

## Original Paper

# Consensus Development from the 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014)

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**Key Words**

Chemotherapy · Hepatocellular carcinoma · Imaging · Surgery · Radiotherapy

**Abstract**

A key mission of the Asia-Pacific Primary Liver Cancer Expert (APPLE) Association is to ensure a coherent view for management of hepatocellular carcinoma (HCC) and to advance new treatment for this difficult disease. At the 5th APPLE meeting, held in July 2014 in Taipei, Taiwan, an APPLE consensus development program was established to facilitate discussion among experts in the Asia-Pacific region on pertinent issues for HCC management, including (1) surgery for intermediate/advanced-stage disease, (2) prevention of HCC recurrence after curative treatment, (3) optimizing imaging diagnosis, (4) radiotherapy: current practice and future clinical trials, and (5) the role of cytotoxic chemotherapy. A pre-congress questionnaire was undertaken with the consensus development committee members to help understand the current practice patterns for HCC in the Asia-Pacific region and to identify issues relating to optimal patient care and further clinical trials for which consensus needs to be developed.

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In this report, the results of the questionnaire are presented, and the pertinent issues identified by each consensus group for further discussion and consensus development are summarized.

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## Introduction

The Asia-Pacific Primary Liver Cancer Expert (APPLE) Meeting was first established in 2010 as a consortium of liver cancer specialists, including surgeons, hepatologists, radiologists, pathologists, and oncologists, in the Asia-Pacific region to improve liver cancer management. Since then, experts from the Asia-Pacific region, as well as experts and key opinion leaders invited from Europe and America, have met every year (2010 in Incheon, Korea; 2011 in Osaka, Japan; 2012 in Shanghai, China; 2013 in Busan, Korea; and 2014 in Taipei, Taiwan) to have in-depth discussions on the management of liver cancer, especially hepatocellular carcinoma (HCC). In 2012, the journal *Liver Cancer*, which is affiliated with APPLE, was launched [Karger, ISSN: 2235–1795 (print), eISSN: 1664–5553 (online)]. In 2013 the APPLE Association was established (<http://www.applecongress.org/>) to consolidate the platform for future communication and collaboration.

A key mission of APPLE is to ensure a coherent view for management of HCC and advanced new treatment for this difficult disease [1]. Although guidelines of clinical practice have been developed, several issues should be considered when we try to implement these guidelines to improve patient care in the Asia-Pacific region [2–5]. The first is the gap between the “best current evidence” and clinical practice. This is especially obvious in the treatment of advanced-stage disease. Many approaches, including radiotherapy (radioembolization, external radiotherapy), cytotoxic chemotherapy (systemic, intra-arterial), and various loco-regional modalities, are used, but the best current evidence is generally based on case series or single-arm clinical trials. Therefore, most of the current HCC guidelines on treatment recommendation are based on experts’ opinions rather than high-quality clinical trials [6–8]. A second issue is proper design of clinical trials to address pertinent clinical questions. A prominent example is the role of surgical resection. In experienced medical centers, the 5-year overall survival rate of early HCC patients (within Milan criteria) who undergo curative surgery can be as high as 60%, and many surgeons will recommend surgery for patients with more advanced disease [9, 10]. However, the criteria for “resectability” in terms of liver function reserves and tumor burden vary widely and are difficult to validate in prospective clinical trials.

In 2014, the 5th APPLE meeting (APPLE 2014) was held in Taipei, Taiwan. The scientific program committee established an APPLE 2014 consensus development program to pursue the APPLE mission. Instead of an overview of HCC management, the APPLE 2014 consensus development program focused on five clinical issues that are pertinent to HCC management in the Asia-Pacific region, i.e., (1) surgery for intermediate/advanced-stage disease, (2) prevention of HCC recurrence after curative treatment, (3) optimizing imaging diagnosis, (4) radiotherapy: current practice and future clinical trials, and (5) the role of cytotoxic chemotherapy. A committee consisting of 10–15 experts from the Asia-Pacific region was organized for each clinical issue (see Appendix A, for all online suppl. material, see [www.karger.com/doi/10.1159/000367732](http://www.karger.com/doi/10.1159/000367732)).

