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Consensus Statement

Surgery for Intermediate and Advanced Hepatocellular Carcinoma: A Consensus Report from the 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014)

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Key Words
Hepatocellular carcinoma · Outcome · Staging system · Surgery

Abstract
Background: The Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy does not recommended surgery for treating BCLC stage B and C hepatocellular carcinoma (HCC). However, numerous Asia–Pacific institutes still perform surgery for this patient group. This consensus report from the 5th Asia-Pacific Primary Liver Cancer Expert Meeting aimed to share opinions and experiences pertaining to liver resection for intermediate and advanced

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HCCs and to provide evidence to issue recommendations for surgery in this patient group. ***Summary:*** Thirteen experts from five Asia–Pacific regions were invited to the meeting; 10 of them (Japan: 2, Taiwan: 3, South Korea: 2, Hong Kong: 1, and China: 2) voted for the final consensus. The discussion focused on evaluating the preoperative liver functional reserve and surgery for large tumors, multiple tumors, HCCs with vascular invasion, and HCCs with distant metastasis. The feasibility of future prospective randomized trials comparing surgery with transarterial chemoembolization for intermediate HCC and with sorafenib for advanced HCC was also discussed. The Child–Pugh score (9/10 experts) and indocyanine green retention rate at 15 min (8/10) were the most widely accepted methods for evaluating the preoperative liver functional reserve. All (10/10) experts agreed that portal hypertension, tumor size >5 cm, portal venous invasion, hepatic venous invasion, and extrahepatic metastasis are not absolute contraindications for the surgical resection of HCC. Furthermore, 9 of the 10 experts agreed that tumor resection may be performed for patients with >3 tumors. The limitations of surgery are associated with a poor liver functional reserve, incomplete tumor resection, and a high probability of recurrence. ***Key Messages:*** Surgery provides significant survival benefits for Asian–Pacific patients with intermediate and advanced HCCs, particularly when the liver functional reserve is favorable. However, prospective randomized controlled trials are difficult to conduct because of technical and ethical considerations.

Introduction

Hepatocellular carcinoma (HCC) is a major cause of cancer deaths worldwide. Despite the widespread implementation of prevention and screening programs, the incidence of HCC remains high, and mortality rates have not improved significantly [1]. The development of safer and more effective therapies (e.g., radiological intervention, external radiation, local tumor ablation, and targeted therapy for HCC) has been attempted. These treatments have improved patient outcomes; however, long-term survival is rare because of the high rate of tumor recurrence after treatment. To date, surgery remains the most effective treatment strategy.

Surgery is effective in treating extremely early and early stage HCCs. Surgery may yield a 5-year overall survival (OS) rate of 91.5% and 77.2% in patients with extremely early and early stage HCCs, respectively [2]. The treatment results of surgery are significantly more favorable compared with those of nonsurgical methods. The European Association for the Study of Liver/American Association for the Study of Liver Disease guidelines, based on the Barcelona Clinic Liver Cancer (BCLC) classification, clearly state that surgery is applicable for patients with single HCC and a completely preserved liver function without portal hypertension [3]. The Asian Pacific Association for the Study of the Liver guidelines for HCC also state that "liver resection is a firstline curative treatment of solitary or multifocal HCC confined to the liver, anatomically resectable, and with satisfactory liver function reserve" [4]. However, it remains unclear whether surgery is recommended for patients with intermediate and advanced HCCs with acceptable liver functional reserve.

When HCC is diagnosed in the intermediate and advanced stages, increased tumor size, multiple tumors, vascular invasion, and extrahepatic tumor spread lead to a higher probability of recurrence and are associated with decreased postoperative survival. Adverse outcomes of liver resection make it undesirable when the surgical risk is high. Based on the results of past randomized trials, transarterial chemoembolization (TACE) is recommended for patients with large and multinodular HCCs. Compared with conservative treatments,

