

# Multidisciplinary management of recurrent and metastatic hepatocellular carcinoma after resection: an international expert consensus

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*Contributions:* (I) Conception and design: T Wen; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Abstract:** Hepatocellular carcinoma (HCC) is the sixth-most common cancer and the third leading cause of cancer-related death in the world. However, 40–70% patients eventually suffer from postoperative recurrence within 5 years. HCC recurrence after surgery severely affects prognosis of the patients. Nevertheless, there is an opportunity to improve patients' prognosis if doctors and researchers can recognize the importance of a standardized perioperative management and study it in clinical and pre-clinical settings. Hence, based on our own experience and published studies from other researchers, we develop this consensus regarding multidisciplinary management of locally recurrent and metastatic hepatocellular carcinoma after resection. This consensus consists of the entire course of recurrent hepatocellular carcinoma (RHCC) management, including prediction of recurrence, prevention, diagnosis, treatment and surveillance of RHCC. Consensus recommendations are presented with grades of evidences (Ia, Ib, IIa, IIb, III and IV), and strength of

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recommendations (A, B, C, D and E). We also develop a decision-making path for RHCC treatment, which can intuitively demonstrate the management for RHCC. It is hoped that we may make some effort to standardize the management of RHCC and ultimately understand how to improve outcomes.

**Keywords:** Recurrent hepatocellular carcinoma (RHCC); multidisciplinary management; consensus

Submitted Dec 01, 2017. Accepted for publication Jun 22, 2018.

doi: 10.21037/hbsn.2018.08.01

View this article at: <http://dx.doi.org/10.21037/hbsn.2018.08.01>

## Introduction

Hepatocellular carcinoma (HCC) is the sixth-most common cancer and the third leading cause of cancer-related death in the world, with more than 50% of new cases being diagnosed in China (1). According to the latest data from China (2), HCC is the fourth-most common malignancy and the third leading cause of mortality. Surgical treatment, including hepatectomy and liver transplantation, is the most commonly used approach to improve the survival of patients. However, 40–70% patients eventually suffer from postoperative recurrence within 5 years (3). Nevertheless, there is an opportunity to improve patient prognosis if investigators can recognize the importance of a standardized perioperative management and study it in clinical and pre-clinical settings. Preoperative evaluation, recurrence prediction, surgical technique, postoperative surveillance and treatment should be standardized for HCC management. A multidisciplinary team (MDT) could thus maximize the advantages of different disciplines and benefits to patients. Based on our own experience and published studies from other researchers, for the first time, we have reached a consensus for the management of recurrence and metastasis after HCC resection. A draft consensus was written by the MDT of West China Hospital. During the preparation of the consensus, all important aspects of MDT management of HCC were discussed with other professors specializing in liver surgery, hepatic tumor, hepatitis and hepatic imaging from West China Hospital. After that, more experts from renowned hospitals in other regions of China joined to update the consensus. We also invited experts from Italy, Korea, Japan and the USA to review and improve the consensus, thus formulating an international consensus. With emerging evidence, this initial version of the consensus needs to be updated and improved in the future.

According to the accepted practice, the grades of evidences are presented in *Table 1* (4). The strength of recommendations is showed in *Table 2* (5).

**Table 1** Grades of evidences

Grades of evidences	Description
Ia	Evidences are originated from the meta-analysis results of various RCTs
Ib	Evidences are originated from the results of at least one well-designed RCT
IIa	Evidences are originated from the results of at least one well-designed perspective non-RCT
IIb	Evidences are originated from the results of at least one well-designed interventional clinical research of other type
III	Evidences are originated from the well-designed non-interventional clinical researches, such as descriptive researches and relevant researches
IV	Evidences are originated from the reports made by committee of experts or the clinical reports of authoritative experts

RCT, randomized controlled trial.

## Consensus recommendations

### *Diagnostic criteria and preoperative evaluation of HCC and recurrent HCC (RHCC)*

#### **Clinical diagnostic criteria for HCC**

It has been recognized that HCC is the only solid tumor for which clinical diagnostic criteria are adopted. In clinically diagnosing HCC, three factors are considered: underlying chronic liver disease, imaging features and serum alpha-fetoprotein (AFP) level. Presently, the internationally recognized clinical diagnosis standards, i.e., meeting 1.1.1+1.1.2.1+1.1.3 or 1.1.1+1.1.2.2 or a biopsy of a suspicious lesion, should be implemented (3,6-11).