A pre-congress questionnaire interview was undertaken with the committee members from all five groups (see Appendix B). The questionnaire interview was designed (1) to help understand the current practice patterns of HCC in the Asia-Pacific regions represented by

**Table 1.** Number of respondents of the questionnaire interview

Region	No.	Consensus development group	No.
China	7	Surgery	6
Hong Kong	3	Prevention	12
Korea	12	Imaging	8
Japan	7	Radiotherapy	7
Taiwan	8	Chemotherapy	11
Others*	7		

\* Singapore (2), India (1), Indonesia (1), Mongolia (1), Thailand (1), and Philippines (1)

the committee members and their institutions and (2) to collect advice from the committee members regarding issues pertinent to Asian-Pacific practice of HCC management for which consensus needs to be developed for optimal patient care and further clinical trials. Results of the questionnaire interview were circulated among the committee members before the APPLE 2014 meeting, when formal discussion and voting on the consensus statement took place.

In this report, the results of the questionnaire interview regarding the current practice patterns of HCC in the Asia-Pacific region are presented, and pertinent issues identified by each consensus group for further discussion and consensus development are summarized.

### Results of the Pre-Congress Questionnaire Interview

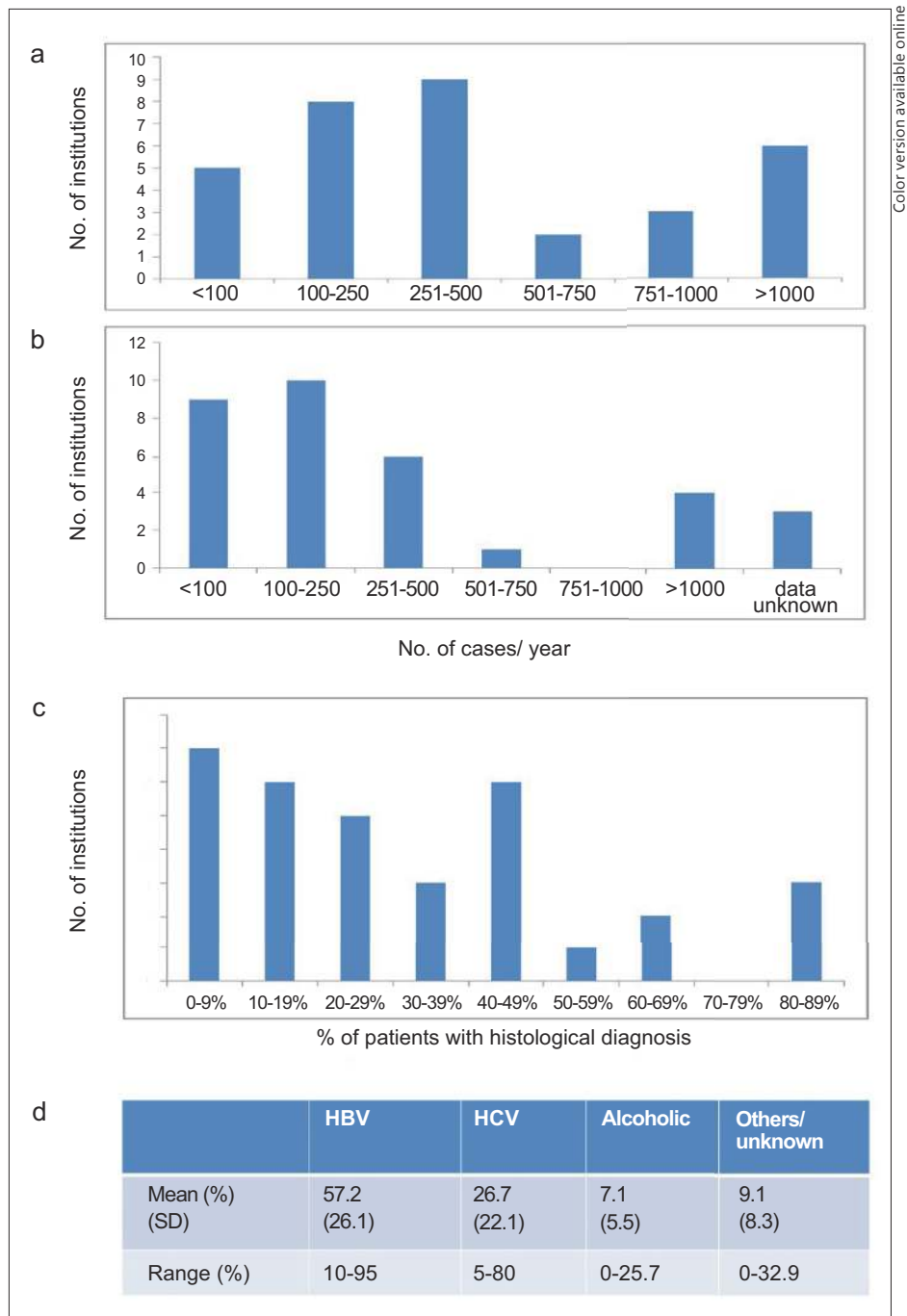
A total of 65 experts were invited to participate in the APPLE 2014 consensus development program (see Appendix A), and 44 experts from 33 institutions responded to the questionnaire interview (table 1).

