

# Development and novel therapeutics in hepatocellular carcinoma: a review

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**Abstract:** This review summarizes the epidemiological trend, risk factors, prevention strategies such as vaccination, staging, current novel therapeutics, including the drugs under clinical trials, and future therapeutic trends for hepatocellular carcinoma (HCC). As HCC is the third most common cause of cancer-related death worldwide, its overall incidence remains alarmingly high in the developing world and is steadily rising across most of the developed and developing world. Over the past 15 years, the incidence of HCC has more than doubled and it increases with advancing age. Chronic infection with hepatitis B virus is the leading cause of HCC, closely followed by infection with hepatitis C virus. Other factors contributing to the development of HCC include alcohol abuse, tobacco smoking, and metabolic syndrome (including obesity, diabetes, and fatty liver disease). Treatment options have improved in the past few years, particularly with the approval of several molecular-targeted therapies. The researchers are actively pursuing novel therapeutic targets as well as predictive biomarker for treatment of HCC. Advances are being made in understanding the mechanisms underlying HCC, which in turn could lead to novel therapeutics. Nevertheless, there are many emerging agents still under clinical trials and yet to show promising results. Hence, future therapeutic options may include different combination of novel therapeutic interventions.

**Keywords:** hepatocellular carcinoma, HCC, novel therapeutics, treatment, management, molecular targeted therapies, clinical drug trial

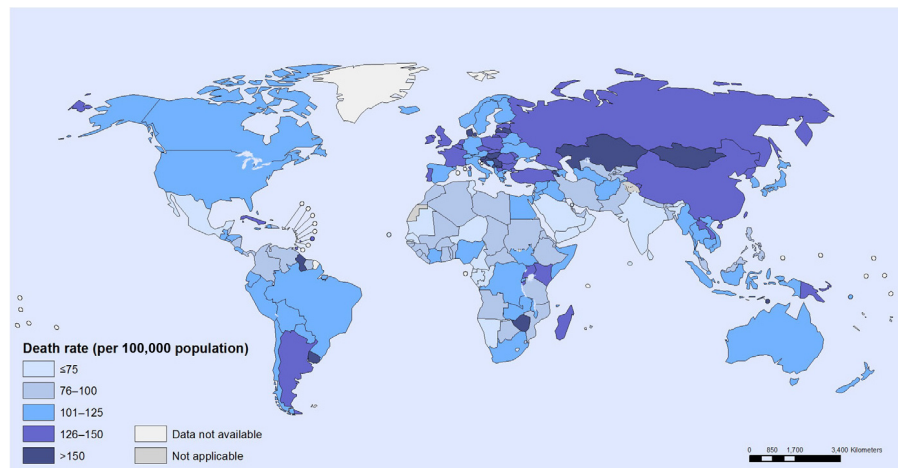
## Introduction

Hepatocellular carcinoma (HCC) is defined as the carcinoma emanating from the liver and also includes various underlying diseases.<sup>1,2</sup> Globally, the cancer prevalence was reported to be 10.9 million per annum, and liver cancer came up as the sixth most common cancer with 749,000 cases<sup>1,2</sup> and was ranked the third highest cause of cancer-related death with 692,000 mortalities per year.<sup>1</sup> However, its geographical distribution is not uniform<sup>1-3</sup> as shown in Figure 1.<sup>4</sup> The highest HCC incidence occurs in resource-poor or developing countries such as sub-Saharan African, East Asia, and Melanesia, which covers 85% of reported global cases.<sup>2,3,5</sup> Contrarily, incidence in developed countries is much lower, except in Southern Europe.<sup>2,3</sup> To date, the mortality rate in the USA increased by 40% between the years of 1990 and 2004 as a result of hepatitis C virus (HCV) events.<sup>2</sup>

Furthermore, HCC incidences increase with advancing age.<sup>1,3,6</sup> The peak age for HCC incidence is at 70 years.<sup>2,3,7</sup> However, peak age of incidence is less than 70 years in Chinese and black Africans.<sup>2,5,7</sup> With regard to sex, it strikes males more than females, with a ratio of 2.4.<sup>3,6,7</sup> Last decade, HCC mortality rose, particularly for male population in Austria, Denmark, Germany, Greece, Ireland, Portugal, Norway, Spain, Switzerland, and UK.<sup>2,3</sup> This paper aims first at describing the current and future therapeutic trends in HCC management, second at identifying the preventative measures in lowering the

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**Figure 1** Cancer mortality: age-standardized death rate per 100,000 population, both sexes, 2008.

