



Perspective

Liver resection in Cirrhotic liver: Are there any limits?



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ABSTRACT

Liver resection remains one of the most technically challenging surgical procedure in abdominal surgery due to the complex anatomical arrangement in the liver and its rich blood supply that constitutes about 20% of the cardiac output per cycle. The challenge for resection in cirrhotic livers is even higher because of the impact of surgical stress and trauma imposed on borderline liver function and the impaired ability for liver regeneration in cirrhotic livers. Nonetheless, evolution and advancement in surgical techniques as well as knowledge in peri-operative management of liver resection has led to a substantial improvement in surgical outcome in recent decade. The objective of this article was to provide updated information on the recent developments in liver surgery, from preoperative evaluation, to technicality of resection, future liver remnant augmentation and finally, postoperative management of complications.

1. Introduction

Liver resection remains one of the most technically challenging surgical procedure in abdominal surgery due to the complex anatomical arrangement in the liver and its rich blood supply that constitutes about 20% of the cardiac output per cycle. The challenge for resection in cirrhotic livers is even higher because of the impact of surgical stress and trauma imposed on borderline liver function and the impaired ability for liver regeneration in cirrhotic livers. Nonetheless, evolution and advancement in surgical techniques as well as knowledge in peri-operative management of liver resection has led to a substantial improvement in surgical outcome in recent decade. The objective of this article was to provide updated information on the recent developments in liver surgery, from preoperative evaluation, to technicality of resection, future liver remnant augmentation and finally, postoperative management of complications.

2. Preoperative liver function evaluation

Liver resection in patients with cirrhosis requires extreme care in determining the function of the liver parenchyma (including evidence of portal hypertension). One of the key considerations is the future liver remnant (FLR), taking into account the amount of liver that needs to be resected. The relationship of the lesion(s) to critical inflow pedicular structures such as bile duct, portal vein and hepatic artery as well as outflow structures such as hepatic veins have significant influence on how the surgery will be performed.

The basic evaluation of functions of the liver can be performed through simple test in Child-Pugh scoring system. In the usual guide, Child's A patients could tolerate major liver resection provided the FLR is sufficient, while major liver resection is generally not encouraged in

patients with Child's B and C status liver function [1,2]. In addition, if there is evidence of portal hypertension, particularly in elevated hepatic venous pressure, oesophageal varices, splenomegaly with thrombocytopenia, the risk of liver resection will also significantly increased as this usually corresponds well to decompensated liver function [3].

The less commonly used methods of liver function scoring for total evaluation before liver resection such as the Liver damage grade and the model for end-stage liver disease (MELD) score are also reported in the literature [4–8]. Liver damage grading proposed by the Liver Cancer Study Group of Japanese has 5 components including degree of ascites, serum albumin and bilirubin levels, ICG-R15% as well as prothrombin activity. Recently, an international study group proposed the use of ALBI grading system to further enhance the ability to discriminate patients with HCC who will benefit from resection versus other treatments. It is reported to be better than the existing grading system such as Child-Pugh score in selecting therapeutic options for HCC patients [9,10].

Further evaluation of the quality and function of the hepatocytes can be achieved by performing the Indocyanine Green (ICG) Clearance test [11]. The ICG dye is exclusively cleared by the hepatocytes and excreted into the biliary system, the amount of ICG retained in the blood at a certain duration after injection can be used to stratify the risk of major liver resection. Imamura et al. proposed the use of Makuuchi decisional algorithm using ICG retention at 15 minutes as follows [12]:

- ❖ < 10% at 15min for trisectionectomy or bisectorectomy of liver
- ❖ 10–19% for hemihepatectomy, right sided sectorectomy
- ❖ 20–29% for segmentectomy
- ❖ 30–39% for limited resection (eg wedge resection)
- ❖ > 40% for enucleation

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In recent years, liver scintigraphy has also been adopted into the algorithm to evaluate the liver function and volume and it has been validated as a tool to assess the total liver function and functional remnant liver before liver surgery. ^{99m}Tc -labeled diethylene-triaminepentaacetic acid galactosyl human serum albumin (GSA) scintigraphy and hepatobiliary scintigraphy (HBS) with ^{99m}Tc -labeled iminodiacetic acid (IDA) derivatives are some of the scintigraphic liver function tests available commercially. Both of them can provide quantitative and visual information on total and regional hepatic function. ^{99m}Tc -GSA SPECT-CT has been used in monitoring FRL after PVE where more pronounced increase in FRL function after PVE was observed compared to the volumetric increase measured with CT volumetry [13,14]. It has also been used to monitor the liver regeneration after hepatic resection in some cases [15].

