REVIEW

Update in management of hepatocellular carcinoma in Eastern population

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Abstract

Hepatocellular carcinoma (HCC) is one of the commonest malignant tumours in the East. Although the management of HCC in the West is mainly based on the Barcelona Clinic for Liver Cancer staging, it is considered too conservative by Asian countries where the number of HCC patients is huge. Scientific and clinical advances were made in aspects of diagnosis, staging, and treatment of HCC. HCC is well known to be associated with cirrhosis and the treatment of HCC must take into account the presence and stage of chronic liver disease. The major treatment modalities of HCC include: (1) surgical resection; (2) liver transplantation; (3) local ablation therapy; (4) transarterial locoregional treatment; and (5) systemic treatment. Among these, resection, liver transplantation and ablation therapy for small HCC are considered as curative treatment. Portal vein embolisation and the associating liver partition with portal vein ligation for staged hepatectomy may reduce dropout in patients with marginally resectable disease but the midterm and long-term results are still to be confirmed. Patient selection for the best treatment modality is the key to success of treatment of HCC. The purpose of current review is to provide a description of the current advances in diagnosis, staging, pre-operative liver function assessment and treatment options for patients with HCC in the east.

Key words: Hepatocellular carcinoma; Liver cirrhosis; Treatment; Management; Evidence; Survival; Update

Core tip: Management of hepatocellular carcinoma (HCC) has changed significantly over the past several decades. However, the management of patients has yet to be standardized. As a result of high prevalence of hepatitis B infection in Asia, the experience of the East helped to develop a more aggressive management algorithm. There has been a lot of advancement in terms of diagnosis, management algorithm, staging and treatment methods. This paper will give an update on the management of HCC in the eastern population.

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the third most common cause of cancer-related deaths worldwide[1]. Because of the high prevalence of hepatitis B virus infection[2], countries in Eastern and Southeast Asia have the highest incidence of HCC in the world[3]. However, the management of patients with HCC has yet to be standardized in aspects of diagnosis, staging and treatment. Although the management of HCC in the West is mainly based on the Barcelona Clinic for Liver Cancer (BCLC) staging[4], it is considered too conservative by Asian countries. With advancement in diagnosis, staging and treatment, management algorithm of HCC is further modified. The aim of the present review is to provide a summary and update for clinical practice to determine the most appropriate treatment for HCC patients.

DIAGNOSIS

With clinical suspicion or screening, the diagnosis of HCC is based on laboratory tests, radiological imaging and, where appropriate, liver biopsy. The American Association for the Study of Liver Disease (AASLD)[5] diagnostic algorithm is widely used for surveillance and diagnosis. In short, nodules less than 1 cm which cannot be precisely characterised in ultrasound are subjected to interval scan. Nodules detected at ultrasound with diameter greater than 10 mm are further investigated with contrast computed tomography (CT) or magnetic resonance imaging (MRI). Nodules with typical feature of arterial enhancement and porto-venous washout are treated as HCC[6].

MRI was reported to have a higher sensitivity compared with CT[7]. In cases in which the diagnosis is uncertain, a serum alpha-fetoprotein (AFP) level > 400 ng/mL has a high positive predictive value[8]. The sensitivity of MRI scan with contrast ranged from 33% to 61.7% according to different studies targeted for lesions smaller than 2 cm[9]. In order to provide better results, the use of gadoxetic acid-enhanced MRI as an investigation tool has been widely investigated. The initial result of Primovist base MRI showed an improved sensitivity from 64% to 86%[10].

Dual tracer positron emission tomography (PET)-CT with ^{11}C-acetate and ^{18}F-fludeoxyglucose (FDG) markers was reported to have high sensitivity and specificity for diagnosis of HCC. The liver helps to maintain glucose homeostasis[11] and there are a variety of different levels of glucose-6-phosphatase activity and glucose transporters in HCC[12-14]. It was reported that well-differentiated HCCs preferentially accumulate ^{11}C-acetate[15] and poorly differentiated tumours tend to preferentially accumulate FDG. Ho *et al*[15] found dual-tracer PET-CT to have a sensitivity of 98% and a specificity of 86% which were considered significantly improved to other imaging modality alone[16]. Apart from higher sensitivity, the ^{18}F-FDG tracer played an additional role in providing prognostic indicators to lesion with poorly differentiated HCCs[17].

Tumour biopsy can be done if non-invasive studies failed to characterize the lesion.

