Review Article

Optimizing hepatectomy for hepatocellular carcinoma in Asia-patient selection and special considerations

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Abstract: Hepatocellular carcinoma (HCC) is a common affliction in Asia. The treatment of HCC depends on the tumor status as well as the underlying liver function. Resection is the cornerstone of surgical management of HCC. For those unfit to undergo resection, local ablative therapy is a viable alternative. For patients with multiple small unresectable HCCs, liver transplantation offers another option, having the simultaneous benefit of removing the cancer in addition to replacing the pre-malignant and cirrhotic liver together. However, the paucity of liver grafts limits the applicability of this operation. In assessing for the appropriate treatment, the traditional TNM staging is not widely applied to HCC. Conventionally, doctors in the West have relied on the Barcelona staging system. Asian surgeons, on the other hand, have long adopted a more aggressive approach for their patients. Borne out of the need for a system which better suited Asian patients, the Hong Kong guidelines have been established. For the surgical resection of HCC, considerations must take into account issues regarding the tumor, the underlying liver and the patient. For the tumor, the size, the presence vascular invasion and presence of extra-hepatic metastasis will determine operability. Another important issue is the liver function and, by extension, the estimated residual liver volume after resection. Thirdly, patient factors i.e., fitness to undergo general anesthesia must be properly assessed. With improved surgical technique and better patient selection, peri-operative morbidity and long-term survival results after operation have improved drastically over the past decades.

Keywords: Hepatocellular carcinoma (HCC); patient selection; optimization; resection

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Introduction

Hepatocellular carcinoma (HCC) is the most prevalent malignancy of the liver. It is responsible for the third most cancer-related deaths in Hong Kong (1).

HCC is especially common in Asia, where hepatitis B viral infection is endemic. Other etiologies for HCC are hepatitis C viral infection, alcoholic cirrhosis, hereditary hemochromatosis and primary biliary cirrhosis.

Although it previously was a disease primarily affecting Eastern countries because of the prevalence of chronic hepatitis B viral infection in the area, its incidence in the West has been increasing due mostly to hepatitis C viral infection, alcoholic liver disease and non-alcoholic fatty liver disease (2,3). The annual incidence of HCC in hepatitis B virus carriers is 0.5%. Liver cirrhosis confers a higher likelihood of harboring HCC, with the incidence around 2.5% annually (4,5).

Treatment of HCC

The protocol for the treatment of HCC differs much from

that of any other malignancy because the prognosis of these patients depends as much on their tumor biology as it does on underlying liver disease.

The patients who are hepatitis B viral carriers should be offered ultrasound monitoring at regular intervals to diagnose early tumors that can be treatable, either by resection or ablation. However, most patients with early diseases are not symptomatic. Liver resection is the cornerstone of the surgical management for HCC. Anatomical resection for HCC proposed by the Makuuchi *et al.* should be considered the gold standard for the treatment for HCC whenever possible (6). However, resection is achievable only in quarter of patients since the tumor is often times too advanced upon presentation. Moreover, HCC patients often suffer from liver cirrhosis as well, making resection difficult if not impossible such as in the case of patients with Child C cirrhosis. Hence the prognosis for the majority of HCC patients remains dismal.

Even for those who are fit to undergo resection, cure is far from guaranteed. Post-resection local recurrence is high, reaching 50% at 5 years (7). Salvage treatment (defined as treatment given for recurrent disease after resection) for recurrent tumors are often challenging, limited by cirrhosis and a small-sized remnant liver after resection. Factors including inadequate liver reserve (both in terms of volume and function), presence of adhesions resulting from old operations, and tumor location in close proximity to major vessels or bile ducts all serve as major impediments to further resection. Therefore, other methods are needed.

The emergence of local ablation has changed the treatment guidelines for recurrent HCCs (8). With technological advances, local ablative therapy using various energy sources has emerged as an effective treatment alternative for patients for whom conventional surgery is not suitable. These include cryoablation therapy, microwave coagulation, and radiofrequency ablation (RFA). Also gaining momentum is high intensity focused ultrasound (HIFU), which is a totally extracorporeal form of local ablation for liver tumors (9,10). HIFU entails the delivery of intense ultrasonic energy from an extracorporeal machine into the target lesion resulting in coagulative necrosis of tumor cells.