^{99m}Tc -mebrofenin is the most liver-specific ^{99m}Tc -IDA derivative. The ^{99m}Tc -mebrofenin circulates in an albumin-bound form and dissociates from albumin after uptake into hepatocytes through organic anion transporters. ^{99m}Tc -mebrofenin undergoes biliary excretion without undergoing biotransformation, similar to ICG. Therefore, the mebrofenin hepatic uptake can be calculated in the same way as for ICG. This uptake rate strongly correlates with the ICG clearance test [16]. Preoperatively measured FRL function with ^{99m}Tc -mebrofenin HBS has been proven to correlate with postoperative FLR function on postoperative day 1 [17]. In patients with normal liver parenchyma undergoing partial liver resection, preoperative measurement of ^{99m}Tc -mebrofenin uptake by the FRL was more accurate in predicting postoperative liver insufficiency and liver insufficiency-related mortality than preoperative measurement of FRL volume [18]. [bib18].

Based on a consensus statement in 2010, the Vauthey report [19] stated that the minimum liver volume required after liver resection was estimated to be approximately 20% for a normal liver, 30% for an injured liver and 40% for a liver with well-compensated hepatic fibrosis and cirrhosis. Furthermore, the Hong Kong team has further proposed using CT volumetric to enhance safety measures of patients who show an ICGR 15 of 14–20% [20]. In patients with borderline liver function reserve for major hepatectomy, roughly 30–40% can be considered safe remnant liver volume.

3. Open liver resection: tips and tricks

During the last two decades, relevant improvements have rendered even extended liver resections in higher-degree cirrhotic patients with portal hypertension possible. However, there are few standard indications for hepatic resections in cirrhotic patients and risk stratifications have to be performed in an interdisciplinary setting for each individual patient [21–23]. The CTP score and Model for End-stage Liver Disease (MELD) can be used to assess the perioperative risk. On the other hand, hepatic resections in cirrhotic patients with portal hypertension show a significantly increased mortality and morbidity. However, surgery is feasible in selected patients with adequate long-term outcome [24]. The recanalized umbilical vein must be preserved if possible if not carefully ligated and it is important point in patients with portal hypertension. To preserve it, we can use J-shape, easier than subcostal laparotomy and the collateral circulations is less affected. Depending on the tumor localization we could conserve the liver ligaments for the same reasons.

The most frequent indication for hepatic resections in cirrhotic patients with and without portal hypertension is HCC. Despite the advances, only 15%–30% of patients with HCC are candidates to resection [4]. As aforementioned, in selected case the portal hypertension should not be a contraindication, several authors have demonstrated that 5-year overall survival as high as 68% in selected patients although the type of resection tends to be limited to less two segments. The degree of portal hypertension becomes another important clinical factor that influences the size and scope of possible resection.

In cirrhotic liver, a minimum of 40% well-perfused liver remnants in the patients after hepatic resection. Normally, these radical resections

are offered to CPT A, MELD < 9 with no or only mild portal hypertension. It would be preferred hepatic resections to be as parenchymal-sparing as possible. In contrast, the latter strategy may enable liver resections in patients with advanced cirrhosis (CPT B) and with mild portal hypertension [25]. Parenchymal-sparing resections via open approach would be more safer, although there has been conflicting data to suggest that both disease-free and overall survival were better with anatomical resection when compared with non-anatomical resections [26–28].

Blood loss and blood transfusions have been defined as independent predictors of postoperative morbidity and mortality. During parenchymal dissection with high blood loss, hilar vascular occlusion can be applied (Pringle maneuver [29]). Although, the Pringle maneuver is not recommended in cirrhotic patients but sometimes to avoid extensive blood loss, it should still be considered as exsanguinating haemorrhage would inevitably lead to shock, and subsequently liver failure [30]. If vascular clamping cannot be avoided, selective clamping of a hepatic lobe, section or segment is recommended to limit ischemic and if longer occlusion is needed, intermittent occlusion, e.g., intervals of 15 min of ischemia and 5 min to reperfusion is preferred over continuous clamping [31]. The liver hanging maneuver facilitates anterior approach of major hepatectomy and minimizes bleeding by elevation of the liver along its deeper parenchymal plane [32]. In case of substantial bleeding from the transection surface, total vascular exclusion is another effective approach to allow examination of the bleeding points and haemostasis. For large bulky tumors, open approach remained the mainstay of treatment but it may become safe and feasible via minimally invasive approach as techniques and experience is advancing. Drainage placement is not recommended because increasing the septic complications, impair the ascites management and prolongation of the length of hospital stay.