Diagnostic strategies vary between guidelines, *e.g.*, European Association for the Study of the Liver[18] and AASLD[19], but the process is generally determined by the size of liver nodules. The recently developed technique of dual-tracer PET-CT may help for atypical lesions.

Knowing that in around 30% patients with HCC, the AFP level remains normal, a high index of suspicion is crucial particularly in area like Southeast Asia where hepatitis B is endemic.

STAGING

Cancer staging is the process of determining the extent to which a cancer has developed and help to select the most appropriate treatment for any particular stage of disease[20]. The prognosis and treatment outcome of HCC is related with tumour staging, liver function and patient's physical status[19]. The BCLC staging system[21] and the newly developed Hong Kong Liver Cancer (HKLC) staging system[22] addresses all these factors. A number of other staging systems for HCC are available, *e.g.*, TNM system[23], The Cancer of Liver Italian Program[24], Okuda staging system[25], *etc.*, but they only included some of these related factors.

In Eastern Asia where the highest incidence rates (> 20/100000 per year) of HCC occur, hepatitis B infection accounts for 70% of HCC cases[26]. While in Europe and North America where lower incidence rates (< 5/100000 per year) of HCC, hepatitis C and alcohol are the major etiologies. In view of the difference in epidemiologic and clinical characteristics, different therapeutic approaches were developed in the East and West centres[4,22,27,28]. Indeed, until recently, studies comparing treatment outcomes of eastern and western experiences with HCC are lacking.

The BCLC is widely used and quoted in the literature. However, it was derived from analysis of cohorts involving mainly Caucasian and may work better in Caucasian populations[29-31]. In Asia, more aggressive treatment options were recommended especially for BCLC intermediate- and advanced-stage patients[32,33]. The differences of treatment algorithms of APASL guideline, Japan Society of Hepatology guidelines, HKLC and BCLC staging systems were summarized in Table 1. These guidelines are followed by the corresponding community. However, the comparison between treatment outcomes following different algorithms is subjected to future study.

Recently, a new HCC classification system has been proposed in Hong Kong in order to provide a better guideline in area where the proportion of HCC and cirrhosis is higher. Although BCLC staging had fairly good discriminatory power in the test set, HKLC staging was significantly better than BCLC staging statistically in stratifying HCC patients into different prognostic groups. Overall, our HKLC treatment algorithm yielded

Table 1 Comparison between treatment algorithms of Asian guidelines for hepatocellular carcinoma and Barcelona Clinic for Liver Cancer staging system

	The HKLC staging system[22]	The JSH guidelines[28]	The APASL guidelines[27]	The BCLC staging system[4]
Parameters included	Performance status Liver function Vascular invasion/metastases Tumour staging	Liver function Vascular invasion/metastases Tumour staging	Liver function Vascular invasion/metastases Tumour staging	Performance status Liver function Vascular invasion/metastases Tumour staging
Definition of vascular invasion	Extrahepatic vascular invasion: main portal vein and inferior vena cava invasion	Portal vein invasion categorized into Vp1-4	Invasion to hepatic/portal vein branches	Portal vein invasion considered as advanced stage
Definition of tumour staging	3 categories: early, intermediate, locally advanced	Categories according to number and size	3 categories: resectable, non-resectable within Milan criteria, non-resectable exceeding Milan criteria	5 categories: very early, early, intermediate, advanced and terminal stages
Criteria for resection	Early tumour, Child A/B and intermediate tumour Child A Left or right portal vein invasion can be considered for resection	Any resectable HCC	Resection can be considered for number ≥ 4 although TACE is the first choice HCC with portal invasion at second or more peripheral portal branch can be considered for resection	Only solitary HCC or 3 nodules < 3 cm are subjected to resection

HKLC: Hong Kong Liver Cancer; JSH: Japan Society of Hepatology; BCLC: Barcelona Clinic for Liver Cancer; HCC: Hepatocellular carcinoma; TACE: Transarterial chemoembolization; APASL: The Asian Pacific Association for the Study of the Liver.

better survival outcomes when compared with the BCLC treatment algorithm, as evidenced by the hypothetical survival curves. The effectiveness of the HKLC treatment guidelines *vs* the BCLC treatment schedule has been clearly observed in the aforementioned patient subsets.The Hong Kong group showed better survival outcomes can be achieved if these patients received a more radical approach of therapies[22].