#### *Diagnosis and Surveillance of HCC*

The annual patient volume of the respondents' institutions ranged from <100 new patients to >1000 new patients, and most institutions were referral centers for HCC treatment (fig. 1A and 1B). Diagnosis of HCC was established by clinical criteria in the majority of patients, as more than half of the responding institutions had fewer than 40% of HCC patients who had a histological diagnosis (fig. 1C). Chronic viral hepatitis was the major underlying etiology (fig. 1D), although the proportion of chronic hepatitis B vs. hepatitis C varied greatly from institution to institution.

All institutions followed specific guidelines for HCC management, including the American Association for the Study of Liver Disease (AASLD)/National Comprehensive Cancer Network (NCCN) guidelines (11 institutions), the Asian Pacific Association for the Study of the Liver (APASL) guidelines (9 institutions), the Korean Liver Cancer Study Group (KLCSG) guidelines (6 institutions), the Japanese Society of Hepatology (JSH) guidelines (5 institutions), the European Association for the Study of the Liver (EASL) guidelines (1 institution), the Chinese guidelines of HCC staging and treatment schedule, 2011 (1 institution), and the Samsung Medical Center protocol (1 institution).

Thirty of the 33 responding institutions reported availability of a screening program for HCC surveillance. The most commonly used methods for surveillance were serum alpha-feto-protein (AFP) levels (25 institutions, 76%) and abdominal sonography (27 institutions, 82%). The imaging modalities used for clinical diagnosis included computed tomography (CT) scans



Color version available online

**Fig. 1.** **a** Approximate numbers of newly diagnosed HCC patients each year. **b** Approximate numbers of HCC patients referred to the respondents' institution each year. **c** Percentage of patients with a histological diagnosis. **d** Proportion of the underlying etiologies.

(33 institutions, 100%), magnetic resonance imaging (MRI) (28 institutions, 85%), gadoteric acid (Gd-EOB-DTPA)-enhanced MRI (26 institutions, 79%), and contrast-enhanced ultrasound (16 institutions, 48%). The Barcelona Clinic Liver Cancer (BCLC) system has been adopted by 24 of the 33 institutions (table 2).