4. Minimally invasive surgery for liver resections

The advantages of minimally invasive liver surgery compared to the classic “open” approach are well known and may result in easier access to the abdomen in cases of future liver transplantation (LT) [33,34]. Moreover, it provides favorable perioperative outcomes including significantly less intraoperative blood loss, shorter hospital stay, and less postoperative morbidity, without affecting the oncological result [35]. Several studies have demonstrated that minimally invasive liver resection is safe, feasible, and particularly effective for parenchymal-sparing procedures, such as those needed in patients with cirrhosis. Advantages of a minimally invasive approach are in fact both surgical and medical, thanks to the reduced surgical trauma and the small impact on fluid management and patient mobilization [36,37]. There are also technical advantages of the robotic platform that make for a more comfortable approach for the surgeon, even to complex procedures that classically requires an extremely skilled laparoscopic surgeon. For example, the TilePro function on the robotic console is an important resource of the robotic platform that displays at the same time the classical endoscopic view and imaging sources such as the US, CT scan, MR images. This represents a valuable improvement compared to standard laparoscopy since the operating surgeon no longer needs to switch from a screen to another to visualize the intra-operative US.

Indocyanine green (ICG) fluorescence is an additional tool to perform guided liver resections, that may be particularly helpful to obtain parenchymal resections respecting the anatomic paradigm [38]. However, the ability of ICG fluorescence to identify HCC nodules may be affected by the presence of cirrhosis and varies according to tumor depth [39,40]. Given the low positive predictive value of this procedure, detection of HCC nodules with ICG fluorescence in cirrhotic patients seems not reliable so far.

Furthermore, it has recently been shown that patients with clinically significant portal hypertension (CSPH) may benefit from a minimally invasive approach instead of an open one. In detail, a study from Spain

comparing 30 patients with HCC and no-CSPH versus 15 patients with HCC and CSPH, demonstrated that the two groups have the same incidence of peri-operative morbidity, and no differences in terms of disease-free and overall survival [41]. Those data were later confirmed from another study including patients undergone minor and major laparoscopic and robotic liver resections and comparing CSPH versus no-CSPH ([18 and 27], respectively) [42]. Those data confirm that indications for minimally invasive liver surgery can be pushed in experienced centers and after a specific learning curve, to guarantee oncological outcomes and patient safety.

5. Future liver remnant augmentation: portal vein embolization versus ALPPS procedure

After the introduction of portal vein embolization (PVE) by Makuuchi et al., in 1990 [43], several Asian centers advocated its safety and feasibility in cirrhotic patients with hepatocellular carcinoma (HCC), and the increased volume of the future liver remnant (FLR) by PVE was approximately 30%–40% [44,45]. A meta-analysis on PVE for major liver resection demonstrated that percutaneous transhepatic approach produces greater increase in FLR volume than transileocolic approach via minilaparotomy [46]. The access route to the portal system can either be ipsilateral (through the tumor-bearing liver) with retrograde embolization, or contralateral (through FLR) with antegrade embolization. Comparisons between these two methods have shown equivalent safety and efficacy [47]. Azoulay et al. were the first to report comparable long-term outcomes after major liver resection for HCC in injured liver with ($n = 9$) and without PVE ($n = 19$) [48]. They systematically performed PVE for patients needing major hepatectomy when FLR was $\leq 40\%$ and described a significant increase in FLR (gain, $46 \pm 24\%$; $p < 0.0001$). None of the patients suffered post-hepatectomy liver failure. A systematic review concluded that patients with preexisting liver damage due to cirrhosis demonstrated less hypertrophy response to PVE compared to normal liver [49]. More recently, Sun et al. reported no significant difference in FLR enlargement 4–6 weeks after PVE between cirrhotic ($n = 12$) and non-cirrhotic ($n = 9$) patients undergoing right hepatectomy for primary liver cancer (HCC, 17; intrahepatic cholangiocarcinoma, 4) [50].

Associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) [51] is gaining momentum as an alternative for liver augmentation for the higher degree and more rapid enlargement of FLR than PVE. The high short-term morbidity and mortality rates reported in the early series have considerably improved over the years due to the establishment of the international ALPPS registry (<http://www.alpps.net/?q=registry>) and technical refinements [52]. However, D'Hasse et al. reported an unacceptably high 90-day mortality of 31% in patients who underwent ALPPS for HCC ($n = 35$), which was almost fivefold higher than that for colorectal liver metastases ($n = 225$; 90-day mortality, 7%, $p < 0.001$) based on the aforementioned registry data. They concluded that ALPPS for HCC should only be employed in highly selected patients < 60 years of age with low-grade fibrosis [53]. Other centers reported varying results of ALPPS for HCC in cirrhotic patients: although the increase of FLR was adequate ranging from 50% to $> 70\%$ in a median of seven to 14 days, the mortality rate still exceeded 10% [54–56]. More recently, Chan et al. reported a landmark study comparing ALPPS ($n = 45$) vs. PVE ($n = 69$) for HCC [57]. This was one of the largest series describing the effect of liver augmentation in a cirrhotic liver [65/114 (57%) patients who underwent resection had cirrhosis]. ALPPS increased FLR by 48.8% over six days and provided higher resectability rate compared with PVE (97.7% vs. 67.7%, $p < 0.001$). The hospital mortality was 6.5%, equivalent to that of PVE (5.8%, $p = 1.00$). It is noteworthy that no significant difference was observed in 5-year overall survival (ALPPS, 46.8% vs. PVE, 64.1%; $p = 0.23$), regardless of tumor stage and without obvious discrepancy in the pattern of disease recurrence. They proposed that ALPPS should be reserved for patients with FLR/estimated standard liver volume $<$

30% and PVE for FLR/estimated standard liver volume 30%–40%, with exception for tumors with macrovascular invasion requiring more rapid regeneration. They also mentioned that a longer interval of two weeks or more is required between the ALPPS procedure and stage II hepatectomy in patients with a cirrhotic liver or those with intraoperative indocyanine green value $> 39.5\%$. Based on the evidence available to date, there are pros and cons of PVE and ALPPS and both techniques are considered to play complementary roles in improving resectability of primary liver cancer in cirrhotic patients. Evidence remain scarce regarding the effect of liver augmentation on tumor microenvironment and well-designed, prospective studies are warranted to establish indications of PVE and ALPPS.

Besides conventional PVE and ALPPS, other innovative techniques have been introduced for further augmentation of FLR in cirrhotic patients.

- i. The use of sequential transarterial embolization (TAE) + PVE for a cirrhotic liver has been advocated by several centers [58–61]. All reported significantly improved disease-free survival; however, whether TAE + PVE induces significantly higher increase in FLR size than PVE alone remains inconclusive [58,60,61].
- ii. Yttrium-90 (^{90}Y) radioembolization is another alternative for PVE. Four centers have reported ^{90}Y radioembolization followed by major hepatectomy in more than 40 patients with cirrhosis, mostly for HCC [62–65]. Although a wide variety exists in the embolization agent, radiation dose, and number of sessions, the procedure is well tolerated with promising oncological outcomes. A systematic review described a significantly higher degree of FLR increase with PVE compared with ^{90}Y radioembolization within a shorter time interval, but this study included both normal and cirrhotic livers [66]. The definitive role of this emerging therapy with special reference to the kinetic growth rate, adverse events, and long-term prognoses needs further evaluation [67].
- iii. Sequential right hepatic vein embolization in cirrhotic patients who showed limited FLR hypertrophy after PVE awaiting right hepatectomy safely and effectively facilitated liver regeneration, although the rate of enlargement was lower compared with that of non-cirrhotic patients [68]. Guiu et al. conducted simultaneous PVE and embolization of the right and middle hepatic veins (extended liver venous deprivation) in non-cirrhotic patients with marked and rapid increase in FLR function and volume [69]. The same team stated that while the increase in FLR volume with this technique is comparable to ALPPS, the FLR functional increase measured by $^{99\text{m}}\text{Tc}$ -mebrofenin hepatobiliary scintigraphy is substantially better than ALPPS [70]; however, whether these findings are applicable to cirrhotic patients remains unknown.
- iv. A recent meta-analysis on the protective role of ischemic preconditioning before the Pringle maneuver (hepatic inflow occlusion) during liver resection concluded that ischemic preconditioning may be beneficial for cirrhotic patients by significantly reducing postoperative morbidity compared with the control group, based on six randomized control trials that enrolled both cirrhotic and noncirrhotic patients [71].
- v. Splenectomy in cirrhotic patients with hypersplenism has been reported to alleviate liver function, improve immunological response, and reduce HCC recurrence [72–74]. A meta-analysis concluded that simultaneous splenectomy and hepatectomy for HCC complicated with hypersplenism increase postoperative white blood cell and platelet counts, ameliorates liver function, and improves disease-free and overall survival rates; however, all pooled studies were retrospective and observational [75].
- vi. In situ hypothermic liver perfusion during liver resection is considered beneficial to reduce ischemic-reperfusion injury; however, there is only one randomized control study that prospectively compared this technique with the gold standard intermittent Pringle maneuver in patients without underlying liver disease

