REVIEW

Towards the optimization of management of hepatocellular carcinoma

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Abstract **Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world, closely correlated with viral hepatitis and liver cirrhosis. The vast majority of HCC patients present at a late stage and are unsuitable for surgery due to limited liver functional reserve. Tumors can involve major vessels or hilar structures, necessitating major liver resection and/or rendering liver resection unfeasible. A series of new technologies have been developed to optimise HCC management. Stem cell therapy improves impaired liver functional reserve prior to liver resection. Intravascular radiofrequency ablation recanalises the portal vein invaded by tumour thrombus and endobiliary radiofrequency ablation restores and extends biliary patency of the bile duct invaded by malignancy. Laparoscopic radiofrequency assisted liver resection minimizes blood loss and avoids liver warm ischemia, while increasing parenchymal sparing. These benefits combined maximize the safety of liver resection.**

Keywords management; hepatocellular carcinoma (HCC); radiofrequency (RF) ablation; laparoscopic liver resection; stem cell; intravascular RF ablation; endobiliary RF ablation

Introduction

Hepatocellular carcinoma (HCC) is the most common primary malignancy of the liver, which accounts for between 85% and 90% of primary liver cancers [1]. Also, it is the fifth most common neoplasm in the world and the third most common cause of cancer-related death [2]. HCC is seen in patients with chronic hepatitis B virus (HBV), hepatitis C virus (HBV) infection, or with long standing alcohol abuse. The prevalence of liver cirrhosis in HCC is about 80%–90% [3]. As a result, a considerable part of the HCC patients' liver functional reserve is limited.

It is well documented that a strong association exists between viral hepatitis and HCC. Ideally, all patients should be vaccinated for viral hepatitis to prevent HCC and surveillance for HCC should be offered to patients with existing infection to detect the disease at an early stage. In a single randomized controlled trial of 6-monthly surveillance with alphafetoprotein (AFP) and ultrasound, Zhang et al. [4]

reported that HCC related mortality was reduced by 37% in the surveillance group compared with the non surveillance group. Similarly, Kuo et al. [5] showed that overall survival was improved in patients in the surveillance group (3-year survival rate: 59.1% versus 29.3%, $P < 0.001$).

Due to lack of early symptoms, patients with HCC present usually at a late stage. HCC is detected after the onset of symptoms and has a dismal prognosis with a 5-year survival of only 0–10% [1]. In contrast, HCC detected at an early stage has a good prognosis with a 5-year survival of more than 50%, following liver resection or liver transplantation [6–8]. However, the vast majority of patients with HCC present at a late stage with poor liver function. In addition, tumor can involve a major vessel necessitating major liver resection requiring resection of a significant amount of hepatic parenchyma. As a result, there is an increased risk of postoperative liver dysfunction or failure which renders liver resection non-feasible. Furthermore, vascular invasion and biliary obstruction by the tumor involving hilar structures often makes liver resection impossible.

However, with the emergence of new equipment and techniques the once impossible task has become achievable. Here we discuss progress towards optimization of the management of HCC.

Intravascular radiofrequency ablation

The liver is supplied by both the portal vein (PV) and the hepatic artery (HA). Liver tumors, whether primary or metastatic, are mainly supplied by the hepatic artery. Therefore, deprivation of the arterial supply of the tumor can cause significant necrosis of the tumor tissue or retard tumor growth [9]. Currently available techniques to occlude arterial blood supply of the tumor rely on the intravascular delivery of embolic material, with or without the use of combined chemotherapy. At present, transarterial chemoembolization (TACE) is widely used as a standard treatment for patients with unresectable HCC or metastatic tumors [10]. However, one recognized disadvantage of using embolic material is the risk of collateral damage to non-target tissue resulting in morbidity for this therapeutic strategy [11]. Non-selective embolization of the liver can lead to severe complications, such as liver failure, cholecystitis and upper gastrointestinal bleeding. To increase precision of the occlusion of tumor blood supply and decrease the risk of injury to the non-target tissue, the Habib™ VesCoag has been invented. VesCoag is a bipolar radiofrequency (RF) endovascular catheter (5 F, length 110 cm) designed for insertion over a standard guide wire (0.014 inch) into either an artery or vein. At the tip of the catheter are two stainless steel ring electrodes. When activated in bipolar mode, a high frequency current runs between these two ring electrodes to coagulate the blood vessel wall so that it is occluded (Fig. 1). VesCoag can also be used in monopolar mode, but a patient grounding pad would then be required. Under fluoroscopic control, VesCoag was manipulated into the target vessel and the RF generator activated at 1 W, which was then increased until a 10% increase in impedance was achieved to produce endovascular tissue coagulation. After endovascular RF ablation, a completion angiogram was performed to document whether the vessel had been occluded. If required, the central channel of the VesCoag catheter can be used to deliver chemotherapy, lipiodol or embolic material [12]. In a recent clinical study, Khorsandi et al. [11] demonstrated the safety and efficacy of this device in occluding the arterial blood supply of primary or secondary liver malignancy.