**Note:** Reprinted from World Health Organisation. WHO: cancer mortality and morbidity. Available from: [http://www.who.int/gho/ncd/mortality\\_morbidity/cancer/en/](http://www.who.int/gho/ncd/mortality_morbidity/cancer/en/). Accessed December 23, 2014.<sup>4</sup>

incidence of HCC, and finally at reviewing the progress in novel therapeutics in developing and developed regions.

### Risk factors

These variations of risk factors link to etiology, complexity, and geographical distribution, particularly between developing and developed regions (Table 1).<sup>1</sup>

### Risk of HCC according to HBV genotype

Individuals with chronic hepatitis B virus (HBV) infection are at increased risk of developing end-stage liver disease

(including cirrhosis, hepatic failure, and HCC), with a cumulative lifetime incidence of 15%–40%.<sup>11–13</sup> Other important risk factors for HCC include the presence of HBV e-antigen – a surrogate marker of active viral replication – and the amount of HBV (ie, viral load) in serum.<sup>14,15</sup>

Several reports<sup>16–19</sup> have also suggested that the genetic characteristics of HBV, including HBV genotype and specific genetic mutations, are associated with the development of HCC. Most of the recent studies suggest that the genetic characteristics of HBV, including HBV genotype and specific genetic mutations, are associated with the development of HCC.<sup>20–22</sup>

**Table 1** The common risk factors in HCC

No	Risk factor	Details	Regions	References
1	HBV	Inactivates tumor-suppressing genes	Africa, People's Republic of China	1–3, 6
2	HCV	Immune response-mediated direct infection that leads to cirrhosis	USA, UK	1–3, 6
3	AFB <sub>1</sub>	Contamination of staple foods by fungi <i>Aspergillus flavus</i> and <i>Aspergillus parasiticus</i>	Sub-Saharan Africa, Eastern Asia	1, 2, 8
4	Hemochromatosis	Leakage of stored iron to hepatocytes in iron excess more than 5 g	Africa	1, 2
5	HIV	Chronic viral hepatitis	USA	1, 3, 6–9
6	Metabolic syndromes (obesity, diabetes, fatty liver disease)	Increased waist circumstances, particularly BMI more than 30 kg/m <sup>2</sup>	USA	1–3, 6, 7, 10
7	Tobacco smoking	Smoking cumulatively 11,000 packs of cigarette during the lifetime increases the risk by 1.7-fold	USA	1, 2, 7, 10
8	Alcohol abuse	Excess of 80 g per day more than 10 years increases risk fivefold	USA, Europe	1, 7, 10
9	Mutation in germline DNA	Genetic predisposition to SNPs in EGF	USA	2
10	MOIVC	Obstruction of hepatic venous drainage by complete-clogged lesion	Africa	2
11	Oral contraception	Hepatocarcinogenic properties of oral contraception	USA	2

**Abbreviations:** HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; AFB<sub>1</sub>, aflatoxin B<sub>1</sub> exposure; SNPs, single nucleotide polymorphisms; EGF, epidermal growth factor; MOIVC, membranous obstruction of the inferior vena cava; BMI, body mass index.

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**Table 2** Child–Pugh classification of severity of liver disease

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time			
Seconds over control	1–3	4–6	>6
INR	<1.8	1.8–2.3	>2.3
Encephalopathy	None	Grade 1–2 <sup>a</sup>	Grade 3–4 <sup>a</sup>

**Notes:** <sup>a</sup>Stage of performance status: 0 fully active; 1 – ambulatory and able to carry out light work; 2 – ambulatory but unable to carry out any work activities; 3 – capable of only limited self-care and confined to bed or chair; 4 – completely disabled.<sup>33</sup>

**Abbreviation:** INR, international normalized ratio.

To date, HBV has been classified in to eight genotypes (A–H), according to intergroup divergence of 8% or more in the complete nucleotide sequence.<sup>23</sup> Recent focus is on the clinically important differences in outcomes that are associated with the different HBV genotypes.<sup>24</sup> The HBV genotypes have distinct geographical distributions<sup>25</sup> and have been reported to have clinical relevance.<sup>26</sup> For example, patients with genotypes C and D have a higher risk of disease progression and a poorer clinical outcome compared to the patients with genotypes A and B. Patients with genotypes A and B have a better response to IFN-based therapy than those with genotypes C and D.<sup>27</sup> However, the association of genotypes B and C with HCC development remains controversial; some studies have shown that genotype C HBV infection is a risk factor for HCC,<sup>28,29</sup> while others did not obtain the same results.<sup>30,31</sup> The reason for these inconsistencies between the results, especially those derived from the same region,<sup>28,32</sup> is unclear.