In patients with multiple unresectable tumors, liver transplantation is an option when all else fails. Transplantation has the advantage of removing the HCC while replacing the native premalignant liver (due to cirrhosis) with a healthy donor graft liver. The availability of deceased donor liver grafts varies worldwide. The cadaveric donation rate in Spain tops the world, accounting for 33.7 donations per one million. However, the cadaveric donations in Asia are scarcer, ranging from 0.05 to 4.3 donations per one million. The lack of available deceased grafts makes liver transplantation for HCC challenging (11,12). To ensure the maximal benefit while harvesting with limited number of liver grafts, various allocation systems have been used internationally. The intent of allocation is to ensure the sickest and those most likely to benefit will receive this valuable resource. The aim when using these allocation systems is to achieve the best results for the most number of patients. Since the opportunity cost of a liver graft is so high, a healthy liver given to a less deserving recipient often time spells doom for another potential recipient. As a corollary, patients with very high MELD (Model for End-stage Liver Disease) scores have priority on the transplantation waiting list. Patients with multiple unresectable HCC but reasonable liver function will have a less priority due to their lower MELD scores.

The survival data after liver transplantation during the developmental stage of this operation was far from encouraging, achieving a 5-year survival rate below 40%. This led to the realization of certain negative prognostic factors in HCC patients undergoing transplantation (13). In support of the Milan criteria (transplantation for solitary HCC less than 5 cm or 2 to 3 tumors each less than 3 cm) established in 1996, Mazzaferro proved that patients with single tumor smaller than 5 cm or two to three tumors each smaller than 3 cm enjoyed better long-term survival than those who fell outside of said criteria (14,15). Better patient selection based on this set of criteria has resulted in the improvement of the 5-year survival to 83%. Internationally, patients with tumor number or size beyond the Milan criteria are not eligible for transplantation and those patients on the waiting lists will disqualified if their HCCs grow to beyond sizes stipulated by the criteria, thereby guaranteeing that deceased grafts are properly given to patients predicted to enjoy the most favorable outcome after transplantation.

In order to make sure patients with growing HCC remain on the waiting list, different appropriate treatment before transplantation, known as bridging therapy, have been tried. These include HIFU, RFA and transarterial chemoembolization. Bridging therapy bore out of the need to suspend tumor progression and to enable patients to remain within the transplantation criteria as long as possible to receive a graft liver.

Despite the discovery of new technology, advances in surgical technique due to accumulation of experience, and better patient selection, the prognosis of HCC treatment is still far from ideal. Upon disease presentation, a majority of patient are not suited for surgical treatment which is the only form of cure. Even for those who undergo operation, the disease will often times recur due to the presence of carcinogenic hepatitis virus infection and background cirrhosis. At the moment, liver transplantation for suitable candidate (i.e., small unresectable HCC) offers the best chance of cure for these patients. For those unfit for surgery, their only hope is usually palliative treatments either in the form of transarterial chemoembolization or targeted therapy, both of which give results that are far from encouraging.

Surgical treatment for HCC

The mainstay of treatment for HCC, also the only hope for cure, is surgery which includes liver transplantation and resection. Transplantation offers superior results to resection for those patients with HCC within transplantation criteria (most notably Milan's criteria, the more inclusive UCSF criteria or even Hangzhou criteria in China). However, due to the paucity of deceased donor organs, it is unrealistic to expect this treatment option to be widely applicable. In other words, resection is still the first-line treatment for HCC patients.

The difficulty with treating HCC patients is the fact that most of these patients are in fact burdened with two disease processes: cancer and underlying cirrhosis. The cause of cirrhosis in Asia is mainly viral hepatitis infection which is endemic, whereas alcoholism contributes more in the West. With cirrhosis, the margin of error for the resection is limited. The issue of liver reserve is important in all liver resection operations, even with normal liver parenchyma as during resection of secondary liver tumors, e.g., colorectal metastasis. Preserving adequate liver reserve is even more pertinent in resection of tumor with background cirrhosis.

Resection can be broadly categorized into anatomical advocated first by the Japanese which is the removal of the entire segment where the tumor is located or non-anatomical, e.g., wedge resection for small tumors. Conventional resection is an open procedure. With good risk patients and suitable tumors based on their size and location, laparoscopic surgery is a proven and safe alternative to open approached, which yields similar survival results and complication profiles but with less post-op wound pain and shorter hospital stay.

Traditionally the resection criteria in the western countries have followed the Barcelona guideline. However, in Asia the same approach can be viewed as too conservative. With the proposal of a more aggressive treatment protocol suggested of the Hong Kong guideline, more patient who were previously deemed hopeless are being treated with significantly better results.