Furthermore, intravascular RF ablation can be used to restore obstructed hepatic blood flow. In HCC, patients who undergo major deterioration of liver function with tumor obstruction of the portal vein or hepatic vein, another device, the Habib™ VesOpen can be used to ablate the tumor thrombus intravascularly and re-establish blood flow to the desired vessel(Fig. 2).

Endobiliary RF ablation

As reported by Lau et al. [13], 3% of HCC patients present with obstructive jaundice. Nevertheless, the consequence of malignant biliary involvement is severe and most of these patients are inoperable. A stainless steel self-expandable metal stent (SEMS) is usually employed for biliary drainage for these patients. However, median SEMS patency is only about 120 days [14] because of tumor ingrowth, epithelial hyperplasia and sludge obstruction. Various methods have been attempted to extend the patency duration of SEMS, but none has achieved a satisfactory result.

In view of the above mentioned difficulty, the Habib™ EndoHPB, an endoscopic bipolar radiofrequency (RF) catheter, has been developed for the palliation of biliary obstructions as a result of unresectable malignancy in order to extend the duration of stent patency. The EndoHPB is a catheter with two stainless steel electrodes at the tip which is compatible with any endoscope that has a 3.2 mm working channel. It uses an 8 F catheter (2.6 mm) which inserts over a 0.035 inch guide wire into the common bile duct (CBD). The catheter is manipulated into the CBD where it is used to heat and coagulate the tissue, effectively ablating the tumor. The electrodes are designed to operate at an efficient energy level and are activated at 10 W for 90 s before the stent is deployed. It allows partial destruction of the tumor prior to stent

Fig. 1   Pre and post VesCoag ablation of the blood supply to a renal metastasis in segment III.

Fig. 2 (A) After application of VesOpen, the blood flow of the right portal vein was restored; (B) HCC + tumor thrombus in right portal vein prior to application of VesOpen.

insertion and can also be used to clear obstructed metal stents. If the obstruction is located in the lower bile duct, the RF catheter can be used with an endoscopic approach (Fig. 3). In cases of hilar biliary obstruction the RF catheter can be inserted by the Interventional Radiologist. In addition, if the tumor has invaded both the right and left hepatic ducts, which was once considered to be an inoperable situation, the surgeon could perform surgical resection of the tumor tissue on one side combined with RF ablation of the bile duct in the residual liver. In a phase I clinical study, Steel *et al.* [15] for the first time showed the 30-day safety and 90-day biliary patency of the Habib™ EndoHPB. This study demonstrates that application of heat energy within a malignant bile duct is safe and efficient. Consequently, this data is the basis for conducting the next stage of controlled trials in this field. We believe longer stent patency could be achieved in these patients in continuous follow-up because the necrosis of the tumor tissue induced by ablation would bring about delayed tumor ingrowth into the stent.

Role of stem cells in liver surgery

The number of patients with end stage liver disease is increasing rapidly because of the rapid spread of viral hepatitis. According to the World Health Organization, over 500 million people are suffering from viral hepatitis B and C worldwide. Globally, 1.5 million die from the disease annually. For patients with end stage liver disease, progressive
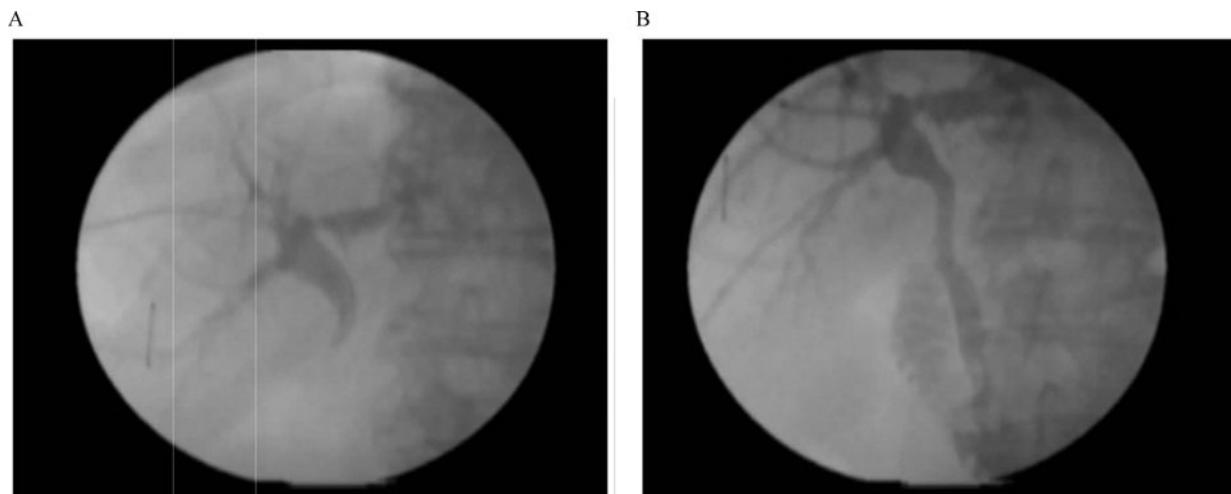

