SURGICAL MANAGEMENT OF HEPATOCELLULAR CARCINOMA

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Abstract

Hepatocellular carcinoma (HCC) is among the three most common causes of cancer death worldwide. Liver resection and liver transplantation are regarded as the standard curative treatment for hepatocellular carcinoma. Although liver transplantation for early stage hepatocellular carcinoma has been shown to have excellent long-term survival outcomes and low recurrence rates, the shortage of donor liver grafts limits its wide application. Liver resection can be safely performed in patients with early stage hepatocellular carcinoma and preserved liver function. Although postoperative recurrence after liver resection of hepatocellular carcinoma is almost universal, the reported five-year overall survival rates are around 50%. Recently, the concept of primary liver resection and salvage liver transplantation has been proposed in patients with early stage hepatocellular carcinoma and preserved liver function. Universal adoption of either liver resection or liver transplantation for hepatocellular carcinoma is unwarranted and overly simplistic. The use of different therapeutic approaches that incorporate liver resection or liver transplantation, depends not only on the availability of donor liver grafts and waiting time, but also on the expertise of individual centres.

Liver resection

With the increased understanding of liver segmental anatomy and the improvements in surgical techniques and peri-operative care, there has been a dramatic reduction in peri-operative mortality and an improvement in survival outcomes after liver resection for HCC in the past two decades. In recent series from the east and the west, a peri-operative mortality rate of less than 5% and a five-year overall survival rate of 40%-50% has been reported. However, a high incidence of post-operative recurrence is universal and continues to be the major cause of late deaths. The cumulative five-year recurrence rate is in the range of 75% to 100%. Recurrence occurs in the liver remnant in 78%-96% of cases as a result of either intrahepatic metastasis from the primary tumour or multilobar occurrence.

Most patients with HCC have underlying cirrhosis. Liver resection for HCC in the presence of cirrhosis is associated with a significant risk of morbidity and mortality. Careful patient selection for liver resection is therefore paramount to avoid post-operative liver failure and death. This involves an adequate assessment of the tumour extent, the severity of the underlying liver disease and the functional liver reserve. Only 10-37% of patients with HCC are amenable to liver resection at the time of diagnosis. A recent study from Australia showed that liver resection and liver transplantation were the primary treatment in only 17% and 16% of the total cohort of 235 patients with HCC respectively. In general, large tumour size with insufficient liver remnant after liver resection, extensive and multifocal bilobar tumours, extrahepatic metastases and tumours with main portal vein thrombosis or hepatic vein/inferior vena cava involvement, are all considered a contraindication to liver resection.

Preoperative assessment of liver function

Because HCC is associated with varying degrees of liver disease, inadequate functional liver reserve after liver resection is always a concern. Determination of the amount of liver that can be safely resected is multi-factorial and depends on the extent of cirrhosis, the functional liver remnant/reserve and the regenerative response following liver resection. In general, a normal liver can tolerate the resection of up to 75% of functional liver parenchyma. On the other hand, the risk of postoperative liver failure and subsequent death are high after major liver resection in patients with cirrhosis.

Pre-operative assessment of liver function and prediction of post-operative functional liver remnant/reserve are of paramount importance to minimise the risk of post-operative liver failure. Measurement of the volume of liver remnant by CT volumetry has been shown to be helpful in selecting patients for major liver resection. Vauthey et al demonstrated that small liver remnant volume was associated with worse post-operative liver function and
On the other hand, Child-Pugh classification (Table 1) is the most simple, widely used and reproducible method to identify the patient at risk of liver failure after liver resection. In general, Child-Pugh class A patients can be considered for resection of up to 50% of the liver parenchyma, whereas Child-Pugh class B patients tolerate resections up to 25%. Patients with Child-Pugh class C cirrhosis are considered as an absolute contraindication for liver resection. Numerous quantitative liver function tests have also been developed and evaluated. However, none of these tests on its own can take into account the complexities of liver failure, nor has been demonstrated to be clearly superior to another in predicting postoperative outcome after liver resection for HCC. In the east, indocyanine green clearance at 15 minutes (ICG15) is the most commonly used quantitative assessment of liver function. The value of ICG15 >20% precludes major liver resection. In the west, selection of candidates for liver resection is often based on the presence of portal hypertension in addition to the Child-Pugh classification.

Table 1. Child-Pugh Classification of the severity of liver disease is graded according to the plasma bilirubin and albumin level, the prothrombin time, the degree of ascites and encephalopathy. A total score of 5-6 is considered Child-Pugh class A; 7-9 is class B; and 10-15 is class C.

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Figure 1. Right portal vein embolisation

(a) CT image of a 5cm hepatocellular carcinoma occupying segments 5 to 8; the tumour was very close to the middle hepatic vein. Segments 2 and 3 were free of tumour. Curative resection would require a right hepatectomy with inclusion of the middle hepatic vein.

(b) On CT volumetry, the left liver volume was 24% of the total estimated liver volume before right portal vein embolisation (PVE).