LIVER RESECTION

Pre-operative patient evaluation and case selection

Liver resection follows the basic principle of surgery. The patients have to be fully assessed for performance status and anaesthesiology fitness together with the tumour status including the tumour locations. Although BCLC criteria do not suggest liver resection for Stage B disease which comprise of tumour larger than 5 cm in size, many centres in Asia does not consider tumour size as an absolute contraindication to surgery. In many of the Asian centres including Hong Kong will consider hepatectomy for HCC as long as there is no extrahepatic disease or multifocal diffuse disease[34].

The other factor that affects liver resection is liver function reserve assessment. More than 80% of patients with HCC are hepatitis B carrier and around half of these patients have different degree of cirrhosis. It is important that patients with poor liver function reserve should not receive excessive removal of liver parenchyma in order to avoid postoperative liver failure. In general only selected patients with Child A cirrhosis should be considered for major hepatectomy[35]. In addition, several adjuvant investigations are crucial as part of preoperative liver function assessment.

Indocyanine green clearance test: Indocyanine green (ICG) is a dye which binds completely to albumin and β-lipoprotein and is exclusively removed by the liver and excreted unchanged in bile without any entero-hepatic circulation[36]. The ICG retention at 15 min (ICGR-15) can be measured with serial blood sampling or pulse spectrophotometry methods[37,38]. ICGR-15 is about 10% in normal person. It was shown to be correlated with hospital mortality so that it was recommended that ICGR-15 for a safe major and minor hepatectomy are 14% and 22%, respectively[35].

Imaging-based volumetry: Liver volumetry is most commonly estimated with 3-D volume CT calculation[39]. The post-operative residual liver volume [future liver remnant (FLR)] can be calculated based on cross-imaging techniques, on each slice FLR are outlined and integrated[40]. The estimated standard liver volume (ESLV) can be calculated with a formula based upon regression analysis of normal population in which body weight and height are included[41,42]. The FLR-to-ESLV ratio was shown to have inverse correlation with increasing risk for post-hepatectomy liver failure and post-operative death.

The critical residual liver volume for patients with normal liver had been reported to be 20%-30% according to different authors[43-47]. In general FLR > 20% is considered safe and with low risk of postoperative hepatic dysfunction[46]. However, most HCCs are associated with cirrhotic liver or diseased liver. The safety of surgical resection is greatly determined by the degree of liver dysfunction due to the underlying liver disease[48,49]. In literature, it is generally accepted that the FLR required is considerably larger than those with a normal liver, given the impaired baseline function of hepatocytes. It was

reported that FLR > 30%-50% are considered safe for patients with diseased liver[50-52].

SURGICAL RESECTION

The aim of hepatectomy is to obtain radical resection with adequate liver reserve. When performed in specialised centres, hepatectomy can achieve 5-year survival above 50%[53]. In the more aggressive APASL guideline, the only contraindication to resection is the presence of distant metastases, main portal vein or inferior vena cava involvement[27]. Even for advanced tumour > 5 cm or multinodular (> 3 nodules), a 5-year survival of 39% was reported[34] comparing with 5-year survival for transarterial chemoembolisation (TACE) was only 6%-19%[54-56]. While following the BCLC protocol, patients with multinodular tumours would be excluded for surgical resection. Vascular invasion was associated with poor prognosis in untreated patients[4]. As liver transplant is contraindicated and TACE or systemic therapy is ineffective, surgical resection remains the only possible curative treatment in patients with good liver reserve. Five years survival of patients with portal vein thrombus underwent liver resection was reported to be 26%-42%[57,58].

Conventionally, liver resection is mainly carried by open approach. In recent years, laparoscopic liver resection for cancer has gaining popularity and many results showed that minimally invasive approach can produce equally good oncological outcome even in patients with liver cirrhosis for minor hepatectomy[59].

Laparoscopic hepatectomy was initially adopted to treat peripheral, benign tumour in a normal liver. Multiple series showed the feasibility of its application for HCC[60]. However, patient selection needs to be careful. Some technical manoeuvres frequently used in open hepatectomy, such as organ mobilization, control of vascular inflow, and hanging manoeuvre are difficult in laparoscopic setting and controlling haemorrhage is also difficult. The Louisville consensus suggested that the laparoscopic approach to left lateral sectionectomy should be considered standard practice[61].