#### **History of hepatitis and/or cirrhosis**

Evidence of cirrhosis and hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection (positive for HBV and

**Table 2** Strength of recommendations

Strength of recommendations	Description
A	Favorable scientific evidences indicate that the medical treatment can provide clear and definite benefits to the patients; physicians are strongly recommended to administer the medical treatment to eligible patients
B	Existing evidences indicate that the medical treatment may provide moderate benefits that outweigh the potential risks; physicians may suggest patients the medical treatment
C	Existing evidences indicate that the medical treatment may provide only little benefits, or the benefits do not outweigh the risks; physicians may suggest or administer the medical treatment selectively based on the patient's condition
D	Existing evidences indicate that the medical treatment would not benefit the patients, or the potential risks would outweigh the benefits; physicians are recommended not to administer the medical treatment in patients
E	There are not enough scientific evidences, or the existing evidences cannot be used, to evaluate the benefits and risks of the medical treatment; physicians should help the patients understand well the uncertainty of this medical treatment

(or) HCV antigen). History of nonalcoholic fatty liver disease (NAFLD)

#### **Typical HCC imaging features**

Magnetic resonance imaging (MRI) and/or computed tomography (CT)-enhanced arterial scan and/or enhanced multi-phase scan indicating that an intrahepatic lesion is inhomogeneous or homogeneous enhancement during arterial phase, with venous or delayed phase washout (12-16). The definitions of techniques, structure and categorization embodied by LI RADS—developed by the American College of Radiology is helpful in defining the imaging findings associated with HCC and RHCC (17).

If the diameter of the hepatic lesion is 1–2 cm, HCC can be diagnosed only when CT and MRI examinations both indicate typical imaging features of HCC. If the diameter of the liver lesion is more than 2 cm, HCC can be diagnosed when either CT or MRI examination indicates the typical imaging features corresponding to HCC.

#### **Increased level of AFP**

Serum AFP  $\geq 400$   $\mu\text{g/L}$  for 1 month or  $\geq 200$   $\mu\text{g/L}$  for 2 months, and when the increase in AFP level due to other reasons can be excluded, including pregnancy, germline embryonic tumor, active liver disease and secondary liver carcinoma. The use of GALAD and BALAD scores have demonstrated significantly improved detection of early stage HCC and are becoming increasingly popular to help determine the likelihood of HCC (18,19).

#### **Criteria of pathologic diagnosis**

Pathologic examination is the gold standard for diagnosis. Samples obtained from the biopsy of a liver-occupying lesion or extrahepatic metastasis or specimens excised by surgery can be diagnosed as HCC by cytologic and (or) histopathologic examination.

#### **Diagnostic criteria of RHCC**

Similar to the diagnostic criteria for primary HCC, imaging examinations displaying typical HCC vasculature are required when diagnosing RHCC (3,7,20-24). Two or even three kinds of imaging examinations can complement one another (3), which is of great significance in accurate staging, prognostic prediction and optimal treatment selection for HCC management. The application of previous therapeutic modalities such as transarterial chemoembolization (TACE) and transarterial radioembolization (TARE) can make it very difficult to determine the presence of RHCC using a single modality. Imaging over several months also dramatically assists in the radiographic diagnosis of RHCC.

In the presence of an underlying chronic liver disease, Gd-EOB-DTPA-enhanced MRI is recommended to identify posterior necrotic foci, hemorrhagic foci, regenerative nodules and HCC (12-16,25).

#### ***Preoperative tumor marker levels, imaging characteristics and other risk factors to predict recurrence after surgery***

**Preoperative AFP level:** The prognosis of patients with apparent AFP increase ( $\geq 400$   $\mu\text{g/L}$ ) is poorer than the prognosis of patients with no AFP increase or slight AFP increase (26-28).

**Imaging characteristics:** The prognosis of patients with HCC accompanied by growth outside the capsule, multiple nodules with fusion growth or with HCC without capsule is poorer than the prognosis of patients with single-nodule HCC (29,30). Imaging studies indicated that a single HCC

lesion with a diameter greater than 5 cm or multi-nodule HCC is associated with a high incidence of microvascular invasion (MVI) (31,32). Additionally, the presence of arterial vessels in tumors on imaging examinations is a risk factor for MVI (33). Likewise, the presence of portal vein tumor thrombus (PVTT) in imaging examinations is indicative of poor prognosis (34,35). Patients with PVTT and (or) lymph node metastasis usually do not benefit from liver transplantation (36). Furthermore, patients whose preoperative imaging examinations indicate 4 or more HCC nodules fail to acquire survival benefit from resection (37).

High expression of HCC stem cell markers (38) and EpCAM-CTC7.5  $\geq 2$  (39) indicate poor prognosis.

HCC patients with increased levels of AFP, AFP isoforms (AFP-L3) and des-gamma-carboxy prothrombin (DCP) before surgery have poor prognosis (40). Therefore, combining tumor size, serum DCP levels and standardized uptake value (SUVmax) in positron emission tomography (PET)/CT examinations can precisely predict MVI. For example, when the tumor diameter was 3.6 cm, DCP level was 101 mAU/mL and SUVmax in PET/CT examination was above 4.2, the sensitivity and specificity of MVI prediction were 100% and 90.9%, respectively (41).