TACE has been shown to improve survival in patients with unresectable HCC [5]. However, it remains unclear whether TACE or surgical resection provides the best outcome for intermediate HCC. Surgery is typically not recommended in patients with these conditions because of the increased risks and limited advantages. The survival benefit of sorafenib in advanced HCC has been evidenced in two double-blind randomized controlled trials (RCT)[6, 7]. Thus, sorafenib is currently recommended as the firstline treatment for advanced HCC. However, TACE and sorafenib are not curative, and long-term survival typically cannot be achieved with these treatments. Many patients who could benefit from radical resection are possibly excluded from surgery if only TACE and sorafenib are considered for intermediate and advanced HCCs. In selected cases of intermediate and advanced HCCs, liver resection may provide a cure without any major adverse effects [8, 9]. Based on encouraging experiences, numerous surgeries are performed for these patient groups if imaging reveals the scope for tumor removal. Guidelines published in the Asia–Pacific region recommend surgery as a treatment modality for patients with large, multiple HCCs and HCCs with vascular invasion, despite the lack of strong evidence [4, 10]. A discussion on the discrepancies between the guidelines and clinical practice is helpful for elucidating the role of surgery in treating intermediate and advanced HCCs and for developing more appropriate treatment strategies that yield the most favorable outcomes for this patient group.

Methods

Thirteen experts from five Asia–Pacific countries were invited to join the Consensus Development Committee of Surgery for Intermediate/Advanced Stage HCC. Eleven surgeons highly qualified in hepatobiliary surgery and liver cancer from 10 Asia–Pacific institutes (Japan: 2, Taiwan: 3, South Korea: 2, Hong Kong: 1, and China: 2) participated in the discussion, and the representatives of the 10 institutes voted for the final consensus. Questions associated with surgery for intermediate/advanced stage HCC were generated in accordance with the recommendations of the committee members prior to the meeting. The questions were categorized into evaluation of the preoperative liver functional reserve and surgery for large HCCs, multiple HCCs, HCCs with vascular invasion, and extrahepatic metastasis of HCC. Finally, the feasibility of conducting RCT for surgery in the treatment of intermediate and advanced HCCs was also discussed. Three consensus meetings were held during the 5th Asia-Pacific Primary Liver Cancer Expert Meeting (APPLE 2014). Moreover, preliminary answers obtained from a premeeting questionnaire and data from the committee members were presented in the first meeting. After a thorough discussion, the questions were modified and subjected to voting in the second and third meetings, respectively. A consensus and recommendations were developed when more than 80% of voters agreed upon a statement. The evidence level and recommendation strength, which were graded according to the system used in the management of *Helicobacter pylori* infection – the Maastricht IV/ Florence Consensus Report [11], were also assigned to each consensus statement.

Results

The voting results are listed in summary form in table 1. The consensus and recommendations are detailed as follows:

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Table 1. Summary of voting results (one voter each from 10 institutes in the Asia–Pacific region)

Question	Results (yes: no)	Consensus Reached
Methods routinely used for the measurement of liver functional reserve	Makuuchi criteria: 2 Volumetry: 6 Child–Pugh score: 9 ICGR-15: 8	No No Yes Yes
Is portal hypertension a contraindication for liver resection?	0: 10	Yes
Is tumor size >5 cm a contraindication for HCC resection?	0: 10	Yes
Is HCC number >3 a contraindication for surgical resection?	1: 9	Yes
Is portal venous invasion a contraindication for surgical resection?	0: 10	Yes
Is hepatic venous invasion a contraindication for surgical resection?	0: 10	Yes
Is extra-hepatic metastasis a contraindication for surgical resection?	0: 10	Yes
Do you think RCTs comparing liver resection and TACE are needed for intermediate stage (BCLC-B) HCC?	3: 7	No
Do you think RCTs comparing liver resection and sorafenib are needed for advanced stage (BCLC-C) HCC?	4: 6	No

Preoperative Liver Function Evaluation

Statement 1a: The Child–Pugh score and the indocyanine green retention rate at 15 min (ICGR-15) effectively predict the morbidity and mortality after liver resection for HCC. Computed tomography (CT) volumetry for evaluating the residual liver volume after resection should be conducted in patients with a marginal liver functional reserve.