## Staging

Introduction of various staging systems by different guidelines helps select the suitable interventions according to HCC classifications<sup>1,3,5,6,33</sup> (Tables 2 and 3).

**Table 3** BCLC staging

BCLC stage	Types of HCC	Performance status	Tumor stage	Liver function status
A1	Early HCC	0	Single, <5 cm	No portal hypertension and normal bilirubin
A2	Early HCC	0	Single, <5 cm	Portal hypertension and normal bilirubin
A3	Early HCC	0	Single, <5 cm	Portal hypertension and abnormal bilirubin
A4	Early HCC	0	Three tumors, <3 cm	Child–Pugh A–B
B	Intermediate HCC	0	Large multinodular	Child–Pugh A–B
C	Advance HCC	1–2	Vascular invasion/extrahepatic spread	Child–Pugh A–B
D	End-stage HCC	3–4	Any	Child–Pugh C

**Notes:** Grade A: 5–6 points (well-compensated disease); grade B: 7–9 points (significant functional compromise); grade C: 10–15 points (decompensated disease).

**Abbreviations:** BCLC, Barcelona Clinic Liver Cancer; HCC, hepatocellular carcinoma.

## Management

### Treatment

#### Resection

Resection is the first-line therapy for localized HCC without cirrhosis.<sup>3,5,6,34–37</sup> Resection is not recommended in cirrhotic patients due to increased risk of perioperative decompensation.<sup>6,37,38</sup> Nevertheless, resection is possible in cirrhotic patients whose liver transplantation (LT) is deemed to be unsuitable, provided that their hepatic function is well preserved.<sup>1,34</sup>

Portal vein hypertension is regarded as an absolute contraindication to resection in EASL–EORTC Clinical Practice Guidelines.<sup>3,35</sup> Studies demonstrated that the 5-year survival rate is only 30% regardless of the Child–Pugh score in the presence of portal vein hypertension and elevated bilirubin level, compared to 70% 5-year survival in patients with normal bilirubin level without portal vein hypertension.<sup>34,37</sup> However, in other studies, it was also demonstrated that the presence of significant portal vein hypertension does not influence the outcomes of resection, even in cirrhotic patients.<sup>38,39</sup>

Larger tumor is associated with higher risk of vascular invasion and dissemination.<sup>34</sup> A cutoff of <2 cm was demonstrated as an independent predictor of survival rates in Japan, and the outcomes of each groups were 66% 5-year survival in <2 cm tumor group, 52% in 2–5 cm tumor group, and 37% in >5 cm tumor group after resection procedure.<sup>3</sup>

Recurrence rate occurs up to 70% after 5 years is the main problem with resection.<sup>1,34,37</sup> However, the evidence to demonstrate the effectiveness of initiating adjunct therapy after resection in preventing recurrence is not conclusive.<sup>5,34</sup>

#### Liver transplantation

LT is the best curative therapy for candidates unsuitable to undergo liver resection as well as for patients with underlying

cirrhosis. However, dismal results as in high recurrence rate and 5-years survival rates below 50% have been recorded due to poor patient selection.<sup>6,37</sup>

Generally, LT can only be performed in patients in early stage of HCC.<sup>34,38</sup> Milan criteria defined patients with single nodule <5 cm, or up to three separate nodules <3 cm, with no evidence of gross vascular invasion and no regional nodal or distant metastases.<sup>5,40,41</sup> Using Milan criteria of patient selection, posttransplantation outcome with 5-year survival rates exceeds 70% (as shown in several studies).<sup>34,35</sup>

Nevertheless, shortage of donor livers has caused an unbearably long transplant waiting time,<sup>34,35</sup> resulting in waiting list exclusion when patients' HCC progression extends beyond the transplantable criteria.<sup>42</sup> The rate of waiting list exclusion may be as high as 25% if the waiting list is longer than 12 months.<sup>34,35</sup> Model for End-stage Liver Disease score was therefore utilized to allocate the organ fairly according to priority.<sup>34,35,41</sup>