When selecting patients with HCC for liver resection, consideration must be given to the following 3 aspect: the liver function, the tumor and the patient's general health. These aspects will be explained further in terms of indication for liver resection, assessment of liver function reserve, general pre-morbid state of the patients and peri-operative measures, all of which must be taken into serious consideration to achieve the best results.

Indication of liver resection: tumor factors including size, macroscopic vascular invasion and presence of extra-hepatic metastasis

Meticulous preoperative assessment of tumor status is paramount to selecting the right HCC patients for operation. Patients with potential resectable HCCs routinely receive chest radiograph and triphasic contrast computed tomography (CT) scan of the abdomen and pelvis. HCC will typically be arterial enhancing, with the characteristic washout during the portovenous phase. If there is any diagnostic ambiguity, a functional scan such as positron emission tomography (PET) with dual tracers (the radio-isotopes of FDG and C-acetate which HCC will take up to give avid signals) will be added. Triphasic CT imaging is relied upon for the delineation of the relationship between the lesions and hepatic vasculature including any involvement of the main portal vein and the inferior vena cava (IVC), and detection of satellite nodules. Magnetic resonance imaging is only needed for diagnosis in patients with unclear anatomy on the CT.

TNM staging system is commonly used to assess tumor status. However, this staging guideline is not widely used when applied to HCC. Traditionally, the Barcelona clinic liver cancer staging system (BCLC) which is recognized d by European association for the study of liver (EASL) and the American Association for the study of liver disease (AASLD) stipulates that only the very early stage and the early stage patients are fit for surgery or ablation therapy which are currently the only forms of cure. However, Asian surgeons have adopted a more audacious approach to the surgical

treatment of HCC. Bore out of the need for a classification system that is more suited for Asian patients with HCC, the Hong Kong liver cancer prognostic classification scheme was established. For patients with early stage disease, the treatment recommendation of both guidelines are similar. What it different is the treatment protocol for intermediate stage. While the BCLC recommends that intermediate staged patients should undergo chemoembolization which is essentially palliative in nature, the HKLC suggests that resection should be considered. In other words, cure is achievable for these patients. Yau *et al.* compared the survival data of patients who underwent treatment according to the recommendations of both systems and found that the HKLC classification scheme better classified patients in both the intermediate and advanced stages of HCC to distinct groups, which resulted in better survival based on to more aggressive treatment guidelines than what was suggested in the BCLC treatment protocol. In conclusion, the HKLC scheme is more accurate than BCLC in recognizing HCC patients who are better suited for a more aggressive approach, thereby generating better long-term outcomes (16).

Conventionally, hepatic resection is only indicated in the absence of extrahepatic disease as well as the absence of involvement of the IVC and the main portal vein. However, the present involvement of IVC (including thrombus extending into the right heart) and main portal vein is not always an absolute contra-indication for liver resection. Some aggressive authors have supported liver resection in the presence of IVC or main portal vein involvement (17,18), although most liver surgeons consider these factors to be relative contraindications for operation since the prognosis is usually guarded with these patients. However, it must be said that liver resection for tumors with invasion into the hepatic veins or major intrahepatic branches of the portal vein is occasionally warranted as long as the patients fully understand the risks involved because favorable outcome may be achieved compared with non-surgical remedies (19,20).

Early diagnosis by screening of hepatitis B virus carrier with imaging have resulted in detection early staged and small HCCs. However, most HCC patients still present with advanced staged tumors occasionally exceeding 10 cm in size. Large size of tumor *per se* is not a contraindication for liver resection (21). Poon *et al.* have shown that liver resection is safe and effective for HCCs larger than 10 cm in size (22). Specifically, patients with a single tumor larger than 10 cm in the absence of IVC or main portal vein invasion enjoy long-term survival after operation. Therefore, liver resection is recommended as a acceptable option for patients with this type of tumor.

The surgical approach towards bilobar HCCs is slightly more controversial. Resection of bilobar tumors are not universally accepted as treatment of choice. Bilobar disease may represent advanced tumors which originate from one lobe to involve the other or may represent multifocal HCCs developed from multicentric carcinogenesis in the background of a cirrhotic liver. However, often times the difference is clinically impossible to differentiate. Anatomical resection in one lobe where the dominant tumor resides combined with wedge excision for the smaller tumor located in the contralateral lobe occasionally feasible. In addition, the dominant tumor can be resected by major hepatectomy while small lesions located in the contralateral lobe can be ablated by techniques such as RFA or microwave ablation. Poon *et al.* have demonstrated that hepatic resection for bilobar HCCs resulted in a better survival outcome than non-surgical therapies. In other words, liver resection should be recommended in selected patients with bilobar tumors, specifically patients with a small and solitary tumors in the contralateral lobe that is suited for wedge resection or ablation such as RFA, microwave or HIFU (23).