#### *Measures of recurrence prevention during hepatectomy*

For large lesions in the right or left liver lobe, especially in the presence of invasion of diaphragm assessed by preoperative imaging, hepatectomy via the anterior approach should be implemented (42).

If blood loss is anticipated to be 600–800 mL during surgery, hepatic inflow occlusion or half-hepatic inflow occlusion should be performed (43,44). There is no evidence demonstrating that hepatic inflow occlusion adversely affects long-term prognosis (45); however, excessive blood loss is a risk factor for reduced survival (46).

Intraoperative ultrasound or ultrasound contrast imaging (47) during operation can further identify satellite nodules, tumor emboli and lesions in the remnant liver. The relation between lesion and first, second and third hepatic portis can be re-evaluated. In addition, intraoperative ultrasound or ultrasound contrast imaging can help determine the resection line and margin.

Confirmed or suspicious lesions found during operation should be simultaneously resected or ablated (48).

Anatomical hepatectomy should be the optimal choice based on the anticipated remnant liver volume, ICG R15 index, cirrhosis degree and tumor extension. Based on these

factors, non-anatomical hepatectomy or local resection with a wide resection margin could be considered (49,50). In patients with liver cirrhosis or simple nodular type HCC with close proximity to the major vasculature, marginal resection can be considered securing sufficient future liver remnant volume (51).

#### *Radical resection criteria for HCC (3,22,47,52)*

##### **Intraoperative evaluation**

- (I) No invasion to adjacent organs or lymphatic and distant metastasis;
- (II) All the tumors can be completely resected. Resection margin >1 cm is preferable; however, if the margin is <1 cm, no residual tumor cells are found at resected cross section;
- (III) The tumor number does not exceed three by intraoperative ultrasound scanning. For patients with 4 or more tumors, TACE or radiotherapy should be considered, rather than proceed to resection.

##### **Postoperative evaluation from pathological reports**

Standard pathological sampling and reports (32) should be adopted. The presence or absence of MVI and satellite nodules, and surgical margin should be mentioned on the pathological report.

##### **Postoperative evaluation from surveillance 2 months after operation (3)**

- (I) Ultrasound scan, CT scan or MRI (two scans are necessary) should be performed 2 months after operation;
- (II) Quantitative determination of AFP should be performed 2 months after operation. The duration for the AFP level to become negative is more than 2 months for a small proportion of patients.

#### *Management of patients who have a risk of recurrence after operation*

##### **Identification of patients at risk of recurrence**

Risk factors for recurrence should be re-evaluated 1 to 2 months after operation according to dynamic changes in blood cell counts, AFP and DCP levels, and surgical outcomes and pathological reports. For example, poor survival is usually observed if the following three risk factors are simultaneously present: platelet to lymphocyte ratio (PLR) <107, presence of MVI and tumor diameter  $\geq 6.8$  cm (53).

There are several risk factors of recurrence after operation including the following:

- (I) Surgical factors: non-anatomical resection (only for 2–5cm HCC) (54), positive histologic margin (55), substantial blood loss, need for transfusion (56) and iatrogenic tumor escape/rupture;
- (II) Clinicopathological factors: poorly differentiated tumor, advanced tumor stage, tumor rupture (57), no intact capsule, tumor diameter >5 cm, tumor number  $\geq 3$  (58), vessel invasion (including vascular and bile duct tumor thrombus) (59), lymph node metastasis (60), satellite lesion, adjacent organ invasion, high level of AFP before operation (59), increased AFP level 2 months after operation (61);
- (III) Underlying liver disease: active hepatitis infection and cirrhosis.

### Recommendation 1

Presence of macroscopic tumor thrombus, MVI, multiple tumors, satellite nodule or lymph node metastasis and lack of change of AFP level from positive to negative at 2 months after operation are clear indicators of a high risk of recurrence; in these cases, postoperative adjuvant therapy might be considered (evidence level II b; recommendation C)

#### *Postoperative surveillance*

HCC patients should be regularly monitored after operation. Liver imaging examination, expression of tumor markers (AFP and DCP), HBV-DNA level, blood cell count and liver function should be evaluated (6,7,62).

### Recommendation 2

Follow-up should be performed every 3 to 4 months within the first 2 years after operation. If all evaluated factors remain normal for 5 years, the follow-up interval could be increased to 6 months (evidence level IV; recommendation B).

#### *Treatment for patients according to the risk of tumor recurrence*

Present evidences (63–65) show that inappropriate adjuvant therapy, such as TACE, for patients without a high risk of recurrence, could possibly damage the remnant liver, which could lead to liver function deterioration, adversely affect long-term survival and even increase the incidence of

extrahepatic metastasis.

### Recommendation 3

Except for systematic antiviral therapy for HBV- and/or HCV-related HCC, postoperative adjuvant therapy is not recommended for patients without recurrent risks (evidence level IV; recommendation B).