Fig. 3 (A) Before application of EndoHPB, the biliary tree was totally obstructed; (B) After application of EndoHPB, the continuity of the biliary tree was restored.

deterioration of liver function until liver failure seems to be their only fate if liver transplantation is not available. However, the constant shortage of donor livers and the ever increasing waiting times make liver transplantation impossible for many patients. Furthermore, the surgical complications, rejection, and high cost of this procedure are also huge problems for the patient. In recent years, it was discovered that hepatocytes could be derived from bone marrow cell populations [16–18]. Combined with advances in understanding of HSC plasticity, the theoretic basis for stem cell transplantation in patients with liver disease was established and clinically carried out by a team at Imperial College London. For the first time a phase I clinical study was conducted on the use of stem cells derived from bone marrow to treat patients with insufficient liver function. The study demonstrated improvement in serum bilirubin and serum albumin without any complications or specific side effects [19]. Furthermore, this team observed a long-term beneficial effect which lasted for about 12 months in the patients who received the stem cell transplantation [20]. In a follow up study, they demonstrated it was also safe and beneficial to use these stem cells in patients with alcoholic liver cirrhosis (ALC) [21]. These clinical data suggest that adult bone marrow stem cells can be employed as an approach to improve liver function (Fig. 4). This approach could be used preoperatively to downstage the MELD score and to make inoperable patients suitable for surgery. Also, the stem cells could be administrated in the contra lateral lobe to induce liver hypertrophy as a preoperative preparation for planned liver resection [22]. What is more, stem cells secreting interleukin 2 and other cytokines could be injected in the tumorous area, combined with intra-arterial RF vessel closure following injection or TACE.
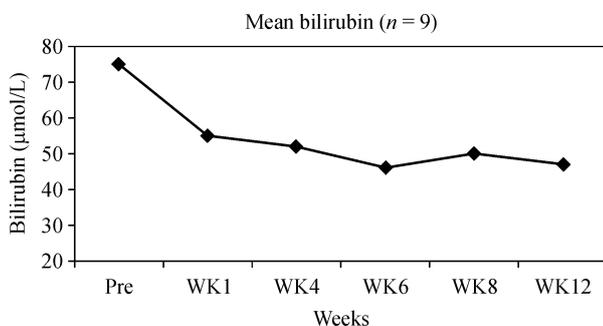

Mean bilirubin ($n = 9$)

Fig. 4 Illustration of change in bilirubin in 9 patients who were Child's B, 7 were converted to Child's A after stem cell therapy.

Laparoscopic RF-assisted liver resection

Laparoscopic hepatectomy (LH) was first described in 1995 by Cuesta *et al.* [23]. With the clinical and social benefits of a shorter hospital stay, faster recovery and better cosmetic results, laparoscopic hepatectomy is carried out with increasing popularity.

However, the risk of massive bleeding during liver transection and risk of postoperative liver dysfunction/failure still leave laparoscopic hepatectomy a challenging surgical procedure. To minimize blood loss during laparoscopic transection of liver parenchyma, various devices have been designed and developed in the last decade. Today, vascular stapling, cavitron ultrasonic aspirator, harmonic scalpel, dissection sealer and water-jet dissection are clinically available and enable more accurate surgery. However, these devices still could not provide reduction of blood loss, and bleeding is still the most serious intra and postoperative complication during laparoscopic liver surgery [24]. In 2002, Weber *et al.* [25] first reported the technique which employed a monopolar radiofrequency (RF) ablation device in open hepatic resection with significant reduction of blood loss at the Hammersmith Hospital, London. Later, this group developed subsequently a bipolar device, the Habib™ 4X and achieved excellent surgical outcomes in liver resection using this device [26]. Based on data reported from Hammersmith Hospital [27], no patient bled postoperatively and the rate of biliary complication was also low (2.1%), which indicated that biliary control and blood vessel control were effective with RF energy. Consequently, there was no need for ligation of the blood vessels or bile ducts with the RF-assisted resection technique. In view of the excellent outcomes in open liver resection with Habib™ 4X, the laparoscopic Habib™ 4X (LH4X), a bipolar radiofrequency device for bloodless laparoscopic liver resection, was developed and has been used widely in clinical practice (Fig. 5). Jiao *et al.* [28] reported excellent results with fast operation times (60 ± 23 min), minimal intraoperative blood loss (48 ± 54 ml), zero transfusion rate, and short hospital stay (5.6 ± 2 days). Similar results have been reported by other groups which verified the efficacy of this device in laparoscopic hepatic resection [27]. With the help of LH4X, there is very little intraoperative blood loss during transection of the liver parenchyma, which facilitates the laparoscopic liver resection and shortens the operative time. In addition, there is a zone of ablative necrosis tissue created by the RF ablation on the resection margin, which ensures reduced local tumor recurrence at the resection plane. As described by Akyildiz *et al.* [29] from Cleveland, favorable blood loss and local recurrence rate can be achieved using the LH4X. To sum up, LH4X is an ideal device designed for minimally invasive liver resection, which minimizes blood loss and risk of regional recurrence while maximizing the safety of liver resection. However, for patients with advanced HCC, the LH4X alone is still not enough to manage the disease. It is the best tool for parenchymal-sparing, but it is unable to restore the liver functional reserve.