Evidence level: 2b Grade of recommendation: B

Statement 1b: Platelet count $<100 \times 10^3$, controllable ascites, or treatable esophageal varices (EV) are not a contraindication for surgical resection.

Evidence level: 2c Grade of recommendation: B

The Child–Pugh score was initially developed for predicting the outcomes of surgery for bleeding EV. The score is now commonly used for predicting the prognosis of chronic liver disease and morbidity and mortality after liver resection. Many practice guidelines, including Cancer of the Liver Italian Program [12], BCLC, and Japan Integrated Staging [3, 13], incorporate the Child–Pugh score into multiple contemporary scoring systems for managing HCC and for selecting patients with a good liver functional reserve and lower portal pressure for more effective treatments. Almost all (9/10) committee members use the Child–Pugh score as a selection criterion for the surgical resection of HCC. However, patients with Child–Pugh A liver function have varying degrees of cirrhosis. Postoperative complications occur in patients with cirrhosis, even if the liver function status is Child–Pugh A. Methods for estimating the hepatic functional reserve after liver resection are required to devise a safe surgical plan. Furthermore, the ICGR-15 is a test reflecting the degree of sinusoidal capillarization; intrahepatic portovenous shunt; and, to an extent, alterations in liver blood flow [14]. In a prospective study, ICGR-15 successfully distinguished patients with and without the risk of surgical mortality [15]. The correlations of ICGR-15 with the level of postoperative hepatic dysfunction and morbidity have been previously reported [16]. Furthermore, compared with the Child–Pugh score, the ICGR-15 value may predict hospital mortality more effectively. Thus, in the Asia–Pacific region, the ICGR-15 test is commonly used alone or in combination with other liver function tests for predicting hepatic dysfunction or morbidity

after liver resection. A decision tree constructed using a combination of conventional liver function tests and the ICGR-15 test can yield a near-zero mortality rate of surgical resection for HCC [14].

In addition to liver function tests, the ratio of the residual liver volume to the total liver volume indicates the postoperative hepatic dysfunction after liver resection. The number of resected segments combined with the ICGR-15 value was identified as an independent predictor of hepatic dysfunction after liver resection [14]. Only limited resections can be performed in patients with ICGR-15 >20%. Moreover, the residual functional liver volume is frequently estimated based on the Couinaud classification. However, variations between patients and different segments result in inaccurate estimations. CT volumetry conducted based on the territory of the portal vein branch is helpful for evaluating the margin and volume of each segment. It is routinely performed by 6 of the 10 committee members for surgical planning. Other members do not routinely employ CT volumetry for preoperative assessments; however, they occasionally conduct the examination when the hepatic functional reserve is marginal or when planning living donor liver hepatectomies.

Portal hypertension with a hepatic venous pressure gradient (HVPG) of ≥10 mmHg in patients with cirrhosis increases the possibility of postoperative hepatic decompensation [17]. It has been suggested that surgical resection be restricted to HCC patients without portal hypertension. Recent evidence revealed that liver transplantation provides more favorable survival for patients with HCC with significant cirrhosis [18]. Recurrence-free survival is more favorable if patients undergo liver transplantation as the primary treatment. However, liver transplantation is technically demanding and not always applicable because of organ shortages. In carefully selected patients, the surgical resection of HCC still provides a significant survival benefit for patients with EV or with a platelet count of <100 000/μL in association with splenomegaly [19, 20]. Typically, HVPG is not routinely measured, but ICGR-15 values are a reliable surrogate marker for ruling out clinically significant portal hypertension and severe portal hypertension [21]. Liver resection may be performed safely in patients with portal hypertension and EV when the ICGR-15 value is deemed acceptable.

Surgery for Large HCCs

Statement 2: Surgical resection may be selected as the primary treatment (firstline treatment) for HCCs >5 cm, even in the presence of satellite nodules or vascular invasion.