For patients who are at risk of recurrence after operation, no widely recognized treatment is recommended. Several studies demonstrate that for patients with vessel invasion, multiple lesions and tumor diameter >5 cm, postoperative TACE could be beneficial for survival.

TACE (34,63,66–69), antiviral therapy (70–72), immunomodulation therapy, such as thymosin  $\alpha 1$  (73–75) or interferon (76–79), sorafenib (80–82) and vitamin K2 (83–87), could be considered for patients who are at risk of recurrence. Alternatively, combined chemotherapy could be considered for these patients (88,89).

### Recommendation 4

The following postoperative therapies may benefit for patients who are at risk of recurrence which are systematic antiviral therapy for HBV-related HCC (evidence level Ia; recommendation A), interferon (evidence level Ia; recommendation B), TACE (evidence level Ib; recommendation B), sorafenib (evidence level Ib; recommendation C), vitamin K2 (evidence level Ib; recommendation C) and thymosin  $\alpha 1$  (evidence level IIb; recommendation C).

#### *Intrahepatic recurrence pattern and clinical significance after resection*

It is generally recognized that intrahepatic RHCC may have a monoclonal (or monocentric) origin when it develops from an intrahepatic metastasis (IM) or have a multiclonal (or multicentric) origin (MO) when it arises from de novo carcinogenesis due to long-term chronic inflammation and cirrhosis from HBV or HCV infection.

The earliest identification of RHCC is based on clinicopathological characteristics. Recurrence occurring within 1 year of surgery is typically defined as IM, while recurrence occurring later than 1 year after resection is defined as MO RHCC (90). IM can also be identified based on pathologic diagnosis (91), whereas MO RHCC can be identified based on tumor differentiation (92,93).

However, the sensitivity and specificity of these techniques are not optimal, because the results can be greatly influenced by subjective factors pertaining to the examining pathologist(s). With the development of molecular biotechnologies and genomic technologies, clinicians and pathologists have explored multiple diagnostic approaches for identifying the origin of RHCC, including loss of heterozygosity (LOH) analysis, microsatellite instability detection, TP53 gene mutation analysis, X chromosome inactivation analysis, HBV-DNA integration detection, DNA methylation analysis, microRNA (miRNA) spectrum analysis and comparative genomic hybridization (CGH) (94-103). By using multi-omics methods and combining clinicopathological characteristics, some scholars (104,105) have explored and identified tumor heterogeneity and origins of multiple-nodule HCC. Among these methods, the detection of LOH has been widely employed to identify the origins of RHCC. Microsatellite DNA is a good marker of the integral stability of DNA. The detection of multiple chromosomes that have a high-frequency of LOH may improve the accuracy of the identification of RHCC origin. Additionally, the required specimen can be easily obtained, because formaldehyde-fixed and paraffin-embedded samples or biopsy samples satisfy the detection requirements of this technique (94).

### Recommendation 5

RHCC with different origins should be distinctly treated. The overall survival (OS) of patients with MO RHCC may be better than that of patients with IM. For patients with IM, intervention therapy or targeted drugs may be beneficial, while second resection or liver transplantation may provide comparable curative effect as the initial resection for patients with MO RHCC (evidence level IIb; recommendation B).

#### *Surgical treatment for patients with intrahepatic recurrence after resection*

##### **Repeat resection for resectable RHCC**

Studies (106,107) have demonstrated that for patients with resectable RHCC after resection, the OS is better after repeat resection than that after TACE. Similar conclusions have also been obtained from a systematic review (108). Some studies (109,110) have demonstrated that patients can even benefit from a third hepatectomy but that more than

three repeated hepatectomy cannot improve survival (111). Additionally, surgical resection is beneficial for resectable extrahepatic metastasis (112). The prognosis of RHCC patients after repeat resection was found to be closely associated with the clinicopathologic characteristics of primary HCC and recurrence interval (113). Repeat resection is usually better for patients with a single tumor without vascular invasion and with a recurrence interval  $\geq 1$  year (113,114).

##### **Preoperative evaluation for patients with resectable RHCC**

Preoperative evaluation for RHCC is usually similar to that before initial operation, in which exclusion of distant metastasis, the performance status (PS), liver function, hepatic reserve function, cirrhosis degree, portal hypertension and future liver volume (FLV) (109,115-117) are considered. For repeated resection, the PS score of patients should be 0-1, Child-Pugh staging should be class A or recovering to class A from B after short-term therapy before surgery, the liver reserve function should be normal, and there should be no apparent dysfunction of other organs. The FLV of patients should be comprehensively considered according to their liver function, liver reserve function and other indicators (118). For patients with cirrhosis, the FLV should be greater than 40% if ICG R15  $< 10\%$ , while the FLV should be greater than 50% if ICG R15 is 10-20% (119-121). Additionally, for patients with liver fibrosis, the FLV should be greater than 30%, and for patients without an underlying liver disease, the FLV should be greater than 20% (122). Repeated resection may be safe and feasible for older patients if their clinical conditions have been strictly evaluated (123).