(c) Percutaneous transhepatic ipsilateral right PVE with Gelfoam particles was performed.

(d) On CT volumetry, the left liver volume was increased to 40% of the total estimated liver volume four weeks after right PVE.

Clinically relevant portal hypertension is defined as the presence of a hepatic vein pressure gradient (HVPG) ≥10mmHg, the presence of oesophageal varices or splenomegaly with a platelet count less than 100x10^9/L. Bruix et al demonstrated that HVPG ≥10mmHg was associated with postoperative liver failure in patients with HCC and Child-Pugh class A cirrhosis. Recently, the model for end-stage liver disease (MELD) score has been shown to be an accurate predictor of postoperative liver failure and death after liver resection. Patients with a MELD score <9 had a reported zero perioperative mortality after liver resection for HCC.

Portal vein embolisation

Because most patients with HCC have impaired functional liver reserve due to hepatitis B or C virus-associated cirrhosis, the amount of liver parenchyma that can be safely resected is limited. In selected patients with a small liver remnant, attempts have been made to improve on the safety of liver resection by redirecting portal blood flow toward the segment of liver that will remain in situ after resection.
Liver resection. Pre-operative portal vein embolisation (PVE) induces atrophy of the embolised segments and compensatory hypertrophy of the unembolised segments of the liver (figure 1). PVE can be performed using an open transileocolic approach, percutaneous transhepatic contralateral approach or percutaneous transhepatic ipsilateral approach. These approaches are chosen on the basis of the type of resection planned, the location of the tumour and the available surgical and radiological expertise. In general, PVE is indicated in patients with a predicted functional liver remnant of <25% in non-cirrhotic patients, or <40% in patients with cirrhosis. A recent meta-analysis has shown that PVE is safe and effective in inducing liver hypertrophy to prevent liver failure after liver resection due to insufficient functional liver remnant. PVE has also been shown to increase the resectability of HCC with comparable long-term survival outcomes.

Liver resection for large or multinodular HCC

Several prognostic staging models have been developed to predict survival and to assess the survival outcomes of HCC treatment. The Barcelona Clinic Liver Cancer (BCLC) staging system is the most widely used in the west and stratifies patients with HCC into four categories – early, intermediate, advanced and terminal. It has been recently integrated into the American Association for the Study of Liver Diseases and the European Association for the Study of Liver guidelines on the management of HCC. The BCLC staging system recommends different treatment options for each stage of the disease. Liver resection is indicated only in patients with early stage HCC, as defined by, within the Milan criteria: a single HCC ≤5cm in diameter or up to three HCCs ≤3cm in diameter; normal clinical performance status; and preserved liver function (absence of clinical portal hypertension and Child-Pugh class A status). There is no doubt that patients with early stage HCC have excellent prognosis after liver resection. Although large tumour size (>5cm) and multiple tumour nodules have been shown to be less favourable prognostic factors for patients with HCC, liver resection remains the only hope of cure in patients with large or multinodular HCC outside the Milan criteria. Previous studies have shown that up to 50% of patients with HCC who underwent liver resection had disease classified as being intermediate or advanced stage according to the BCLC algorithm. In a multi-institutional study, Ng et al demonstrated that liver resection could be safely performed in patients with large or multinodular HCC, providing the functional liver reserve is acceptable. A five-year overall survival of 39% and a five-year disease free survival rate of 26% could be achieved.

Liver transplantation

The first successful liver transplant for HCC was performed on a 19-month-old girl by Starzl and his team in July 1967. In theory, liver transplantation is a better treatment option than liver resection as it simultaneously removes the tumour, the underlying cirrhosis and cures the portal hypertension. Early experience with liver transplantation for HCC was, however, associated with a high tumour recurrence rate and poor long-term survival. These poor results were presumably due to the broad selection criteria used, with inclusion of extensive and bulky tumours two decades ago. In 1996, Mazzaferr et al published a landmark paper in which they validated the tumour characteristics associated with superior survival outcome following liver transplantation. The four-year overall and disease-free survival rates were 85% and 92% respectively with a tumour recurrence rate of 8.3%. These constitute the Milan criteria – a single HCC ≤5cm in diameter or up to three HCCs ≤3cm in diameter. These results are comparable with those of non-cancer liver transplant recipients. To push the boundary further, the University of California San Francisco (UCSF) group demonstrated that size criteria could be expanded without compromising the survival outcome. The UCSF criteria consist of single HCC ≤5cm or up to three HCCs with the largest tumour ≤4.5cm and total tumour diameter ≤8 cm, without gross vascular invasion. One-year and five-year overall survival rates of 90% and 75.2%, with tumour recurrence rates of 11.4% were reported. Chen et al analysed and validated these excellent survival outcomes of liver transplantation for HCC in Australia and New Zealand. One-year and five-year overall survival rates were 88% and 74% respectively in patients within the Milan criteria, and 87% and 73% respectively in patients within the UCSF criteria. In patients outside the UCSF criteria, the survival outcomes were poor, with one-year and five-year survival rates of 71% and 36% respectively. Although tumour recurrence is much less a problem after liver transplantation for HCC within the Milan or UCSF criteria, there are other complications specific to transplantation that compromise long-term survival, such as graft rejection, opportunistic infections and the development of other malignancies as a result of immunosuppression. In addition, the major drawback of liver transplantation for the treatment of HCC is the scarcity of deceased organ donors. Many patients with HCC either die before the organ becomes available or drop out from the transplant waiting list because of tumour progression. The dropout rate can be as high as 25% to 37.8% in 12 months. It has also been shown that the results of liver transplantation were adversely affected by increasing waiting times with a two-year intention-to-treat survival falling from 84% for 62 days of waiting time, to 54% for 162 days of waiting time. The survival benefit of liver transplantation over liver resection has been shown to disappear once the waiting time for a donor liver graft exceeds six months.