If technically feasible, liver resection offers the best chance of survival for advanced tumors with macroscopic vascular involvement (e.g., main portal vein, IVC or right atrial thrombus), since all other available methods are not effective. It is important to remember that while the results with such aggressive and occasionally risky approach are suboptimal compared with small tumors without macrovascular invasion, resection is still the only option which offers any form of hope for patients harboring such advanced tumors. For small tumors less than 5 cm in size without macroscopic vascular involvement, it is a different story. Debate exists regarding whether liver resection or transplantation is more beneficial for patients with Child's A cirrhosis and HCC with normal liver function. Some studies have shown better long-term results in patients who underwent transplantation compared with those who were treated by liver resection (23-26). Others have shown that long-term data after resection for small tumors less than 5 cm was similar to those treated by transplantation (27-29). Since availability of liver grafts is unable to meet the demand, liver resection should be considered as the first-line option for patients with small tumors and normal liver function. The long-term results of liver resection in

135 patients with small HCCs that matched the criteria for liver transplantation as stipulated by Milan's criteria was published and the 5-year overall survival achieved after operation was 70%, which was similar to the 5-year overall survival results of transplantation in the literature (5). Unfortunately, the 5-year disease-free survival was lower due to the high likelihood of local recurrence. It is because with transplantation, not only is the tumors removed, the pre-malignant cirrhotic liver is also replaced with a healthy graft liver. The majority of the recurrent tumors were small/solitary or oligo nodular, i.e., less than 3 nodules due to early detection by aggressive imaging surveillance. These recurrences were suited for further treatments such as re-resection, RFA or HIFU. In addition, 79% of the recurrences in that study fall within the transplantation criteria and are eligible for salvage transplantation (defined as transplantation performed for recurrent HCC). Furthermore, a significant portion of patients with small HCCs survive with no recurrence even 10 years after liver resection. Therefore, it is difficult to recommend performing transplantation on patients with small tumors and preserved function status because of the practical issue of graft scarcity and the concurrent issues associated with transplantation including lifelong immunosuppression and the resulted opportunistic infection and the side effects of the medication in the long run. Liver resection as the first-line treatment and salvage transplantation only reserved for recurrent disease, appears to be a reasonable recommendation for patients with small tumors and preserved liver function. With that being said, a group of patients with oligonodular tumors and cirrhotic livers might have fared better undergoing transplantation as a first line treatment because of less satisfactory long-term outcome after liver resection.

Assessment of liver function: pre-op liver function and estimated standard liver volume

Besides thorough assessment of tumor status, care must be taken to ensure the adequacy of the post-resection liver reserve. Calculation of liver volume is central to selecting patient for liver resection in order to prevent liver failure and death. This is of particular salience in HCC patients (as opposed to colorectal liver metastasis) since they also suffer from underlying cirrhosis. Although some surgeons rely solely on clinical and biochemical parameters such as the Childs-Pugh scoring system in assessing the liver function of potential surgical candidates (30), it is now common practice to adopted a more meticulous and objective method of evaluation such as indocyanine green (ICG) retention test to better anticipate and prevent the chance of postoperative liver failure (31-33). The ICG retention test is required for patients undergoing major liver resection because multivariate analysis has demonstrated that this test is the most accurate in predicting post-operative mortality after major resection for HCC (32). ICG retention with excretion less than 14%, 15 minutes after injection is established as the safety margin for major liver resection. Major hepatic resection is defined as resection of 3 or more segments of liver (34). With better perioperative support including appropriate central venous pressure, and improved technical prowess resulting in less blood loss, limit of the ICG could be stretched. The postoperative mortality and morbidity of 25 patients with ICG exceeding 14% after major liver resection was similar to the results of 92 patients whose ICG was below 14%. The average value of ICG assessment of these patients with expanded safety limit was 17.4% (35). It is safe to expend the limit of ICG retention incrementally in certain good-risk patients. As a result of the published findings, it has since been acceptable for the upper limit of ICG to reach 20% for major liver resection in certain cases. However, it must be stressed that for patients with borderline ICG retention (ranging from 14% to 20% at 15 minutes), attention must be paid to the functional liver reserve and severity of the cirrhosis to prevent liver failure after operation.