Evidence level: 2b Grade of recommendation: B

Large HCCs are typically associated with a higher incidence of vascular invasion and metastasis and higher histological grades [22]. An increased tumor size is associated with poor postoperative outcomes of HCC. However, not all large HCCs are aggressive. Large HCCs can potentially be cured through a complete resection [23]. A 5-year OS rate of more than 50% may be achieved through surgery for tumors larger than 5 cm [22]. Postoperative disease-free survival and OS are similar between patients with large and small HCCs when the tumor is solitary [24]. All committee members agreed that a tumor size >5 cm is not a contraindication for the surgical resection of HCC. Surgery is recommended for large HCCs when the tumor is solitary and can be resected completely.

Vascular invasion, cirrhosis, satellite lesions, or multicentricity in patients with large HCCs result in poor survival [25]. In previous retrospective studies on the feasibility of surgery for large HCCs, patients undergoing surgical resection tended to have a solitary tumor, less vascular invasion, unilobar tumor extent, and a more favorable liver function. To reduce the bias caused by these confounding variables, an analysis after propensity score matching revealed that patients who underwent surgery had higher 1-, 2-, and 3-year OS rates compared with those who underwent TACE (69.7%, 58.6%, and 51.7% vs 40.2%, 33.9%, and 18.5%, respectively, p<0.001) in a cohort of patients with HCC ≥10 cm [26]. Furthermore, curative resec-

tion provided 5-year disease-free survival and OS rates of 12% and 47%, respectively, in patients with multiple tumors, and 12% and 27%, respectively, in patients with major portal vein thrombus when the primary tumor was ≥10 cm [27]. Most of the committee members (9/10) agreed that surgery may be selected as the primary treatment for HCC >5 cm, even if satellite nodules are present or vascular invasion is observed during imaging.

In addition to tumor characteristics, the resection margin is a major concern when selecting the type of surgery for large HCCs. A positive surgical margin is more likely to be associated with tumors that are centrally located and are closely adjacent to a major vessel [22]. It is occasionally not possible to define an adequate surgical margin and simultaneously preserve sufficient liver parenchyma. The effect of the surgical margin on HCC recurrence after resection of large HCCs is controversial. Furthermore, gross residual tumors after resection are a risk factor for poor survival in patients with large HCCs [23]. Previous studies have not reported a significant effect of the surgical margin on tumor recurrence and long-term survival in patients with large HCCs [22]. In these studies, noncurative resection was strongly associated with multiple tumors with portal vein thrombus. A survival benefit can be obtained only when the tumor does not have macroscopic tumor thrombus [28]. However, the histopathological detection of tumor at the surgical cut edge indicates recurrence at the section margin. Treatment after tumor recurrence may prolong patient survival. It is possible that tumor invasiveness, and not solely the section margin, determines the long-term prognosis of large HCCs. The committee members selected different primary treatments for large HCCs when resection can be performed only along the tumor margin (possible R1 resection: resection, 7; TACE, 3).

Surgery for Multiple HCCs

Statement 3a: Surgical resection for multiple HCCs may be performed when the liver function is well preserved and complete tumor resection can be achieved.

Evidence level: 2b Grade of recommendation: B

Statement 3b: The presence of more than three tumors is not a contraindication for the surgical resection of HCC.

Evidence level: 2b Grade of recommendation: B

Statement 3c: The presence of multiple HCCs involving both lobes of the liver is not an absolute contraindication for surgical resection.

Evidence level: 4 Grade of recommendation: C

Statement 3d: Satellite nodules are not a contraindication for surgical resection in patients with two or three primary tumors.

Evidence level: 5 Grade of recommendation: D

Multiple tumors are caused by intrahepatic metastasis or the multicentric occurrence of HCC. Surgery is one of the most effective treatment options. A 5-year OS rate of approximately 60% can be achieved using advanced surgical techniques and perioperative management in patients with well-preserved liver function [29]. In a large retrospective study conducted in Taiwan, surgery for multiple HCCs yielded a significantly higher survival rate than did TACE and the most favorable supportive care, even if the patients were stratified according to different staging systems [21]. In patients with two or three radiologically diagnosed small HCCs (size <5 cm) and no vascular invasion, the OS rate was significantly higher in the surgical resection group than in the TACE group (48.1% vs 28.9% at 5 years, $p<0.005$) [30]. Moreover, transplantation may be performed in this patient group. When the tumor number and size increase, liver transplantation becomes costly because of the shortage of donors and likely further recurrence after transplantation. Either surgical resection or TACE is selected for HCC beyond the Milan criteria when the liver functional reserve is acceptable. For

patients beyond the Milan criteria, surgery still yields a better survival rate than does TACE [21]. A consensus was reached (9/10) that multiple tumors are not a contraindication for the surgical resection of HCC, even when more than three tumors are present.