**Table 2.** Use of the BCLC staging system in the respondents' institutions

A. Adoption of BCLC as a staging system in the respondents' institutions						
	China	Hong Kong	Korea	Japan	Taiwan	Others
Yes (24 institutions)	3	1	4	6	5	5
No (9 institutions)	2	1	4	1	0	1
B. The approximate distribution of BCLC stages in newly diagnosed HCC patients						
	Very early (%)	Early (%)	Intermediate (%)	Advanced (%)	End stage (%)	
Mean (SD)	11.5 (12.3)	26.6 (16.8)	24.7 (10.7)	25.8 (15.3)	10.6 (11.5)	
Range	0–50	0–80	9–60	0–65	0–40	

*Treatment Approaches: Curative Treatment*

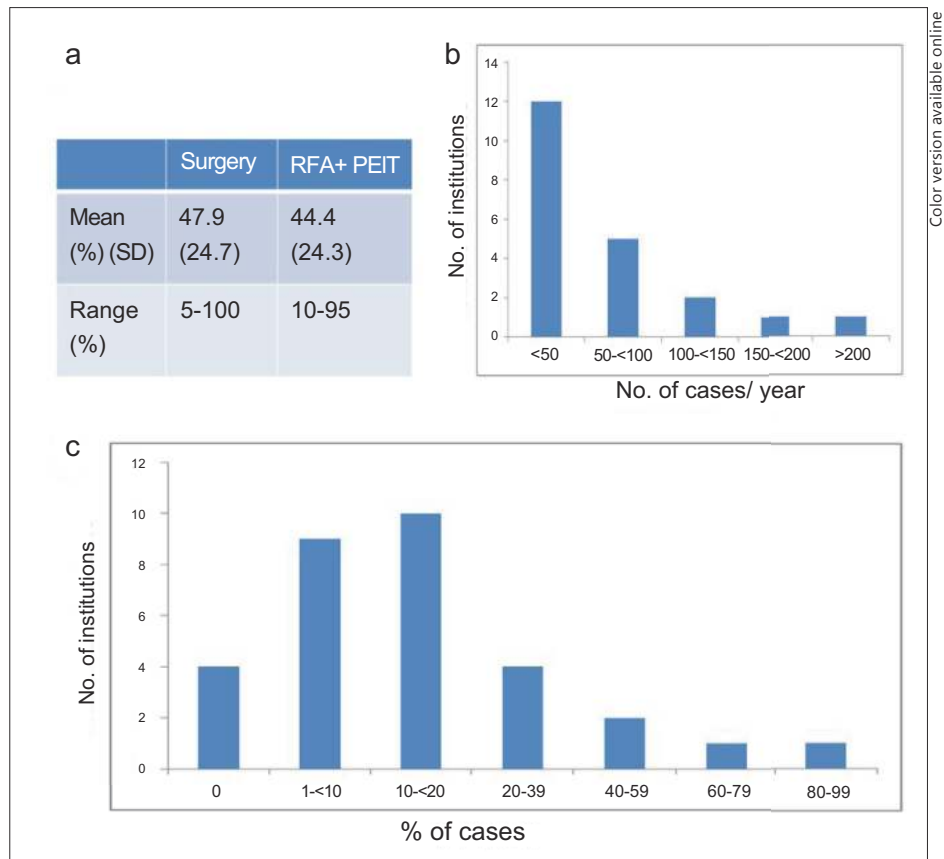
Surgery and ablation therapy [including radiofrequency ablation (RFA) and percutaneous ethanol injection] are the major curative treatment approaches, but the proportion of patients who received either treatment varied widely in individual institutions (fig. 2A). Twenty-one institutions performed liver transplantation for HCC treatment (fig. 2B). It is noteworthy that the majority of institutions performed surgery with curative intent in selected patients with BCLC intermediate/advanced-stage diseases (fig. 2C). Laparoscopic surgery and robotic surgery were used for HCC treatment in 24 and 8 institutions, respectively, but the proportion of patients who received these novel surgical approaches was generally below 30% of all HCC patients treated by surgery in individual institutions.

*Treatment Approaches: Palliative Treatment*

The approximate distribution of HCC patients who received different first-line palliative treatments is summarized in table 3. For patients with intermediate-stage disease, trans-arterial chemoembolization (TACE) was the treatment of choice, but surgery or ablation therapy was used in about 20% of patients as first-line treatment (table 3A). After progression from the first-line therapy, TACE was still considered by most institutions (26 of 33, 79%) as salvage therapy, followed by surgery/ablation (17 institutions, 52%), sorafenib (10 institutions, 30%), hepatic intra-arterial infusion chemotherapy (HAIC) (9 institutions, 27%), radio-embolization (8 institutions, 24%), systemic chemotherapy (3 institutions, 9%), and radiation therapy (3 institutions, 9%).