undergoing right (extended) hepatectomy [76]. Whether it can be safely and effectively applied in cirrhotic patients warrants further investigation.

- vii. Two-stage hepatectomy with portal vein ligation has been widely accepted for noncirrhotic patients with multiple bilobar colorectal metastases and yields satisfactory short- and long-term outcomes [77]. Its indication in cirrhotic livers has yet to be defined.

5.1. Postoperative management and management of complications

Attentive postoperative management forms a core element in ensuring an uneventful and speedy recovery after major hepatectomy, especially in cirrhotic livers. A tight fluid balance should be maintained throughout the perioperative phase [78]. Supplementary intravenous albumin infusion in the first few postoperative days helped to maintain adequate oncotic pressure in the intravascular compartment and urine output. Opioids should be avoided for pain control due to the risk of paralytic ileus and non-steroidal anti-inflammatory agents is preferred. Early postoperative oral nutrition that promoted liver regeneration should commence as soon as possible and could be supplemented by branched chained amino acids [79]. An enhanced recovery program has been shown to hasten recovery and shorten hospital stay [80–82]. Active spirometry exercise should be practiced to reduce the chance of atelectasis or pneumonia.

Vigilance for subtle abnormal clinical signs such as borderline tachycardia, pyrexia, oliguria or prolonged ileus facilitated early detection of postoperative complications that remained crucial to avoid fatality. Exploratory laparotomy is indicated if there are clinical signs suspicious of haemorrhage [83]. In case of portal vein thrombosis, emergency thrombectomy via operative approach [84] or radiological approach with thrombolysis [85,86] were both effective measures. For postoperative biliary leakage, endoscopic retrograde cholangiopancreatography with stenting allows early detection and timely intervention to seal off the leakage [87–89]. For large volume (i.e. > 200ml/day) of biliary leakage, early operative repair was still preferred due to the risk of antibiotic resistant biliary sepsis caused by prolonged biliary fistula.

One of the most dreadful complications, for both surgeons and patients, was post-hepatectomy liver failure (PHLF) that was frequently associated with mortality. A substantial reduction of liver mass after major hepatectomy gave rise to a phenomenon in analogy with ‘small for size syndrome’ in living-related liver transplantation [90]. The increased portal flow and pressure to the small remnant liver after hepatectomy caused significant hepatocyte damage owing to the increased sinusoidal stress [90]. PHLF could be classified into three grades according to the recommendations by the International Study Group of Liver Surgery (ISGLS) [91] while serum platelet counts and the albumin-bilirubin (ALBI) score provided good predictive value for PHLF [92–94]. With regard to management, Grade A PHLF usually resolved on conservative management while a more aggressive treatment approach for grade B PHLF in the form of fresh-frozen plasma, albumin infusion, diuretics and branch-chained amino acids supplementation were indicated. Postoperative somatostatin infusion to reduce the portal pressure should also be considered providing the portal pressure was > 20mmHg [95]. On the other hand, the evidence to support the use of molecular adsorbent recirculating system (MARS) was still lacking [95]. For grade C PHLF, a timely referral for liver transplantation before occurrence of septicemia should be considered in order to improve the outlook of the patient [96].

6. Conclusion

A detailed preoperative evaluation, choosing the appropriate operative approach and surgical maneuver to minimize intraoperative bleeding, followed by attentive postoperative management form the cornerstones for a safe liver resection in cirrhotic livers.

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Albert Chan: Conceptualization, Data curation, Formal analysis, Project administration, Writing - original draft. **Alfred Kow:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Taizo Hibi:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Fabrizio Di Benedetto:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing. **Alejandro Serrablo:** Formal analysis, Data curation, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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