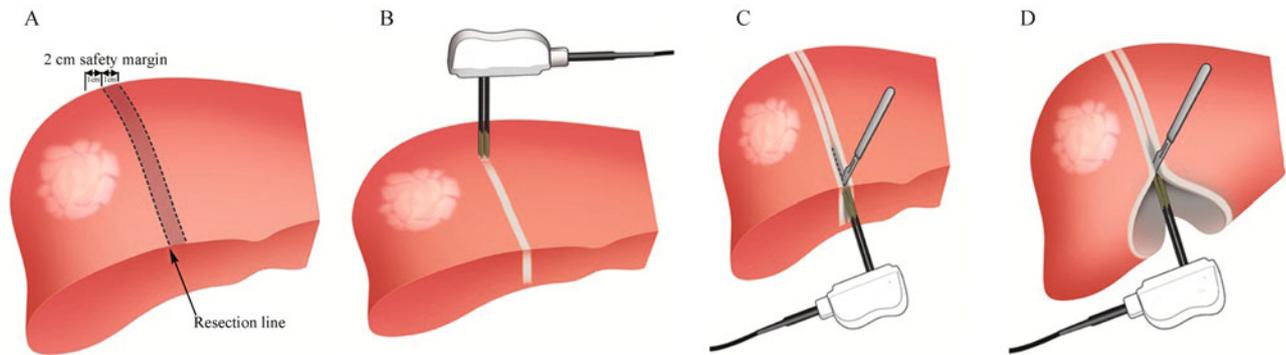The authors would like to conclude this article with a clinical scenario which might represent the future

Fig. 5   The steps to achieve liver resection using laparoscopic Habib 4X.

management of patients with advanced HCC (Fig. 6): A 40 year old male patient with a hypervascular lesion 10 cm in diameter located in the right lobe, with moderate liver cirrhosis and tumor thrombosis in right branch of the portal vein. Except for moderate decrease of serum albumin level (30 g/L) and elevation of AFP (1200 ng/ml), laboratory findings are within normal range. The first step would be to recanalize the obstructed left branch of the portal vein with the Habib VesCoag RF catheter followed by the injection of stem cells derived from bone marrow into the left hepatic artery to induce left lobe hypertrophy. Then chemoembolic materials together with stem cells secreting interleukin-2 (IL-2) would be selectively introduced into the right hepatic artery which would then be occluded by the Habib VesCoag. When the tumor in the right lobe shrinks and enlargement of the left lobe is seen, curative resection would be performed with the help of the laparoscopic Habib 4X system and the tumor thrombosis in right branch of the portal vein would be remedied by the Habib VesOpen. The surgical procedure would be made possible because of the left lobe hypertrophy induced by re-establishment of the portal vein blood supply and stem cells derived from bone marrow which restored the impaired liver functional reserve. Also, the tumor is down staged by TACE-VesCoag and IL-2 secreting stem cell therapy. Then, the laparoscopic Habib 4X system would minimize blood loss while increasing parenchymal sparing with no hepatic inflow control and no liver warm ischemia during hepatic resection, which would contribute to an eventless postoperative recovery.

Some of the above approaches have already been performed successfully in the clinic, whereas others are researches in progress. Both the theoretical basis and clinical techniques are developing rapidly and impact on each other significantly. This progress has brought about potential new strategies to deal with the difficult disease of HCC which may improve the survival of HCC patients in the future.

Step 1 – Clearance of portal vein cancer thrombus + Stem cells in contralateral liver

Step 2 – TACE + IL 12 secreting stem cells in the tumor for vaccination

Step 3 – Tumor resection with the Laparoscopic Habib 4X

Fig. 6   Ideal steps toward optimization of advanced HCC patient.

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