Compared with traditional laparotomy, laparoscopic hepatectomy is characterized as being minimally invasive and to have shorter recovery time (124). Many studies (125-129) have indicated that there are no significant differences in disease-free survival (DFS) and OS between RHCC patients undergoing laparoscopic operation and traditional laparotomy. However, it should be noted that in some of these studies, there may have been a selection bias regarding tumor size and location before laparoscopic operation (126,127,130).

### Recommendation 6

RHCC patients could benefit from a second or a third resection. However, before surgery, the liver function,

liver reserve function and FLV should be strictly evaluated (evidence level IIb; recommendation B). Laparoscopic hepatectomy could be performed at experienced centers. To avoid unnecessary conversion, the relevant indications should be strictly evaluated (evidence level IIb; recommendation B).

#### *Ablative therapy for intrahepatic RHCC*

The currently available loco-regional ablative techniques include radiofrequency ablation (RFA), microwave ablation (MWA), high-intensity focused ultrasound ablation (HIFU), cryotherapy (CRA) and percutaneous ethanol injection (PEI) (131-134).

Studies (114,135-137) have demonstrated that patients with RHCC after resection may benefit from RFA and even obtain comparable OS and DFS to those of patients undergoing repeat resection. Compared with repeat resection, the obvious advantages of ablation are minimal invasion, fewer complications and better repeatability. Additionally, the risk factors associated with recurrence and the interval of recurrence after the first operation can be neglected. The indications for RFA for RHCC patients are similar to those for primary HCC patients (138). For RHCC, the indications for RFA (139) are as follows: single tumor diameter  $\leq 5$  cm; tumor number  $\leq 3$  and maximum diameter  $\leq 3$  cm; absence of vessel tumor thrombus or invasion into adjacent organs; accessible ablation path evaluated by ultrasound scanning. Notably, for tumors with diameters  $>3$  cm, overlapping modes of multiple ablations should be applied to complete ablation (140), or MWA could be performed (141-146).

Many studies have compared curative efficacy among CRA, RFA and MWA for treating HCC tumors  $<5$  cm in diameter, but the differences in OS and DFS among groups were not significant. However, for tumors from 3 to 4 cm in diameter, local recurrence after CRA was lower than that after RFA (147,148). A study showed that HIFU has similar efficacy to RFA in treating RHCC meeting the Milan criteria (149). In addition, PEI could precisely be applied to ablate HCC  $\leq 2$  cm in diameter (150-153).

#### **Recommendation 7**

Patients with intrahepatic RHCC could benefit from ablation treatment. To avoid incomplete ablation or side effects, the appropriate ablation treatment should

be carefully selected after preoperative evaluation, and standardized ablation procedures should be implemented (evidence level Ia; recommendation A).

#### *Liver transplantation for intrahepatic RHCC*

Many studies (154-157) have reported that salvage liver transplantation can provide survival benefit to patients with RHCC. Some studies (154,156) have even suggested that the OS was significantly better in patients with RHCC who underwent salvage liver transplantation than in patients who underwent repeat resection. In these studies, there were patients with HCC both within (155,157-159) and beyond (160,161) the Milan criteria before the initial operation; however, there was no major vascular tumor thrombus during the initial operation in the majority of patients. Most of the centers included in the studies required the tumors to meet the Milan criteria for the patients to be eligible for salvage liver transplantation (154,155,158,159,162); in addition, the recurrence interval after the initial operation could be  $>6$  months or even  $>12$  months. However, some centers adopted other criteria, such as the Kyoto criteria (163), the Kyushu University (KU) criteria (156), the Hangzhou criteria (160), and the up-to-seven criteria (161). Multiple studies (154,156,163) have also confirmed that living donor liver transplantation is safe and effective for RHCC patients. Nevertheless, there is a lack of comparative research on the prognosis of RHCC patients who have undergone deceased-donor liver transplantation or living donor liver transplantation.

#### **Recommendation 8**

Although patients with RHCC could benefit from liver transplantation, the RHCC must meet specific transplant criteria. Living donor liver transplantation could be equally safe and effective in salvage liver transplantation (evidence level, IIa; recommendation, B).

#### *Surgical indications of resectable RHCC with macrovascular or bile duct invasion*

There is still insufficient data on whether RHCC patients with macrovascular or bile duct invasion should undergo surgical resection. Further information may be presented in the updated version of this consensus in the future.