Neoadjuvant therapy, such as chemoembolization and percutaneous ablation, can be employed to maintain the tumor burden within the ranges of the Milan criteria and prevent dropout from the waiting list, especially if transplant waiting time exceeds 6 months and patient's condition worsens.<sup>6,34,35</sup> However, the long-term benefit of the therapy is still uncertain as there are several studies showing no survival benefit in employing these interventions.<sup>37,41</sup>

**Percutaneous ablation**

Percutaneous ablation is the best treatment option for patients with early-stage HCC (BCLC 0-A tumors) who are not suitable for resection or LT.<sup>34,35</sup> The most common techniques are percutaneous ethanol injection (PEI) and radiofrequency ablation (RFA).<sup>36</sup> Currently, RFA has progressively replaced PEI<sup>35,37,38</sup> because RFA requires lesser treatment sessions and results in higher complete necrosis

rate and long-term survival rates than PEI, as demonstrated in many studies.<sup>43-46</sup>

When comparing therapeutic outcomes of RFA with surgical resection, resection is more effective than RFA for larger tumors (>3, <5 cm) in terms of disease-free survival and overall survival, while RFA is more cost-effective than surgical resection for smaller early HCCs (<2 cm).<sup>47,48</sup>

**Chemoembolization**

Chemoembolization is used as a palliative treatment for patients with inoperable HCC.<sup>49</sup> It is the recommended first-line therapy for patients with intermediate-stage (BCLC stage B) disease having well-preserved liver function and asymptomatic multinodular tumors without vascular invasion or extrahepatic spread (Table 4).<sup>3</sup>

Another technique called radioembolization, involving infusion of Iodine-131 or Yttrium-90 into hepatic artery, has been shown to exhibit antitumor results, but it is not recommended as a standard therapy as further research trials are needed to evaluate the efficacy.<sup>3</sup>

**Systemic therapies**

**Perspectives on drug therapies**

HCC is among the most chemoresistant tumors, and until 2007, no systemic chemotherapy was recommended for patients with advanced tumors (Tables 5 and 6).<sup>51-53</sup> Systemic chemotherapy with cytotoxic agents, such as doxorubicin, gemcitabine, cisplatin, 5-fluorouracil, or combined regimens for palliative care, was associated with low response rates (<10%) with only marginal improvements in survival. Moreover, these drugs are poorly tolerated in patients with underlying liver cirrhosis. Interferon (IFN) therapy, anti-androgens, or tamoxifen used in the treatment of advanced HCC show contradictory results without obvious benefit.

**Table 4** Types of chemoembolization

Types of chemoembolization	TACE	Chemoembolization with TACE-DEB
Method	TACE involves catheterization of hepatic artery followed by injection of chemotherapy drugs (doxorubicin, mitomycin, and cisplatin) mixed with lipiodol and embolizing agents (gelatin or microspheres).	TACE-DEB is a new technique which delivers embolizing particles loaded with chemotherapeutic agent in the same manner as TACE.
Studies to prove effectiveness of chemoembolization	Studies have shown patients achieving 15%–55% partial responses and delay in tumor progression plus vascular invasion were noted. Moreover, median survival for patients increased from 16 to 20 months after chemoembolization.	In a Phase II trial, TACE-DEB with 150 mg doxorubicin achieved objective rates of 70% and insignificant systemic toxicity due to controlled elution over 1 week.

**Note:** Data taken from studies.<sup>3,14</sup>

**Abbreviations:** TACE, transarterial chemoembolization; DEB, drug eluting beads.

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Table 5 Molecular-targeted therapies