A variety of bridging therapies, such as transarterial chemoembolisation and radiofrequency ablation, have been advocated as a means to address the prolonged waiting time. In theory, these therapies slow down tumour progression, decrease tumour cell dissemination during recipient total hepatectomy and lower the risk of post-operative recurrence. While some studies demonstrated favourable results of bridging therapies in decreasing the drop-out rate, others reported similar drop-out rates of 15% at six months and 25% at 12 months, but longer...
waiting times for liver transplantation.56,57,58 Although most transplant physicians and surgeons would agree that bridging therapy is useful, there is currently no evidence to support its use. Future studies are required to confirm the efficacy of bridging therapies before liver transplantation for HCC. The questions of which therapy and when to commence the therapy, also require further evaluation.59

**Live donor liver transplantation**

As a consequence of deceased donor shortage, live donor liver transplantation (LDLT) for adults has developed as an alternative over the past decade.53 The shortage of deceased donor liver grafts is particularly severe in the east. The deceased donor rates are fewer than five donors per million in the east, compared with those of 10 to 35 donors per million population in the west.54 With HCC being the most common cancer and the most frequent indication for liver transplantation in the east, the enthusiasm for LDLT therefore continues to surge. In theory, LDLT can provide an unlimited source of donor liver grafts and eliminate the uncertainty of prolonged waiting times and the risk of dropout due to tumour progression.55

Using a decision analytical model taking into account the risk of dropout while waiting (4% per month), the expected survival of the recipient (70% at five years) and the risk for the donor (0.3% to 0.5% mortality), Sarasin et al demonstrated that patients with HCC waiting more than seven months for a deceased donor liver would benefit from LDLT.56 Previous studies on LDLT for HCC also demonstrated favourable long-term survival outcomes.57,58 However, the question of whether the outcome after LDLT for HCC is comparable with that of deceased donor liver transplantation remains unclear.53

More importantly, LDLT poses an ethical dilemma to all transplant physicians and surgeons – “First do no harm”.59 Donor hepatectomy is a surgical procedure that subjects a healthy volunteer to a major operation with 20% morbidity and 0.5% mortality, without direct therapeutic benefits.60 Currently, LDLT remains a novel treatment for HCC with unresolved issues regarding indications and results.

**Liver resection v liver transplantation**

The superiority of liver transplantation over liver resection remains a topic of debate. In specific clinical circumstances, it is clear that liver transplantation may be the only option, namely for patients with early stage HCC that clearly do not have sufficient functional liver reserve to tolerate liver resection. On the other hand, liver resection may be the only curative option in patients with large HCC without cirrhosis. The controversy remains over the management of patients with early stage HCC and well compensated cirrhosis that would tolerate liver resection or transplantation.61 There are no randomised control trials that directly compare the two modalities.

Using the best available evidence, patients with early stage HCC who are eligible for either liver resection or transplantation, have a better survival with liver transplantation than resection. The tumour recurrence rates are also significantly lower in the liver transplantation group.62,63 Therefore, in an ideal world with unlimited organs, liver transplantation would offer improved oncologic outcomes over liver resection. However, because of the growing shortage of donor liver grafts throughout the world, the superior outcomes of liver transplantation may be significantly compromised by patients dropping out of the transplant waiting list, largely from tumour progression. Recently, the concept of primary liver resection and salvage liver transplantation has been proposed in patients with early stage HCC and preserved liver function. It has been shown to be a feasible strategy, as up to 80% of patients with tumour recurrence after liver resection may still be amenable to liver transplantation.64,65 Salvage liver transplantation has also been shown to be as safe and efficacious as primary liver transplantation, with no difference in morbidity and perioperative mortality. In addition, the long-term survival outcomes are comparable.64

In summary, universal adoption of either liver resection or liver transplantation for HCC is unwarranted and overly simplistic. The use of different therapeutic approaches that incorporate liver resection or transplantation should be dictated by the clinical and local situation. Factors will include not only medical and surgical expertise, donor graft availability and anticipated waiting times, but also patient and tumour specific factors.

**References**