Complete tumor resection is crucial for the long-term survival of patients with multiple HCCs. Complete resection is possible when the tumors are located within one liver lobe (i.e., confined to the right or left portal vein territory). Surgery is often not recommended when tumors are present in both lobes of the liver because of the increased surgical risk and difficulties in complete resection. In addition, bilobar HCCs are typically associated with more satellite nodules and microscopic vascular invasion, which lead to poor postoperative outcomes [31]. An international cooperative study group on HCC comprising both Western and Eastern institutes reported that the tumor number and bilaterally distributed lesions are predictors of poor OS of HCC in univariate analysis. However, these factors were not significant in multivariate analysis. Instead, the alpha-fetoprotein level, tumor size, major vascular invasion, extrahepatic metastasis, and a positive surgical margin were the major predictors of poor outcomes [32]. The distribution of the tumor is possibly not associated with the survival of patients with multiple HCCs. In selected patients with low operative risk and satisfactory liver function, complete tumor resection in patients with bilobar disease may result in better survival rates than other nonsurgical therapies [33]. All committee members (10/10) agreed that surgical resection may be performed for bilaterally distributed HCC when two or three tumors are present. Nine of the 10 committee members did not consider bilaterally distributed HCC to be a contraindication for surgery when more than three tumors are present.

Satellite nodules, defined as tumors ≤2 cm in diameter and within 2 cm of the primary nodule, may reflect the dissemination of tumor cells from the primary tumor. A wider resection margin is typically recommended to ensure the complete resection of micrometastasis. When patients with multiple tumors present with satellite nodules, complete tumor resection is unlikely to yield beneficial results. All committee members (10/10) agreed that satellite nodules are not a contraindication for surgical resection in patients with two or three primary tumors. However, a consensus was not reached (7/10 agreed to perform resection) when satellite nodules were observed in patients with more than three primary tumors.

Surgery for HCC with Vascular Invasion

Statement 4a: Surgical resection may be performed for HCCs involving the ipsilateral portal vein.

Evidence level: 2b Grade of recommendation: B

Statement 4b: Main portal vein trunk thrombosis is not an absolute contraindication for HCC resection.

Evidence level: 4 Grade of recommendation: C

Statement 4c: Surgical resection may be performed in patients with hepatic vein and/or inferior vena cava (IVC) invasion when R0 resection is feasible.

Evidence level: 4 Grade of recommendation: C

Statement 4d: No definite survival benefit is obtained when the tumor thrombus extends to the right atrium.

Evidence level: 4 Grade of recommendation: C

Venous dissemination of tumor cells is a major route of HCC metastasis. It can occur even in small HCCs. The metastatic tumors, which are not preoperatively detected, may develop into "recurrent" lesions after resection of the primary tumor. Grossly identifiable vascular metastasis has been suggested as a contraindication for the surgical resection of HCC because complete resection of the metastatic tumors is questionable. Furthermore, targeted therapy is recommended for patients

with major venous invasion. The best survival rate was reported from a subgroup analysis in the SHARP trial, in which the median survival was 8.1 months for patients with portal invasion [34]. The extension of venous thrombosis results in poor prognosis. A 4.3-month median survival was reported for patients with tumor thrombus in the main trunk or first branch of the portal vein [35]. A 5-year survival rate of 7.6% was reported with a combination therapy of interferon- α /5-fluorouracil in 102 patients with advanced HCC and tumor thrombi in the major branches of the portal vein (Vp3 or Vp4) [36]. Further efforts are required to improve the prognosis of HCC patients with vascular invasion.