Drugs	Types	Indication	Details of clinical trials	Side effects	Extra information	Reference
<b>First and only US FDA approved systemic therapy in 2007</b>						
Sorafenib	Oral multi-tyrosine kinase inhibitor of VEGFR, platelet-derived growth factor receptor and Raf	Patients with well-preserved liver function and with advanced tumours/those tumours progressing upon loco-regional therapies	Sorafenib HCC Assessment Randomized Protocol (SHARP) trial <ul style="list-style-type: none"> <li>Median overall survival: 10.7 months with sorafenib and 7.9 months with placebo</li> <li>31% decrease in relative risk of death</li> <li>Median time to radiologic progression: 5.5 months with sorafenib and 2.8 months with placebo</li> </ul> Phase III study in Asia <ul style="list-style-type: none"> <li>Overall survival: 6.5 months with sorafenib and 4.2 months with placebo</li> </ul>	Hand-foot skin reactions (8%–16%) Diarrhea (8%–9%) Weight loss Hypophosphataemia Fatigue	Currently being tested <ul style="list-style-type: none"> <li>As an adjuvant after resection or complete local ablation for initial stages</li> <li>In combination with chemoembolization for intermediate stages</li> <li>In combination with Erlotinib/systemic doxorubicin in advanced stages</li> <li>As first line treatment for Child–Pugh B patients</li> </ul>	50
<b>Under clinical development and clinical trials</b>						
Brivanib alaninate	Oral VEGFR and FGFR tyrosine kinase inhibitor		Phase II studies <ul style="list-style-type: none"> <li>Median overall survival: 10 months in first line patients with advanced tumor and 9.8 months in second line treated group</li> </ul> Phase III studies <ul style="list-style-type: none"> <li>Median overall survival: 9.4 months with brivanib and 8.2 months with placebo</li> <li>Median time to progression: 4.2 months for brivanib and 2.7 months for placebo</li> </ul>	Hypertension (17%) Fatigue (13%) Hyponatremia (11%) Decreased appetite (10%)	Currently being tested in three phase III clinical trials <ul style="list-style-type: none"> <li>First line blinded to sorafenib</li> <li>Second line blinded to placebo</li> <li>In combination with chemoembolization</li> </ul>	3
Bevacizumab	Recombinant, humanised monoclonal antibody against VEGF		Monotherapy <ul style="list-style-type: none"> <li>Median time to regression of 6.5 months</li> <li>Objective responses of 10%</li> </ul> With EGFR targeting agents <ul style="list-style-type: none"> <li>Median survival of 15 months for mixed HCC patient populations</li> </ul> With chemotherapy (gemcitabine, oxaliplatin, capecitabine-based regimens) <ul style="list-style-type: none"> <li>Objective responses of 10–20%</li> <li>Median survivals of 9–10 months</li> </ul>		Approved for colorectal cancer, non-small cell lung cancer, and breast carcinoma treatment No phase III investigations	3, 51
Sunitinib	Multi-targeted tyrosine kinase inhibitor and PDGFR	Presently not recommended for treatment of HCC	Used in phase II & III clinical trials for HCC treatment	Thrombocytopenia (29.7%) Neutropenia (25.7%) Bleeding (37.1%)	Blockade of angiogenic receptors and reduces HCC development	3, 38, 51, 52

(Continued)

Table 5 (Continued)

Drugs	Types	Indication	Details of clinical trials	Side effects	Extra information	Reference
Erlotinib	Tyrosine kinase inhibitor of the EGFR	Maintenance treatment of patients with locally advanced or metastatic NSCLC whose disease has not progressed after four cycles of platinum-based, 1st line chemotherapy	<ul style="list-style-type: none"> <li>Median overall survival times of 7.9 months</li> <li>Median relative dose intensity, 66.6% vs sorafenib, 71.3%</li> <li>Phases I, I-II, II, III are under evaluation</li> <li>Survival times of 15.6 months</li> <li>Survival times of 6.8 months</li> <li>Median of 13 and 6.3 months in 2 single-arm studies</li> <li>Response rate of 25% and &lt;10% in single-arm studies</li> <li>Phases II, III are under evaluation</li> </ul>	Diarrhea led to dose reductions as a result of thrombocytopenia (6.7%), hand-foot syndrome (6.5%), and neutropenia (4.0%)	<ul style="list-style-type: none"> <li>GIST after disease progression on or intolerance to imatinib mesylate</li> <li>Show anti-tumor activity in three phases II studies of patients with advanced HCC</li> <li>Being tested in phase III pivotal trials for regulatory approval</li> </ul>	36, 52, 53
Linifanib	Tyrosine kinase inhibitor targeting PDGFR and VEGF					38, 52
Tivantinib	Oral MET receptor tyrosine kinase inhibitor				<ul style="list-style-type: none"> <li>Being tested in phase III pivotal trials for regulatory approval</li> <li>Effective in the treatment of the HCC with an acceptable safety profile in a single-arm phase II clinical trial</li> <li>Has synergistic effect against HCC when added to sorafenib</li> <li>Used as a second-line agent for the treatment of HCC in previously unresectable HCC who progressed or could not tolerate first-line systemic therapy</li> </ul>	38
Rapamycin (sirolimus) and its analogs (temsirolimus and everolimus)	Growth factors and proliferative pathway inhibitors (mTOR inhibitor)		Tested in preclinical and early clinical investigation		<ul style="list-style-type: none"> <li>Everolimus</li> <li>Used for kidney cancer therapy</li> <li>Being tested in phase III for a second line indication</li> </ul>	3
Vazalanib, axitinib, cediranib	Anti-angiogenic		Being tested at early clinical investigation			3