PORTAL VEIN EMBOLISATION AND THE ASSOCIATING LIVER PARTITION WITH PORTAL VEIN LIGATION FOR STAGED HEPATECTOMY

Hepatectomy is the only option for long term survival for many patients with HCC. However, the resectability rate for HCC is approximately 20%-30% with normal liver, and further reduced in patients with cirrhotic liver[62]. Portal vein embolisation (PVE) is one of the methods to stimulate growth of the FLR. Kinoshita *et al*[63] reported the first preoperative PVE in 1986. Various techniques for PVE were reported and percutaneous transhepatic technique has become the standard technique for PVE.

The mean period between PVE and hepatectomy was reported to be 37 d (range: 21-84 d) and the mean hypertrophy rate of FLR was reported to be 38%[64]. On the other hand, approximately 10% of patient cannot have the surgery performed because of failure of PVE, inadequate hypertrophy, complication leading to unresectability and local tumour progression[64].

The associating liver partition with portal vein ligation for staged hepatectomy approach associates in-situ splitting to portal vein ligation. It has been shown to be effective for the induction of rapid FLR hypertrophy so as to improve the respectability[65]. It was proposed that the portal flow deprivation in future resected liver and accentuated inflammatory response induces faster regeneration compared to traditional portal vein occlusion methods[66]. Therefore, the approach may reduce dropout in patients with marginally resectable disease but the midterm and long-term results are still to be confirmed.

LOCAL ABLATION THERAPY

Local ablation therapy is used in patients with early-stage HCC who are not suitable for surgical resection[67]. The currently preferred methods included radiofrequency ablation, microwave ablation and High Intensity Focused Ultrasound (HIFU).

Radiofrequency ablation (RFA) utilises alternating electrical current with a frequency 200 k-20 MHz in the range of radio-waves and causes coagulative necrosis and tissue desiccation[68]. RFA has largely replaced percutaneous ethanol injection because it produces better recurrence-free survival and requires fewer treatment sessions[69]. RFA can be performed percutaneously under image guidance or during surgery guided by intraoperative ultrasound. Complete ablation of small lesions is possible in more than 90% of cases[70]. The overall 5-year survival rates between 33% and 55% in selected series[71]. and lower mortality and morbidity rates were reported[72]. Therefore, RFA is considered as an alternative to resection especially for small HCC. Three randomized controlled trials are available comparing hepatic resection and RFA[73-75]. Although they reported conflicting results, it seems reasonable to offer RFA to very small HCC (< 2 cm) with no technical contraindications[76]. Except for the use of RFA on solitary tumours, multifocal tumour prevalence was also high in ablated patients. Rather than competing techniques, RFA can sometimes be combined with hepatectomy tailored to suit the anatomical condition.

Microwave ablation (MWA) utilizes electromagnetic methods for tumour destruction with frequency $\geq$ 900 MHz[77]. Microwave ablation can achieve higher temperature[78] shorter ablation time[78-81] and does not require the placement of ground pads. Several studies[82-84] showed that the local tumour control, complications and long-term survival were equivalent for RFA and MWA in the treatment of HCC.

HIFU is a non-invasive modality that uses an

extracorporeal source of focused ultrasound energy[85]. It is able to induce coagulative necrosis in selected tissues. HIFU ablation utilizes a unique frequency of ultrasound wave of 0.8 to 3.5 MHz, which can be focused at a distance from the therapeutic transducer. The accumulated energy at the focused region induces necrosis of the target lesion by elevating the tissue temperature to above 60 ℃. Temperature outside the focus point remains static as particle oscillation remains minimal. As ultrasound energy travels much better in water than in air, the presence of ascites in HCC patients actually facilitates energy propagation to the target HCC. Passage of energy without the puncture of a physical instrument and its superior performance in patients with ascites give HIFU ablation superiority over other treatment modalities for HCC. Initial results of HIFU ablation in the management of HCC were promising with a complete ablation rate of 28.5% to 68% for single treatment[86]. This non-invasive approaches has shown to produce very little collateral damage to the normal liver parenchymal in patients with cirrhosis and is well tolerated even in selected patients with Child Pugh C liver cirrhosis. HIFU was also shown to be safe and effective to reduce the drop-out rate of liver transplant candidate[87].