TACE is often conducted to treat HCCs with macroscopic venous invasion. A meta-analysis of eight controlled trials revealed that TACE significantly improved the 6-month [hazard ratio (HR), 0.41; 95% confidence interval (CI): 0.32–0.53; z, 6.28; p=0.000] and 1-year (HR, 0.44; 95% CI: 0.34–0.57; z, 6.22; p=0.000) survival of patients with portal vein thrombosis compared with conservative treatments [37]. Furthermore, TACE is significantly beneficial when the tumor thrombus involves only the segmental branches or above. The survival benefit existed even when the tumor thrombus extended to the superior mesenteric vein or inferior vena cava (IVC) [37]. TACE appears to be a promising treatment for HCC patients with vascular invasion.

In addition to TACE, surgery has been attempted to remove all tumors detected during imaging in patients with vascular invasion [8]. In a previous study detailing the technique of removing tumor thrombus in the portal vein, 1-year and 3-year survival rates of 52% and 11.6%, respectively, were unexpectedly found [38]. However, the role of surgery in advanced HCC with venous invasion was insufficiently defined. When portal venous thrombus is confined to the first or second branch of the main portal vein, complete tumor resection and tumor thrombectomy may result in 3- and 5-year OS rates of 22.7% and 18.1%, respectively. When the tumor thrombus extends into the main portal vein trunk, the 3- and 5-year survival rates decreased to 5.7% and 0%, respectively [8]. These rates, although unsatisfactory, are better than those reported for patients who received targeted therapy. In a retrospective study analyzing the treatment results of patients with tumor thrombus invading the main trunk, the first-order branch of the portal vein, or the IVC, the 5-year OS rate after hepatectomy was 20%, which is better than that of patients who underwent TACE alone. The survival benefit was even more significant in patients with a satisfactory response to TACE who underwent a subsequent tumor resection [39]. Resection for HCC with portal venous thrombus, compared with case-matched controls who received TACE, revealed a significant survival benefit when the tumor thrombus was limited to the right, left, or segmental portal venous branch [40]. The advantage of surgical resection diminished when the tumor extended to the main portal vein branch and superior mesenteric vein. All committee members (10/10) agreed that macroscopic tumor thrombus in the portal vein branch and main portal vein trunk is not an absolute contraindication for HCC resection. A consensus was not reached when the tumor thrombus extended to the contralateral portal vein. Seven of the 10 committee members do not perform surgical resection for HCC with contralateral portal vein thrombosis.

Hepatic vein invasion is a predictor of extrahepatic metastasis of HCC [41]. Surgical resection was not recommended for HCCs with macroscopic hepatic vein or vena cava invasion because of the high 90-day mortality rate (28%) and limited life expectancy (3–5 months) [42]. However, in selected cases, surgery still provides a survival benefit for this patient group. When the tumor thrombus is limited to the peripheral hepatic vein or main hepatic vein, patients who undergo complete tumor resection may have a median survival of 5.27 years or 3.95 years, respectively [43]. IVC tumor thrombus is associated with a higher risk of

tumor recurrence and poor patient survival. However, surgery still provided survival benefits in patients with a favorable hepatic functional reserve [43]. A consensus was reached (10/10) regarding HCC invasion to the hepatic vein and/or IVC not being a contraindication for surgical resection. The resection of HCC with tumor thrombus extending into the right atrium is limited to case reports. Early recurrence within 6 months occurred in almost all patients, even if the patients underwent complete tumor resection [44]. However, surgical resection of metastasis to the right atrium may relieve associated symptoms. Seven of the 10 committee members do not perform surgery for HCC with right atrium invasion.

Surgery for Distant Metastasis of HCC

Statement 5: Surgical resection may be performed for both intra- and extrahepatic HCCs when they are controllable and localized, respectively. Intrahepatic HCC progression and metastases involving more than one organ are contraindications for surgical resection.