CT volumetry as a measurement of the volume of liver remnant is useful in the selection of patients for major hepatic resection (36). Not surprisingly, it has been shown that the smaller the volume of the liver remnant, the worse postoperative liver function will be. This is also correlated with a higher chance of complication after liver resection (37). Occasionally preoperative assessment of the degree of cirrhosis can be achieved with the use of biopsy of liver parenchyma. This would reveal the histological grade of fibrosis and reflect the portal pressure. However, this invasive method is not commonly adopted since it is not without risk. It is not practical and the risks associated with the invasiveness are difficult to justified (38,39). Some have advocated for the use of laparoscopic visualization to gauge of the degree of cirrhosis and estimate the size of the liver remnant in deciding the tumor operability in HCC patients (40). The caveat of such an approach is that accuracy of evaluation will have much inter-observer variation and will be subjectively dependent on the experience of the surgeon.

In patients who are anticipated to have insufficient liver reserve after resection, preoperative measures such as embolization of portal vein, either by radiological or by surgical means, has been employed to augment the size of the liver remnant (36,37). There are postulations that portal vein embolization may be less useful in cirrhotic liver because of the reduced regenerative capability due to the fibrosis of the liver parenchyma. This has not been demonstrated. Studies show pre-operative portal vein embolization successfully enlarges the liver remnant and therefore decreases complications in patients with mild degree of cirrhosis undergoing liver resection for HCC (41-43). More recently, ALLPS has been attempted with success to achieve a similar goal with faster results. Associated liver partition with portal vein ligation for staged hepatectomy (ALLPS) is relatively new technique which involves a two-stage operation. During the first operation, the liver parenchymal is dissected and the portal vein is divided to facilitate the shunting of blood to the remnant liver. The second stage of the operation, typically schedule one week afterwards involved the complete hepatectomy procedure (44). This technique may result in decrease in drop-out rate for patient with advanced tumor but further studies are need to confirmed the long-term results.

General status of patients: pre-op fitness for general anesthesia

The fitness of patients to undergo general anesthesia which is a reflection of their cardiovascular health is another important consideration in the selection of HCC patients for liver resection. Concomitant medical conditions are known to increase the risk of post-op morbidity and mortality (31). Comorbidities are common and unavoidable among elderly patients, and hidden medical disease which manifests itself peri-operatively is to be anticipated. Performing liver surgery on elderly patients occasionally poses additional technical challenges such as encountering a rigid ribcage which hinders proper exposure. Additionally, from the anesthetic point of view, it might be difficult to lower the central venous pressure which is needed during liver transaction to reduce bleeding without disturbing the arterial blood pressure. Old age alone should not, however, be regarded as an absolute contraindication for major liver surgery as satisfactory post-operative results can be obtained with good surgical risk elderly patients, granted the patient selection process is thorough (45). With the improved accuracy of liver function assessment, the presence of concomitant illness is a more pertinent factor in predicting the peri-operative and long-term results of patients undergoing liver resection. In an analysis of negative prognostic factors for post-op complication after surgery for HCC, medical comorbidities were one of the two independent variable predictive of mortality, the other being the need for perioperative blood transfusion (46).

Serious comorbidities such as congestive heart failure, chronic renal impairment and poorly controlled chronic obstructive pulmonary disease are considered a contraindication for major liver resection, patients with less severe forms of these conditions can, however, still benefit from hepatic surgery granted that perioperative care and postoperative support is sufficient and readily available. A common example of such comorbid illness among patients with cirrhosis is diabetes mellitus. The Japanese have shown that diabetes mellitus was a poor prognostic factor for increased morbidity and mortality after liver surgery (47). However, Poon *et al.* has demonstrated that postoperative complication rates and survival statistics after liver resection for HCC patients with diabetes mellitus were similar to those without the condition (48). The key is to achieve optimal perioperative blood glucose control and ensuring that meticulous postoperative monitoring is available.

A more qualitative assessment of the patient's general health can also be used. One such example is the ECOG performance status grading (Eastern Cooperative Oncology Group) which stratifies patients based on their ability to carry out activities of daily living.

