We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Liver Resection for Hepatocellular Carcinoma

Mazen Hassanain, Faisal Alsaif,
Abdulsalam Alsharaabi and Ahmad Madkhali

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/54175>

---

1. Introduction

Hepatocellular carcinoma (HCC), an epithelial tumor derived from hepatocytes, accounts for 80% of all primary liver cancers and ranks globally as the fourth leading cause of cancer-related deaths. Annual mortality rates of HCC remain comparable to its yearly incidence, making it one of the most lethal varieties of solid-organ cancer. Well-established risk factors for the development of HCC include hepatitis B carrier state, chronic hepatitis C infection, hereditary hemochromatosis, and cirrhosis of any etiology, as well as certain environmental toxins. HCC treatment is a multidisciplinary and a multimodal task with surgery in the form of liver resection and liver transplantation representing the only potentially curative modalities. Here we going to discuss the liver resection as treatment modality for HCC in detail.

1.1. Pathology of HCC

Three gross morphologic types of HCC have been identified: nodular, massive and diffuse. Nodular HCC is often associated with cirrhosis and is characterized by well-circumscribed nodules. The massive type of HCC, usually associated with a non-cirrhotic liver, occupies a large area with or without satellite nodules in the surrounding liver. The less common diffuse type is characterized by diffuse involvement of many small indistinct tumor nodules throughout the liver. *Histologically*, six growth forms of HCC can be differentiated. The most common form is the trabecular type, usually comprising highly differentiated carcinomas with polygonal tumor cells similar to hepatocytes; they grow in multilayered trabeculae and enclose blood spaces lined with endothelium (usually without Kupffer cells). The pseudoglandular type is generally found in combination with the trabecular form. It is characterized by the formation of gland-like structures containing detritus and bile or liquid material. The scirrhous type shows excessive deposits of sclerosed connective tissue, which is relatively low in cells. The

Surgical:
Liver resection
Liver transplantation
Locoregional:
- Ablation:
Radiofrequency ablation (RFA)
Percutaneous ethanol injection (PEI)
Cryotherapy
- Embolization:
Bland embolization
Transarterial chemoembolization (TACE)
Radioembolization
Systemic treatment:
Sorafenib
External beam radiation therapy and stereotactic radiotherapy

Table 1. Different treatment modality of HCC

moderately differentiated tumor cells lie between the septa, which resemble connective tissue. This type is mostly found after chemotherapy or radiation therapy. The solid type is an undifferentiated HCC, with the tumor cells displaying considerable cellular polymorphism; the trabecular tissue pattern has disappeared. The tumor is compact due to compression of the sinusoids. Differentiation is, however, only possible in rare cases, since there is often considerable heterogeneity within the tumor, i.e. different tissue types may be found in the same HCC. Fibrolamellar HCC is rare; it consists of solid cell trabeculae with connective-tissue septation and a capsule. Spindle cell-like differentiated HCC is likewise a very rare histological form with a fascicular-sarcomatous growth pattern. Prognosis is significantly poorer than with other forms of HCC.

1.2. Preoperative evaluation

The preoperative evaluation for resection of HCC should focus on the likelihood of disease being confined to the liver, and whether the anatomical location of the tumor and the underlying liver function will permit resection (table 2).

Preoperative checklist for HCC patient	
Chick points	Remark
History:	
Age	
Comorbidities	
Liver disease	Symptom of liver cirrhosis
Alcohol /smoking	

Medication (warfarin, aspirin)	
Previous surgery	
Physical status	
Examination:	
Stigmata of liver disease	
Chest /CVS/abdomen	
Nutritional assessment	
Laboratory:	
CBC	Platelet level is an indirect reflection of portal hypertension in cirrhosis.
LFT	Bilirubin level for synthetic liver function and for Child Pugh score
Coagulation	PT/INR for synthetic liver function and for Child Pugh score
Chemistry	For electrolyte imbalance in cirrhotic patient and assessment of renal function
Albumin	Liver synthetic function, nutritional status and Child Pugh score
AFP	Tumor marker for HCC
Hepatitis screen	HBV and HCV
Radiology:	
US	Screening image for high risk patient It evaluate liver lesion and liver parenchyma
CT and /or MRI	- Number and size of lesion and it's relation to major vessel - If it is classic HCC appearance by one image no need to be supported by another imaging. - Assessment of future liver remnant - Role out metastasis
Portal Portal vein pressure	If patient cirrhotic and he is candidate for surgery with questionable portal hypertension
Portal vein embolization	If future liver remnant small
Biopsy:	
Core biopsy (tumor)	If CT and /or MRI are not classical for HCC
Liver biopsy	If cirrhosis is not clear and sometime to know the cause of cirrhosis
Others:	
Child Pugh score	If patient cirrhotic
ICG	For assessment of adequate liver reserve before major resection (in some centers)
Pre anesthesia evaluation	