**Abbreviations:** US FDA, United States Food and Drug Administration; VEGFR, vascular endothelial growth factor receptor; FGFR, fibroblast growth factor; PDGFR, platelet derived growth factor receptor; Raf, rapidly accelerated fibrosarcoma; EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor; GIST, gastrointestinal stromal tumor; NSCLC, non-small cell lung cancer; HCC, hepatocellular carcinoma.

**Table 6** HBsAg carriers before and after initiate universal vaccination in high HBV prevalence countries

High HBV prevalence countries	HBsAg carriers before and after initiate universal vaccination % (year)		References
	Before	After	
Taiwan (children aged <15)	9.8 (1984)	4.0 (1994)	57
Gambia	10.0 (1986)	0.6 (1999)	58
Malaysia (children aged 7–12)	1.6 (1997)	0.3 (2003)	59
People's Republic of China (newborn)	2.1 (1992)	9.4 (2006)	60

**Abbreviations:** HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

A meta-analysis of seven RCTs, including 898 patients, evaluated tamoxifen versus conservative management and showed neither antitumor effects nor survival benefits for tamoxifen. Subsequent large RCTs reported negative results in terms of survival. Cisplatin, IFN, doxorubicin, and fluorouracil (PIAF) used in combination showed promising activity in a Phase II study. A randomized Phase III study including 188 patients with HCC was conducted to investigate the effect of PIAF combination compared to doxorubicin alone. The median survival rate of the PIAF group did not significantly differ from the doxorubicin group (8.67 versus 6.83 months), and patients treated with the PIAF regimen experienced a significantly higher rate of myelotoxicity.<sup>50–53</sup>

## Prevention

Understanding risk factors of HCC supports the rationale for designing of prevention strategies, which aids in avoiding infection, chronic liver damage, and carcinogenesis process as well as early diagnosis of the disease and reduces the risk of recurrence.<sup>54,55</sup>

## Vaccination

HBV is attributable to more than 50% of the cases of HCC globally, it accounts for 15% of HCC in developed countries and 80%–90% of HCC in developing countries such as Asia and Africa.<sup>54,55</sup> World Health Organization (WHO) introduced universal vaccination to all newborns and high-risk groups as routine immunization.<sup>54,56</sup> Most of the studies showed that hepatitis B core antibody, hepatitis B surface antigen (HBsAg) carriers, HCC incidence, and HCC-related mortality were decreased following initiation of universal vaccination (Table 6).<sup>57–61</sup> Therapies stratified according to stage along with the treatment strategies and rational of HCC were summarized (Table 7).<sup>62–65</sup>

## Antiviral treatment

Studies have shown that antiviral treatment of chronic HBV and HCV infections may reduce the risk of HCC.<sup>3,37,66</sup> Chen et al<sup>14</sup> demonstrated that incidence of HCC is associated with serum HBV DNA, which further supports the analysis showing that low viremia levels decreases the risk of HCC development. Therefore, antiviral therapy is used for HCC

**Table 7** Therapies stratified according to stage

Stage of HCC	Treatment option
Early-stage HCC	In patients with early-stage disease, liver resection remains the first choice, but it is being challenged by local ablative therapy. If the Milan criteria are met, LT still offers a better outcome; however, local ablative therapy can be a substitute when transplantation is not feasible. Often, local ablation such as radiofrequency ablation or percutaneous alcohol injection can be used not only as an effective treatment but also as a bridge therapy to maintain the status of patients on the liver transplant list.
Intermediate-stage HCC	Intermediate-stage patients are typically treated with transarterial chemoembolization, but have a high rate of disease recurrence.
Advanced-stage HCC	The multikinase inhibitor sorafenib is the most used treatment option for patients with advanced-stage HCC. This stage-based approach to therapy not only provides acceptable outcomes but also improves the quality of life of HCC patients. Sorafenib has demonstrated a significant survival advantage in these patients. Several other studies have assessed other novel targeted therapies in this setting, but none have shown superiority to sorafenib.