For patients with advanced-stage disease, the treatment choices were more varied. Although sorafenib is recommended by most clinical practice guidelines as the reference treatment, TACE and HAIC were still used in a significant proportion of patients as first-line therapy (table 3B). After progression from the first-line therapy, salvage therapy included sorafenib (30 of 33 institutions, 91%), TACE (23 institutions, 70%), surgery/ablation (8 institutions, 24%), HAIC (8 institutions, 24%), radio-embolization (6 institutions, 18%), systemic chemotherapy (5 institutions, 15%), and radiation therapy (5 institutions, 15%).

Twenty-one of the 33 institutions performed external-beam radiation therapy for HCC treatment. The most commonly used modalities included intensity-modulated radiation therapy (IMRT, 9 institutions), tomotherapy (5 institutions), three-dimensional conformal radiation therapy (3 institutions), and proton beam radiation therapy (3 institutions). The annual volume of patients receiving external-beam radiation was <100 patients in most of the in-



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**Fig. 2.** Patterns of curative treatment. **a** Proportion of patients treated with curative intent who received surgery or ablation therapy in the respondents’ institutions. RFA, radiofrequency ablation; PEIT, percutaneous ethanol injection therapy. **b** Annual patient volume of transplantation for HCC treatment (21 institutions). **c** Approximate proportion of HCC patients who have BCLC intermediate/advanced-stage disease and receive surgery with curative intent.

stitutions. Seventeen institutions performed radioembolization therapy for HCC treatment. The annual volume of patients receiving radioembolization was <50 patients in most of the institutions

*Clinical Trial Activities for HCC*

Table 4 summarizes the clinical trial activities reported by the responding experts. The survey results indicate that Asian-Pacific medical centers are actively participating in clinical trials for HCC.

*Clinical Outcome of HCC Management*

Sixteen institutions reported the availability of a registry database within the institution to monitor the outcome of HCC management. Representative data of overall survival provided by individual institutions are summarized in Appendix C. In general patients with early-stage disease (BCLC stage A, American Joint Committee on Cancer or Union for International Cancer Control stage I, or Japan Integrated Staging score 0–1) had a 5-year overall survival of more than 50%, whereas the survival of patients with more advanced stage disease varied widely.

**Table 3.** Approximate distribution of treatment for intermediate/advanced-stage HCC

A. First-line treatment for BCLC intermediate-stage HCC						
	TACE (%)	HAIC (%)	Surgery/Ablation (%)	Radio-embolization (%)	Others (%) <sup>a</sup>	
Mean	62.7	3.1	20.6	4.7	5.2	
(SD)	(22.6)	(8.1)	(17.6)	(6.3)	(9.8)	
Range	20–100	0–40	0–60	0–20	0–40	
B. First-line treatment for BCLC advanced-stage HCC						
	Sorafenib (%)	TACE (%)	HAIC (%)	Systemic chemotherapy (%)	Radio-embolization (%)	Others (%) <sup>a</sup>
Mean	33.8	13.2	29.0	2.8	4.8	19.4
(SD)	(24.2)	(18.6)	(29.8)	(6.3)	(6.9)	(17.2)
Range	5–90	0–75	0–80	0–30	0–30	0–50

<sup>a</sup> Including clinical trials, radiotherapy, and alternative treatment.