LIVER TRANSPLANTATION

Liver transplantation treats HCC together with the underlying liver disease. The Milan criteria (single tumour ≤ 5 cm, up to 3 tumours each ≤ 3 cm in diameter) is the gold standard for selection of deceased donor liver transplantation (DDLT). The disease-free survival at 4 years for patients within the criteria was reported to be 92%[88]. Many centres extended the criteria as evidence showed that patients outside the Milan criteria also have favourable outcomes after liver transplantation. In the west, the University of California, San Francisco criteria (single tumour ≤ 6.5 cm, up to 3 tumours at most with the largest ≤ 4.5 cm, and total diameter ≤ 8cm) had been shown with comparable outcome with Milan criteria[89]. Asian centres extended the HCC transplant criteria further because the majority of liver grafts were from living donor[90-93]. Living donor organ is considered a "gift" and there is less societal concern of equity[94].

In Asia, the organ donation rates remain the lowest worldwide[90]. As a result, living donor liver transplantation (LDLT) comprises the major workload and becomes an important treatment option for managing HCC in Asia. The overall survival rates were shown to be the same with studies comparing outcomes of DDLT and LDLT[95-99].

In view of the shortage of donated organ in Asia, multiple strategies had been developed, including using marginal livers, domino donors, and split liver transplant. Also bridging therapy with ablative and transarterial interventions aims to prevent tumour progression[100]. However, in survey up to 2005, 96% of liver transplant for HCC in Asian centers were from live donors[90].

TRANSARTERIAL LOCOREGIONAL THERAPY

TACE is the most widely used treatment for HCCs which are unresectable or cannot be effectively treated with percutaneous intervention for over 3 decades[54,101,102]. During the procedure, iodized poppy seed oil (lipiodol) and chemotherapeutic agents are administered through the feeding artery of the tumour, followed by arterial embolization. TACE results in delay tumour progression and vascular invasion and result in a survival benefit compared with conservative management. The most important aspect is the selection of patients, *i.e.*, patients should have preserved liver function, with no portal vein thrombosis and extrahepatic spread. A meta-analysis of six trials found a survival benefit for TACE over conservative management[101]. Two-year survival rates were reported as 31% *vs* 11% for conservative treatment[54]. TACE can be combined with other ablative therapies such as RFA[103,104].

The use of drug eluting bead (DEB) in TACE was reported in 2007[105,106] for its safety and efficacy. Microspheres composed of synthetic polymers or natural materials such as albumin, gelatine, chitosa or aliginate roughly fall into two categories - 15-60 μm and 100-250 μm[107]. Drugs included doxorubicin, mitomycin C, cisplatin, *etc.*, can be loaded to the beads[107]. DEBs have potential to simplify and standardize the TACE procedure by preloading the embolic with drug followed by controlled drug elution in target tissue[107]. A randomized controlled trial in 212 patients with HCC demonstrated that DEB-TACE is better tolerated than conventional lipiodol-based TACE, but this trial failed to demonstrate superiority in tumour response[108].

Transarterial radioembolization (TARE) using yttrium-90 microspheres can be used for patients with portal vein thrombosis[109-115]. Tumoricidal radiation doses are delivered with minimal toxicity to functional liver and there is minimal to moderate embolization (micro-embolization) and minimal alteration in vascularity with TARE. Several authors have compared outcomes following TACE with TARE in matched patient cohorts, and reported comparable efficacy for TACE and TARE in terms of tumour response and overall survival[116-119]. However, randomized controlled trials comparing their efficacy with other therapies are lacking[120].

SYSTEMIC THERAPY

Systemic chemotherapy had a disappointing record in management of HCC[121]. With recent knowledge of hepato-carcinogenesis, there has been encouraging development in target therapy of advanced HCC. Sorafenib is an oral multikinase inhibitor that has activity against several serine/threonine kinases and tyrosine kinases. It was the first systemic therapy shown to prolong survival in patients with HCC, and is approved for use in advanced HCC[122]. The Sorafenib HCC Assessment Randomized

Protocol trial[123] is a large, placebo-controlled phase Ⅲ trial in patients with advanced HCC and preserved liver function (Child-Pugh class A). It demonstrated prolonged median survival for approximately 3 mo in sorafenib group. Cheng *et al*[124] in another study involving 271 Asian patients showed a 2 mo prolongation in survival in patients with advanced HCC. Many other novo agents were being investigated at the moment but it was only Sorafenib that has demonstrated the effect of providing significant longer overall survival.

CONCLUSION

Management of HCC has changed significantly over the past several decades. However, the management of patients has yet to be standardized. As a result of high prevalence of hepatitis B infection in Asia, the experience of the East helped to develop a more aggressive management algorithm. To ensure the most effective treatment to be offered for HCC patients, a good patient selection for the right modality need to be practised.

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