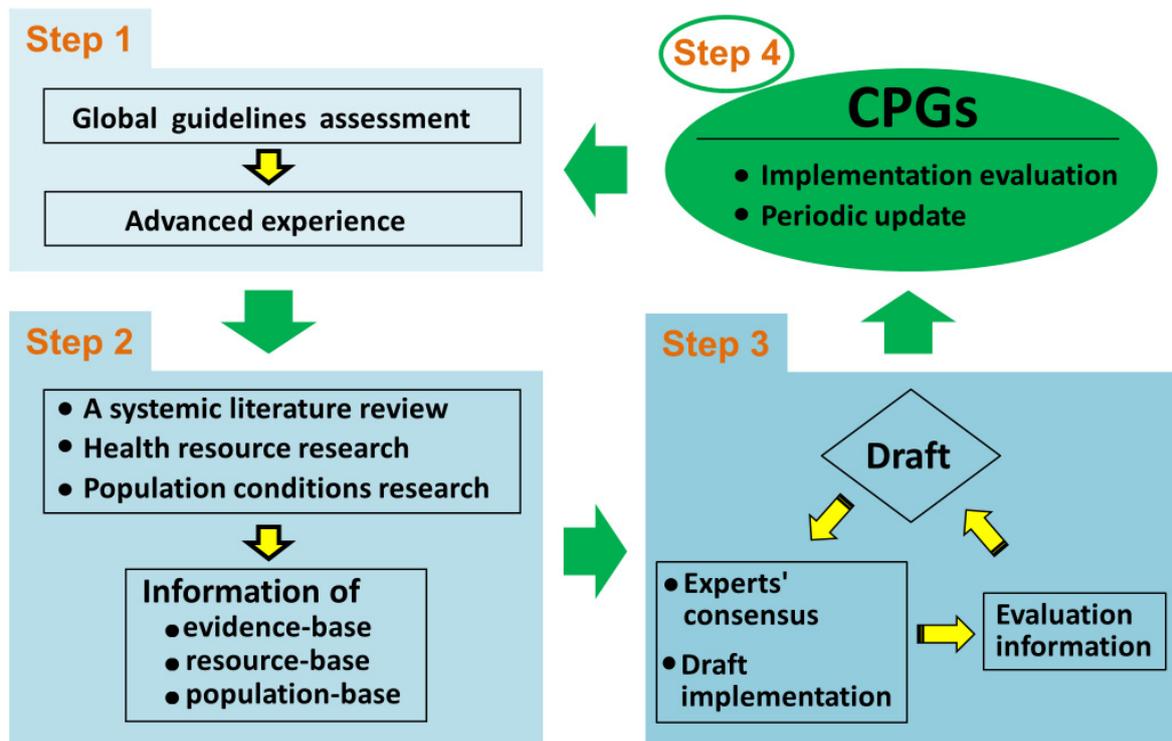


Figure 1. Approach for constructing and implementing evidence-based CPGs for HCC.

of implementation. So it is necessary to conduct draft implementation to get the most up-to-date evidence, especially the evaluation information about how CPGs influence clinical decision-making for clinicians and health resource distribution for health policy-makers, as well as outcomes for patients with HCC.

*Step 4: Evaluation on guideline implementation and periodic update with incorporation of new evidence.* After establishment of evidence-based CPGs for HCC, promotion of CPGs to be widely accepted and fully implemented is one of the most important challenges. Systematic evaluation is necessary to be conducted to examine the implementation effect of CPGs for HCC, including evaluation of awareness and influence of CPGs for clinicians, outcomes of adhering to CPGs for patients, efficient resource allocation for health policy-makers, and so on. In addition, evidence-based CPGs for HCC is in accordance with EBM, especially in achieving current best evidence to guide clinical practice, so evidence-based CPGs for HCC should be periodically updated with incorporation of new evidence every 3-4 years.

#### 4. Conclusion

"Knowledge into action", with the development of EBM, evidence-based CPGs for HCC are urgently needed to transfer current best evidence into clinical practice to improve medical treatment for patients with HCC. In order to achieve current best evidence and promote evidence-based CPGs 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 4 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.

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