### Indications of TACE for RHCC

Previous randomized controlled trials (RCTs) (164,165) have demonstrated that HCC patients with lesions localized within the liver without vascular invasion could benefit from TACE. Researches demonstrated that there was no superiority between TACE and bland embolization when treating HCC patients (166). Besides, Drug-eluting beads and conventional chemoembolization could also reach comparable results (167). Although TACE is not a radical treatment for HCC, approximately 10% of HCC patients achieve complete remission after receiving sequential TACE (168). In RHCC patients with  $\leq 3$  lesions and tumor diameter  $\leq 5$  cm, the effects of TACE and RFA may be comparable (169); in particular, for patients with multiple intrahepatic recurrences after resection or transplantation, TACE could effectively improve survival after recurrence (170). Investigators (107) have revealed that for RHCC within the Milan criteria, TACE and RFA/resection may exert the same effect on early RHCC, but RFA/resection may be better than TACE for late RHCC. Jin *et al.* (171) compared the effect of TACE, resection and RFA for RHCC with MVI. Their results indicated that TACE for MVI-positive RHCC patients resulted in better OS and DFS than did resection and RFA, especially in patients who experienced recurrence within 1 year of resection. Yang *et al.* (172) retrospectively analyzed the effect of TACE combined with RFA and TACE or RFA alone on RHCC and demonstrated that the 5-year survival was significantly higher in the combined treatment group than that in the TACE-only or the RFA-only group. Therefore, the indications for TACE are as follows (114,173): (I) presence of an RHCC lesion adjacent to an important vessel or bile duct preventing resection or ablation; (II) presence of multiple recurrent tumors within the liver; (III) incidence of early intrahepatic RHCC (within 1 year of resection); or (IV) patient's willingness to receive TACE.

### Recommendation 9

For patients with early intrahepatic RHCC (within 1 year after hepatectomy), if the lesion cannot be resected or ablated because of being adjacent to important vessels or bile duct and for patients with multiple RHCC lesions within the liver, TACE may control the progression of HCC and provide survival benefits (evidence, IIa; recommendation, A).

### Radiotherapy for RHCC

Radiation therapy is one of the effective and safe therapeutic

approaches for RHCC (174). Studies demonstrate that the 5-year survival rate for patients with HCC tumors  $\leq 5$  cm in diameter after radiotherapy can be more than 60% (175,176) and that the expected OS resulting from radiotherapy can be almost identical to that from RFA for HCC tumors  $< 3$  cm (177). However, there are only a few studies comparing the curative outcomes between radiotherapy and resection. Patients with RHCC may be ineligible for resection due to the location, size or number of tumors, large vascular tumor thrombosis, liver dysfunction or other factors. In addition, extrahepatic metastasis in the lung, bone and other organs is often observed in patients. Hence, appropriate radiotherapy could be repeatedly used to suppress tumor progression, alleviate disease symptoms and prolong patient survival. Studies have demonstrated that after radiotherapy, the 2-year survival rate of HCC patients with lung metastasis is 70.7%, and the median OS of HCC patients with bone metastasis is approximately 7.4 months (178-184). Additionally, the progression of RHCC can be effectively controlled in patients after liver transplantation. Radiotherapy can also be combined with other interventions to improve the prognosis of patients with advanced RHCC (185).

In several studies, patients with HCC who received TACE combined with doxorubicin-eluting beads (186) and radioactive microspheres (187) displayed high tumor necrosis rates and low progression rates. Nevertheless, the role of radiotherapy in treating RHCC remains to be further clarified.

### Recommendation 10

Patients with RHCC tumors  $\leq 5$  cm in diameter that are not suitable for surgical resection could be treated with radiotherapy (evidence level, IIb; recommendation, B). Radiotherapy could also be used for RHCC patients with extrahepatic metastasis (evidence, III; recommendation, B).

### General therapy for RHCC

#### Antiviral therapy

HBV can be reactivated by surgery, TACE or chemotherapy. Antiviral therapy can reduce the recurrence of HCC and improve patient survival after TACE and surgery. Therefore, for patients with HBV infection and active replication, antiviral therapy using oral nucleotide/nucleoside analogs is recommended (70,72).

## Anti-tumor therapy

### Molecular targeted drug

Sorafenib has been recognized as a molecular targeted drug for the treatment of advanced HCC. Two large international multi-center phase III trials have demonstrated that sorafenib confers survival benefit to advanced HCC patients in different countries, regions and with different underlying liver diseases (82). Additionally, regorafenib has been approved as a second-line molecular target for advanced HCC recently.

### Systemic chemotherapy

Oxaliplatin has been approved for the treatment of HCC that is not suitable for resection or local treatment in China (188). The indications for this therapy are as follows: (I) advanced HCC with extrahepatic metastasis; (II) HCC lesions that are not suitable for surgical treatment or TACE; (III) HCC with tumor thrombus in the main portal vein or vena cava; (IV) vascular obstruction due to repeated TACE; and (V) recurrence after TACE treatment.

### Immunotherapy

Immunotherapy for HCC includes immunomodulatory agents (thymosin  $\alpha$ 1, interferon  $\alpha$ ) (74,189), immune checkpoint inhibitors (e.g., CTLA-4 inhibitors, PD-1/PD-L1 inhibitors), tumor vaccine (such as dendritic cell vaccine) and cellular immunotherapy (190). The anti-tumor effects of these therapies need to be verified in large-scale clinical studies.