**Note:** Data from studies.<sup>62–65</sup>

**Abbreviations:** HCC, hepatocellular carcinoma; LT, liver transplantation.

risk reduction, while viral suppression also reverses cirrhosis, another risk factor of HCC development.<sup>66,67</sup>

Oral nucleoside analogs (NAs) have been used to treat chronic hepatitis B.<sup>67</sup> The use of first-generation NA is limited due to the development of resistance and virological relapse after treatment cessation.<sup>61</sup> Newer generation NA with high antiviral and low drug-resistant potency, such as entecavir and tenofovir, are available.<sup>66,68</sup> At the same time, combination therapy of pegylated IFN with ribavirin works well in preventing HCC development associated with HCV infection.<sup>68,69</sup>

## Surveillance

Surveillance is a diagnostic test applied periodically to patients at risk of developing a disease, aiming to reduce disease-related mortality through early diagnosis (Table 8).<sup>3,35</sup>

Serological and imaging tests are used in HCC surveillance, ultrasonography is the most widely used.<sup>3</sup> Surveillance is mainly based on ultrasound examination as measuring alpha-fetoprotein levels, which is an example of serological test, has demonstrated inadequate sensitivity and specificity in recent studies.<sup>35</sup>

## Other preventive measures

WHO recommends implementation of an integrated and comprehensive strategy based on five key elements as listed in Table 8, aiming at preventing transfusion-transmitted HBV and HCV infection, especially in sub-Saharan African countries where there is relatively high risk of such mode of transmission. On the other hand, risky behaviors such as tattooing, body piercing, and unprotected sexual intercourse should be avoided to prevent transmission of HCV and HBV, along with implementation of related health policies by governmental health agencies (Table 9).<sup>3,55,70</sup>

## Discussion

### Current novel therapeutics

Surgical intervention that includes liver resection and LT is the mainstay of treatment of HCC, but the selection criteria for

**Table 8** Categories of patients suitable for surveillance

#### Surveillance for HCC is recommended for the following categories of patients

- Cirrhotic patients, Child–Pugh stage A and B.
- Cirrhotic patients, Child–Pugh stage C, waiting for LT.
- Noncirrhotic HBV carriers with active hepatitis or with family history of HCC.
- Noncirrhotic patients with chronic hepatitis C and bridging fibrosis.
- Chronic hepatitis B patients who remain at risk of HCC development.
- Patients with HCV-induced advanced fibrosis or cirrhosis, even after achieving sustained virological response.

**Note:** Data from study.<sup>3</sup>

**Abbreviations:** HCC, hepatocellular carcinoma; HBV, hepatitis B virus; HCV, hepatitis C virus; LT, liver transplantation.

**Table 9** Strategy to prevent transfusion-transmitted HBV and HCV infection by WHO

Key elements	
1	Establish a nationally coordinated blood transfusion service
2	Collect blood from regular, voluntary, nonremunerated donors from low-risk populations
3	Test for transfusion-transmissible infections, blood group, and compatibility using quality-assured procedures
4	Reduce unnecessary transfusion through appropriate use of blood
5	Implement quality systems for the entire transfusion process, from donor recruitment to the follow-up of the recipients of transfusion

**Note:** Data taken from studies.<sup>71–73</sup>

**Abbreviations:** HBV, hepatitis B virus; HCV, hepatitis C virus; WHO, World Health Organization.

both differ in different published clinical guidelines, resulting in difficulty in selecting the most appropriate therapy in treating HCC.<sup>74–79</sup> Certain groups of patients who are defined to have well-preserved liver function and are deemed to be fit to undergo resection (Child–Pugh A score) may be regarded as not suitable for resection due to other circumstances such as the presence of portal vein hypertension.

Meanwhile, the gold standard in selecting patients for LT, Milan criteria, possesses some limitations that may exclude some of the potential patients.<sup>18</sup> University of California at San Francisco criteria have been proposed, in which selection is based on having a single tumor nodule up to 6.5 cm or three or fewer tumors, the largest of which is <4.5 cm with the sum of the tumor diameters <8 cm.<sup>80</sup> Its outcome is comparable to patients who are selected by using Milan criteria.<sup>40</sup> Nevertheless, more studies should be conducted to confirm the validity of this extended criteria. However, it is still preferable to establish a standardized universal classification system in evaluating the liver status in patients with HCC to ensure the most appropriate option is selected for the patients, for both resection and LT procedure.