**Table 4.** Clinical trial activities of the respondents' institutions

Types of trials	No. of institutions	No. of trials ongoing each year in the past 5 years (median/range)	No. of subjects enrolled each year (median/range)
Surgery/other curative modalities	15	1 (1–4)	15 (2–400)
Adjuvant therapy after curative treatment	18	2 (1–5)	15 (2–75)
TACE/TACE plus drug therapy	20	2 (1–5)	17.5 (4–140)
Radiotherapy	8	2 (1–8)	10 (2–120)
Systemic therapy (for advanced-stage disease)			
First line	15	3 (1–12)	12 (5–120)
Second line	14	3 (1–16)	11 (5–60)
Early-phase drug trials that enroll HCC subjects	7	3 (1–5)	7 (3–30)

## Pertinent Issues for Consensus Development

### *Surgery for Intermediate/Advanced-Stage Disease*

Surgical resection, including resection and transplantation, remains the treatment for cure of HCC. With advances in surgical techniques and perioperative management, complete tumor resection may be achieved with a mortality of less than 5% [11]. However, coexisting liver diseases and their comorbidities, such as hyperbilirubinemia and portal hypertension, lead to more complications after HCC resection than after other treatment modalities. Higher recurrence rates after surgery for multiple HCCs and tumors with portal venous invasion or extra-hepatic metastasis make surgery for intermediate/advanced-stage HCC debatable. Thus, discrepancy exists between the guidelines developed by different countries and institutes. The consensus development committee addressing surgery for intermediate/advanced-stage

disease aimed to develop a consensus recommendation to improve the survival of this group of patients with acceptable morbidity and mortality.

To overcome the complexities of tumor status of intermediate/advanced-stage HCC, the committee members first defined the major issue of concern into simple and clear questions. The questions were categorized as (1) pre-operative liver function evaluation, (2) tumor size, (3) tumor number, (4) vascular invasion, and (5) extra-hepatic metastasis. Data and publications related to these topics were presented by the committee members. Differences of clinical practices and guidelines among institutes and countries were discussed. Sub-classification and restraint conditions for each question were clarified to reach a more concise and accurate conclusion. Consensus and recommendations were then created by voting of the committee members without much controversy, although strong evidence is lacking to support the recommendations. The feasibility of conducting prospective randomized trials comparing surgical resection with transarterial chemo-embolization in intermediate-stage HCC and with sorafenib in advanced-stage HCC was also discussed in the consensus meeting.

#### *Prevention of HCC Recurrence after Curative Therapy*

Although surgical resection or RFA is the treatment of choice for early HCC, one of the main reasons for poor prognosis in HCC is the high recurrence rate. The 5-year recurrence rate after surgical resection for HCC can be as high as 70%. Prevention of HCC recurrence after curative therapy is an important issue.

To address this issue, the committee members first presented and reviewed the published data. Topics to be discussed were categorized into three parts. Part A was antiviral therapy for prevention of HCC recurrence after curative therapy; Part A was further sub-classified into hepatitis B virus (HBV)-related HCC and HCV-related HCC. Part B was non-antiviral therapy for prevention of HCC recurrence after curative therapy, and Part C was cost-effective issues for prevention of HCC recurrence after curative therapy. Consensus and recommendations were then created by voting of the committee members without much controversy. The evidence level and recommendation strength were assigned to each consensus statement after voting if an agreement of more than 80% was made by the committee members. High consensus was reached for topics in part A. However, there was still a lot of debate for topics in Part B and Part C.

#### *Optimizing Imaging Diagnosis*

Currently, there is no standardized imaging diagnosis of HCC worldwide, and many different guidelines have been published by various international working groups. For example, The AASLD definition of typical HCC appearance on imaging includes a tumor size larger than 1 cm and arterial hypervascularity and washout in the venous or delayed phase [in four-phase multidetector CT (MDCT) or dynamic MRI] in chronic hepatitis B or cirrhotic patients. A second dynamic contrast-enhanced imaging modality is required only if the first imaging modality is not diagnostic. The APASL definition of typical HCC on imaging is similar to that of the AASLD guidelines, but a lesion size larger than 1 cm is not required. Unlike the AASLD guidelines, the APASL guidelines suggest using contrast-enhanced (per-fluorobutane microbubbles) ultrasound or superparamagnetic iron oxide-enhanced MRI for a hypervascular lesion that does not have washout in the portal or delayed venous phases. The rationale is that HCCs generally have low Kupffer cell density, but benign hypervascular lesions and pseudolesions tend to have normal or elevated Kupffer cell density. Recently, the hepatocyte-specific MR contrast agent Gd-EOB-DTPA has been shown to be useful for early detection of small HCCs [12] and has been used as part of the algorithm for HCC diagnosis commonly used in Japan.