Evidence level: 2b Grade of recommendation: B

Extrahepatic metastasis of HCC implies a systemic spread of tumor cells. The most frequent sites of extrahepatic metastasis of HCC include the lung, followed by the bone, brain, and adrenal gland. The survival of patients with extrahepatic metastasis has been poor because the condition was considered incurable, and limited treatments were administered to these patients [45]. Most patients with advanced intrahepatic disease and extrahepatic metastasis die of progressive intrahepatic disease, but not because of extrahepatic metastasis. Multidisciplinary treatments combining therapies for both intrahepatic HCC and localized extrahepatic metastasis have been recommended to improve the OS rate [46]. Moreover, when extrahepatic metastasis occurred in the adrenal gland, patients who underwent local resection and TACE had longer survival than patients who received chemotherapy, radiotherapy, or supportive care alone [45]. Patients with longer disease-free intervals and fewer pulmonary metastases can benefit from pulmonary metastasectomy of HCC [47].

Uncontrollable intrahepatic lesions, the extent of vascular invasion, and the performance status are independent predictors of poor prognosis of HCC with extrahepatic metastasis [48]. The survival of HCC patients with extrahepatic metastasis may be improved significantly if the intrahepatic lesions exhibit a partial or complete response postoperatively; a median survival of 521 days may be achieved compared with 170 days for patients without an objective tumor response [49]. All committee members agreed that HCC resection may be performed when extrahepatic metastasis is localized. Intrahepatic lesions are not a contraindication for surgery, except when intrahepatic HCCs are progressing or metastases involve more than one organ.

Future Clinical Trials

To date, surgical resection has been recommended for treating selected patients with BCLC intermediate or advanced HCCs in many institutes in the Asia–Pacific region. Several agreements were reached, but disagreements persist. Because strong evidence is lacking, a well-designed prospective randomized controlled study is required to provide a solid base for treatment recommendations. When a clinical trial examining intermediate and advanced HCCs is planned, patients assigned to the control arm should receive a standard-of-care therapy; in brief, chemoembolization and sorafenib should be administered to patients with intermediate and advanced HCC, respectively [50]. Certain crucial factors should be considered prior to conducting the trials: (1) Surgery is the only treatment able to achieve long-term survival in certain cases of intermediate and advanced HCCs, although the survival difference may not be statistically significant. Patients may be holding out for a cure, even when the pos-

sibility is low. It is difficult to randomize all patients into groups undergoing surgery or TACE or receiving sorafenib. (2) The resectability of HCCs is determined based on the balance between surgical risks and survival benefits, and both factors are difficult to quantify with precision. Resection may not be feasible for patients assigned to the surgical arm. In addition, it is unethical to include only patients with resectable HCC, because previous reports have sufficiently shown the survival benefit of surgery in the treatment of intermediate HCCs [9]; however, a selection bias may exist. (3) Patients with intermediate and advanced HCCs occasionally require multimodality treatment, which may include surgery and TACE, sorafenib and TACE, or sorafenib and resection. To obtain the best treatment outcomes, no treatment modality should be precluded from the trial. Allocating patients to a purely surgical or nonsurgical group is difficult. Thus, only a few committee members consider a prospective randomized controlled trial comparing surgery and TACE and sorafenib in BCLC stage B (3/10) and C (4/10) HCC to be feasible.

Summary

BCLC intermediate and advanced HCCs have different clinicopathological characteristics that may predict a higher possibility of tumor recurrence and poor postoperative survival. Strong evidence supports the use of TACE and targeted therapy for ensuring the most satisfactory patient outcomes. Surgery is not recommended because of greater complications and unproven survival benefit. With the advancement of surgical treatments and significantly reduced surgical complications, sufficient evidence has accumulated to support the advantages of surgery in treating intermediate and advanced HCC patients. However, prospective RCT are unavailable. Surgery can cure patients with a satisfactory liver functional reserve and with less aggressive tumors. Additional clinical characteristics (e.g., tumor location, distribution, and serological and image markers) that may predict the radicality of resection may be incorporated into the staging system to select patients who may benefit from surgery. In conclusion, guidelines for HCC treatment should consider the favorable outcomes of liver resection for treating intermediate and advanced HCCs. Indications for hepatectomy should be expanded so as not to exclude patients from radical therapies that can improve patient outcomes.

Conflicts of Interest:

None of the authors report any conflicts of interest.

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