To date, sorafenib is the first and only available systemic therapy approved by FDA for treatment of HCC.<sup>3</sup> Nevertheless, many emerging agents are still under clinical trials and yet to show promising results.<sup>51,81</sup>

### Future therapeutic trends

Living donor liver transplantation (LDLT) is proposed as it provides advantages to reduce the waiting time and increase the number of patients benefit from LT due to severe shortage of deceased donor livers. By comparing LDLT with deceased donor liver transplantation (DDLT), the waiting time is significantly shorter and dropout rate has reduced from 18% to 0%.<sup>40</sup> However, it is still uncertain whether



the outcome of LDLT is equivalent or more favorable to that of DDLT.<sup>82</sup>

For tumors with size <2 cm and with the BCLC stage A, both PEI and RFA achieve complete responses in more than 90% of cases with good long-term outcome, which may substitute the roles of surgical intervention in early HCC in the future. In future, technical developments may achieve ablation areas of 5 cm or more in diameter, which will make percutaneous ablation an effective alternative to surgery even for tumors measuring 3 cm or more.<sup>38</sup>

Future therapeutic options may include different combination of novel therapeutic interventions. Combination of TACE-DEB has lesser complications than TACE due to slow release of chemotherapeutic drug.<sup>83</sup> TACE-DEB was also better tolerated and significantly decreased liver toxicity and adverse events and showed improved antitumoral effect.<sup>3,84</sup>

There are also studies revealing the possibility of combination therapy of sorafenib with either TACE or radioembolization as both these combinations had demonstrated better therapeutic outcomes with improved overall survival and time to progression.<sup>3,39,83,84</sup> More studies need to be conducted to examine this possibility as well as to solve the uncertainties regarding dose, frequency, and duration of sorafenib in combination therapy.

Universal vaccination is also one of the therapeutics interventions for HCC, especially in developing countries. A cost-effectiveness analysis by Hung and Chen<sup>84</sup> demonstrated that universal vaccination shows high cost-effectiveness in reducing long-term sequelae of acute hepatitis B infection, HCC death, and chronic illnesses,<sup>56,85</sup> which is further supported by another cost-effectiveness analysis by Hong et al<sup>85</sup> in Vietnam.<sup>80</sup>

However, an effective prophylaxis vaccine for HCV is not yet available. Thus, preventing HCC is completely dependent on antiviral therapy for patients, until an effective vaccine is developed.<sup>68</sup> Antiviral therapy with nucleotide analogs may be preferable than IFN treatment due to less adverse side effects and can be considered as a cost-effective adjuvant therapy for HCC after curative treatment.<sup>80</sup> However, the exact role of antiviral treatment in preventing HBV-related HCC has been difficult to establish, due to the slow biological evolution of HBV.<sup>66</sup>

## Future technical aspect or extended indications for liver resection for HCC

Recent improvement in surgical techniques and perioperative care has increased the safety and expanded the indication of hepatic resection for HCC to include large tumors that require extended hepatectomy in cirrhotic patients. Selection of appropriate candidates for hepatectomy depends on

careful assessment of the tumor status and liver function reserve. Evaluation of the general fitness of patients is also critical because comorbid illness is an important cause of postoperative mortality, even if the patients have good liver function reserve. With careful patient selection and surgical expertise, the current operative mortality of hepatectomy for HCC is approximately 5% or less in major centers. Improved long-term survival results after resection of HCC have also been reported recently, with an overall 5-year survival rate of approximately 50%. The improved perioperative and long-term survival results have strengthened the role of hepatectomy as the mainstay of treatment for HCC despite the availability of a number of other treatment options for localized HCC.<sup>86</sup>

The main clinical advantage of laparoscopy for cirrhotic patients is probably the significantly lower rate of postoperative ascitic decompensation, which was reported in four comparative studies and three meta-analysis. This finding could be explained by the preservation of portosystemic venous collateral circulation around the liver and parietal abdominal wall, limited mobilization and manipulation of the liver, restricted fluid requirements, and decreased blood loss. Gaillard et al<sup>87</sup> advocated that the positive pressure of the pneumoperitoneum might exert a tamponade effect on bleeding from intra-abdominal varices, which are a low-pressure system, thus decreasing blood loss. Lower blood transfusion requirement is also an advantage of the laparoscopic approach in this very risky group of patients.<sup>87</sup>

## Disclosure

The authors report no conflicts of interests in this work.

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