Imaging modalities for the diagnosis of HCC include contrast-enhanced ultrasound, MDCT, MRI, and angiography in most clinical practice guidelines. The 12 committee members reviewed recent papers and discussed topics related to detection methods (algorithms), diagnostic methods, evaluation methods, and functional methods in HCC using these imaging modalities. The evidence level of each statement on a related topic was labeled and specific comments were given to each statement after voting if agreement was more than 80% among the committee members.

#### *Radiotherapy: Current Practice and Future Clinical Trials*

Radiation therapy (RT), including external-beam RT (EBRT) and selective internal RT (SIRT), is recommended in NCCN guidelines as a locoregional therapy option for HCC patients with unresectable liver tumor(s) and for patients who are not candidates for transplantation. Stereotactic body radiotherapy (SBRT), a type of EBRT, and yttrium-90 resin- or glass-microspheres, types of SIRT, are selectively used in HCC. However, the exact role of RT is not clearly defined in the other North American, European, and Asia-Pacific guidelines. The main reason for this is the low level of evidence supporting the use of RT in published studies. No prospective randomized studies have compared local disease control, patterns of failure, and survival between patients undergoing and not undergoing RT. The important issue of urgently establishing evidence was addressed by the expert committee of the meeting.

The committee members first presented and reviewed the most promising data for EBRT and SIRT in HCC treatment. The discussions that followed were focused on the potential integration of RT in future HCC guidelines. Given the absence of high-level evidence for RT, voting on this issue was not controversial. Experts on both modalities took the opportunity to discuss collaborative trial ideas involving the combination of SBRT and SIRT for HCC patients with main portal vein thrombosis, which remains the most challenging subgroup with mostly dismal outcomes.

#### *The Roles of Cytotoxic Chemotherapy*

Cytotoxic agents are used as part of trans-arterial chemo-embolization (TACE), hepatic intra-arterial infusion chemotherapy (HAIC), or systemic therapy. Although TACE is the standard therapy recommended by most clinical practice guidelines for intermediate-stage HCC (multi-nodular tumors without vascular invasion or extra-hepatic spread), the optimal chemotherapeutic agents or regimens to be used for TACE remain undetermined. HAIC was recommended by a Japanese consensus-based guideline for the treatment of HCC with vascular invasion [13]. An objective response rate for HAIC of more than 30% has been reported, but its impact on survival is not clear [14]. Systemic chemotherapy is seldom used as first-line therapy for advanced-stage HCC (vascular invasion or extra-hepatic spread) because of increased toxicity in patients with cirrhosis, especially myelosuppression. However, recent randomized trials have suggested that cytotoxic chemotherapy may have a modest impact on survival [15, 16]. Currently, only the APASL guidelines say that cytotoxic chemotherapy may be considered in highly selected patients whose general and hepatic conditions are adequate.

The committee members considered it appropriate in the consensus development sessions to discuss and reach consensus on how to confirm if there is a role for cytotoxic chemotherapy in advanced HCC. First, chemotherapy in non-cirrhotic HCC patients is still an “under-explored area,” and its role in places with limited access to sorafenib or in patients in whom sorafenib treatment has failed warrants further exploration [17]. Second, better supportive care during cytotoxic therapies, including antiviral agents and antiemetic agents, can make chemotherapy more tolerable for HCC patients. Third, many single-arm phase II trials have reported promising anti-tumor activities of chemotherapy combined with molecular targeted therapy. To verify the impact of cytotoxic chemotherapy on clinical practice, consensus on

clinical trial design and the target patient population, including a clear definition of tumor extent, prognostic factors, and organ function reserves, needs to be established.

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