Improved surgical technique

Liver resection for tumors with background cirrhosis is associated with high risk of morbidity and mortality. Previously, the mortality rate after liver resection for patients with cirrhosis was in the range between 15% and 30%. The extent of surgery in cirrhotic patients was mainly limited to segmental or wedge resections (49-51). During the late 80s, the post-op mortality for major hepatectomy at our centre was 15% (52). Improvement in the techniques of liver surgery has resulted in improved survival with dramatic decline in the operative death and allowed major hepatectomy in cirrhotic patients to be carried out (34,53,54). Even major liver resection can safely be performed in cirrhotic patients with acceptable risks of morbidity and mortality similar to those of patients undergoing less extensive liver surgery (55). Liver centers worldwide report a hospital mortality rate around 5% to 7% after hepatic resection for HCC (30,56-58). Locally in Hong Kong, zero

mortality rate was observed in a consecutive series of 150 patients undergoing liver resection for HCC (59). Similar findings have also been published by other centers (60).

The application of new surgical devices achieving better hemostasis during liver transection has contributed to the improved outcomes. The advent of an ultrasonic dissector has reduced blood lost during liver transection, rendering the traditional crush-clamp technique obsolete (61). With the help of anesthetists experienced with liver surgery, maintenance of a low central venous pressure during dissection reduces bleeding, and the resultant need for transfusion. The judicious use of Pringle maneuver is helpful in reducing the blood loss during transection (62). Belghiti *et al.* (63) reported that the combination of inflow control (i.e., Pringle maneuver) and outflow control (total vascular exclusion) was effective in curtailing blood loss. Pringle maneuver is employed more often because it is better tolerated while total vascular exclusion is associated with considerable ischemic injury to liver. Studies had further elaborated on the Pringle maneuver, showing that a limit of 120 minutes in an intermittent manner is tolerable in most patients. Beyond the specified time limit, damage to the liver should be anticipated (64). Coupled with experience and caution, the use of the ultrasonic dissector has allowed hepatectomy to be routinely performed without the help of Pringle maneuver. The use of vascular stapler gaining the control over hepatic veins has also been incorporated into our practice. This is specifically helpful when handling the middle hepatic vein deep in the transection plane during either extended right or left hepatectomy (55).

Right or extended right hepatectomy for sizable right lobe tumor is one of the more challenging types of resections for liver tumor. Mobilizing the right lobe from the retroperitoneum and anterior surface of the IVC in the traditional manner might tear the right hepatic vein or the venous branches between the right lobe and the IVC resulting in torrential bleeding. Prolonged rotation leading to kinking of the inflow and outflow supply results in ischemic injury of the remnant liver. Worse yet, overzealous mobilization and manipulation may disseminate malignant cells into the bloodstream. Large vascular tumors may rupture during dissection if manipulation is too rough, with the dreaded consequence of torrential blood lost and dissemination of cancer cell into the peritoneal cavity. Rupture increases the risk of postoperative mortality. Moreover it also impacts the long-term survival. A solution to this problem is the utilization of dissection from the anterior approach. The parenchyma is approached from the anterior surface down to the IVC after control of the right portal inflow before mobilizing the right liver. The division of the pedicle will provide demarcation which guides the direction of the dissection. The right liver is dissected away from the IVC and the diaphragm only after transection is completed. This method results in less bleeding, reduces the need for transfusion, and lowered the post-op mortality when compared with the conventional approach for large HCCs (65). In addition, the disease-free and overall survival periods were also improved with the anterior approach.

Results

With proper patient selection, operative mortality and long-term survival results after operation for HCCs have improved dramatically over the past decades (57,66). Both the overall and disease-free survival results improved as well (66). Reduced perioperative blood transfusion was a major factor for the improved results. Another factor was the increased proportion of subclinical HCCs detected by screening. On the other hand, perioperative blood transfusion was found to be an independent negative prognostic factor in long-term survival after liver resection (67); transfusion related immune modulation accounts for this phenomenon. Therefore, the surgeon's intra-operative performance in terms of hemastasis and hence need blood transfusion not only influences the operative mortality but also the long-term survival (67).

At the moment, the overall 5-year survival after surgery for HCC is about 50% (66). A similar figure has also been published elsewhere (57). The major problem is the rate of recurrence after surgery. The disease-free survival after liver resection is low because of intrahepatic recurrence (7). Although target therapy has been developed for HCC, the results are far from satisfactory. As medication has yet to help in the prevention of recurrence after resection of HCC (7,68) aggressive approaches to manage recurrent disease have been adopted. These include various methods such as surgical resection, transarterial chemoembolization, local ablation or radiotherapy. These have been shown to prolong the survival after recurrence (69,70). To further improve the survival outcome after liver resection, more research is needed to identify a neoadjuvant or adjuvant therapy which works synergistically with surgery.

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Footnote

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