### Palliative treatment

Moderate rehabilitation exercise, use of analgesics, improvement of sleep, increased nutrition, psychological therapy and other palliative treatment may enhance immunity and improve the quality of life and prognosis of patients.

### Comprehensive treatment for recurrence after resection

In China, the management of HCC is multi-faceted and multidisciplinary. However, there is a contradiction between treatment approaches based on a hierarchical medical system and the implementation of well-organized and standardized HCC management system (3). Accordingly, the establishment of rational and standardized therapeutic options and comprehensive treatment for HCC under an MDT is extremely important, especially for the treatment of RHCC. Treatment with TACE, sorafenib and thymosin  $\alpha$ 1 in patients with a high risk of recurrence after resection, who have been treated with antiviral therapy, and treatment with RFA and TACE for patients with intrahepatic RHCC (172) are examples of combination therapies that improve

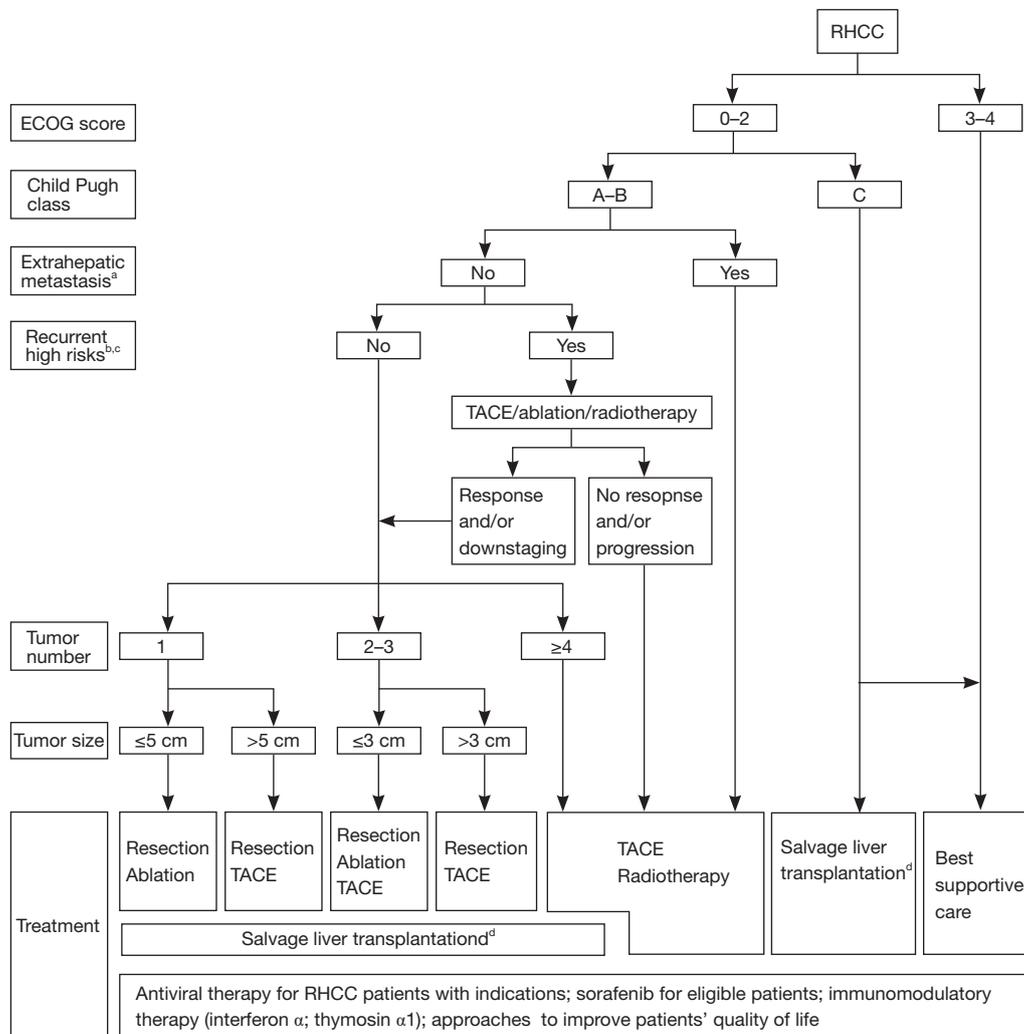
survival.

Based on opinions demonstrated above, a decision-making path for RHCC treatment is presented in *Figure 1*. This decision-making path is according to the National Health and Family Planning Commission of the People's Republic of China-Diagnosis, management, and treatment of HCC (V2017) (3).

A treatment decision for a RHCC patient should be prudent. PS and liver function need to be considered in the first place. Characteristics of the initial HCC are important factors. TACE, ablation or radiotherapy should be attempted at first, if a RHCC patient with recurrent high-risk factors which are recurrence interval from initial resection to recurrence <1 year; presence of vascular invasion and/or multiple tumors in the initial HCC from operation findings or pathological reports. According to mRECIST criteria, if RHCC shows no response and/or progression after TACE/ablation/radiotherapy, radical therapies may not benefit for these patients. When RHCC presents response and/or downstaging after TACE/ablation/radiotherapy, treatment decision should be based on the number and size of the RHCC. Since there are few studies on the treatment for RHCC patients with PVTT (PVTT), it is difficult to provide a recommendation for these cases. Hence, we generally reach a consensus that patients with PVTT are recommended to be treated according to the Chinese Expert Consensus on multidisciplinary Diagnosis and Treatment of HCC with Portal Vein Tumor Thrombus (2016 edition) (35). For RHCC patients whose liver function show Child Pugh class C, if their ECOG score are 0–2 and within specific enlistment criteria for liver transplantation (e.g., Milan criteria, Hangzhou criteria, Kyoto criteria, Kyushu University criteria, Up-to-seven criteria, UCSF criteria, etc.), salvage liver transplantation could be considered. Otherwise, best supportive care should be given to these patients. Besides, general therapies should be taken into consideration during the whole process of the treatment for RHCC patients. General therapies include antiviral therapy for patients with indications, sorafenib for eligible patients, immunomodulatory therapy and any approach to improve patients' quality of life.

### Future perspectives

It is necessary to reiterate that this consensus for RHCC management is in its initial version, and thus the evidence from several studies may not be strong enough. For



**Figure 1** Chengdu system on multidisciplinary management for recurrent hepatocellular carcinoma. <sup>a</sup>, patients with a single resectable extrahepatic metastatic RHCC, could benefit from resection. <sup>b</sup>, “recurrent high risks” indicates recurrence interval from initial resection to recurrence, which is less than 1 year; presence of vascular invasion and/or multiple tumors in the initial HCC from operation findings or pathological reports. Except for the “Recurrent high risks” which is about the characteristics of initial HCC, other conditions all represent characteristics of RHCC. <sup>c</sup>, patients with PVTT are recommended to be treated according to Chinese Expert Consensus on multidisciplinary Diagnosis and Treatment of Hepatocellular Carcinoma with Portal Vein Tumor Thrombus (2016 edition) (35). <sup>d</sup>, salvage liver transplantation could be performed based on patient’s tumor staging which is within specific enlistment criteria according to different liver transplantation centers. ECOG, Eastern Cooperative Oncology Group; RHCC, recurrent hepatocellular carcinoma; TACE, transarterial chemoembolization; PVTT, portal vein tumor thrombus.

researchers, especially Chinese researchers, to achieve proper RHCC management a standardized guideline based on the situation in China is indispensable. Additionally, with emerging evidence and many related RCTs in progress, we hope that this initial version of the consensus can be further revised and validated.

The following aspects should be considered for the clinical management of RHCC: (I) An MDT is important for HCC management. Through a collaborative and effective MDT, great progress could be made in the prevention and treatment of RHCC after resection, thereby improving the overall prognostic outcomes of

HCC patients; (II) the recurrence of HCC after resection prevents improvements in patient survival. The RFS and OS of patients are important indicators for the evaluation of curative effect. Efforts should also be made to improve the patients' quality of life even when they are living with tumors; (3) the incidence of RHCC after resection is high in China and the conditions are complicated. Thus, there is a need to conduct RCTs and validate more effective methods of RHCC management. Additionally, the establishment of an RHCC sample database is necessary to discover the intrinsic molecular mechanisms of the occurrence and dissemination of RHCC. Furthermore, explorations of molecular classifications, targeted therapies and related translational treatment approaches for of HCC could potentially provide more evidence for the accurate treatment and prevention of HCC in China.

### Acknowledgements

This article is supported by Chinese Society of Liver Cancer, Chinese Medical Doctor Association and Surgical Technology Innovation and Promotion Association, NAHIEM, China.

*Funding:* This work was in part supported by grants from the State Key Scientific and Technological Research Programs (2017ZX10203207-003-0020) and the Scientific and Technological Support Project of Sichuan Province (2018SZ0204, 2016SZ0025 and 2015SZ0049).

### Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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**Cite this article as:** Wen T, Jin C, Facciorusso A, Donadon M, Han HS, Mao Y, Dai C, Cheng S, Zhang B, Peng B, Du S, Jia C, Xu F, Shi J, Sun J, Zhu P, Nara S, Millis JM; MDT of West China Hospital. Multidisciplinary management of recurrent and metastatic hepatocellular carcinoma after resection: an international expert consensus. *HepatoBiliary Surg Nutr* 2018;7(5):353-371. doi: 10.21037/hbsn.2018.08.01