Table 2. Preoperative checklist for HCC patient

1.3. Determining the extent of tumor involvement

Anatomic delineation of tumor extent is best achieved with dynamic multiphase CT or MRI scanning. Arterial phase imaging detects 30 -40 % more tumor nodules than conventional CT and may be the only phase to demonstrate the tumor in 7 -10 % of cases. Typical picture of HCC on CT will be an enhanced lesion on arterial phase (figure 1(a)) and early washout of contrast on venous phase (figure 1(b)).

Figure 1. (a) Enhanced lesion on arterial phase in HCC (b) Early washout of contrast on venous phase in HCC

There is no general rule regarding tumor size for selection of patients for resection. Certainly, patients with smaller tumors are less likely to harbor occult vascular invasion and have a better outcome after therapy. Size alone is not a contraindication for resection of multinodular HCC.

Lymph node metastases are uncommon overall (between 1 - 8 %), but their presence portends a worse outcome. Preoperative detection of nodal metastases is limited by the frequent

presence of benign nodal enlargement, most often involving the porta hepatis and portacaval space, in patients with cirrhosis. Highly suspicious nodes based on enhancement similar to the intrahepatic HCC lesions indicate the need for biopsy in a patient being considered for resection. However, involved nodes are not a contraindication to surgery for fibrolamellar HCC; these patients should have a formal lymph node dissection.

A chest CT is recommended to complete the staging evaluation and bone scan if suspicious bone pain or hypercalcemia. HCC has lower FDG accumulation in well-differentiated and low-grade tumors than in high-grade tumors. In a study by *Khan et al*, the sensitivity of PET in diagnosis of HCC was 55% compared with 90% for CT scanning, although some tumors (15 %) were detected by PET only (including distant metastases). So, PET imaging may help assess tumor differentiation and may be useful in the diagnosis, staging and prognostication of HCC as an adjunct to CT. However, the utility of PET scanning for detection primary and occult distant metastatic disease is uncertain, need to be explored further and not recommended in guidelines from the National Comprehensive Cancer Network (NCCN).

1.4. Assessment of hepatic reserve

Operative mortality is related to the severity of the underlying liver disease; it is 7- 25% in cirrhotic and less than 3% in non-cirrhotic patients. In patients with cirrhosis, surgical resection is most safely performed in those with Child-Pugh class A (table 3) disease who has a normal bilirubin and well preserved liver function. However, even Child-Pugh class A patients may develop rapid hepatic decompensation following surgery due to limited functional hepatic reserve.

CHILD – PUGH SCORE			
Clinical and laboratory parameter	Scores		
	1	2	3
Encephalopathy (grade)	None	1-2	3-4
Ascites	None	Slight	Moderate
Albumin (g/dL)	> 3.5	2.8-3.5	< 2.8
Prothrombin time prolonged (sec)	1-4	4-6	6
Bilirubin (mg/dL)	< 2	2-3	> 3
For primary biliary cirrhosis	< 4	4-10	> 10

Class A = 5–6 points; Class B = 7–9 points; Class C = 10–15 points.
Class A: Good operative risk
Class B: Moderate operative risk
Class C: Poor operative risk

Table 3. Child Pugh score

Although helpful, the Child-Pugh classification and other tools for assessing underlying liver disease, such as the Model for End-stage Liver Disease (MELD) score, are not adequate to select patients with sufficient hepatic reserve for major resection.

Multiple studies have demonstrated that a normal serum bilirubin level and the absence of clinically significant portal hypertension (i.e., hepatic venous pressure gradient <10 mm Hg) are the best available indicators of acceptably low risk of postoperative liver failure after liver resection. In the absence of an elevated serum bilirubin and portal hypertension, survival after PH can exceed 70% at 5 years. Survival after liver resection in patients with significant portal hypertension alone decreases to < 50% at 5 years. However, in patients with both an elevated serum bilirubin and significant portal hypertension, survival drops to < 30% at 5 years, regardless of Child-Pugh score. Direct measurement of portal pressure is not necessary in patients with clinical signs of severe portal hypertension, including esophageal varices, ascites, or splenomegaly associated with a platelet count less than 100,000/mL.

In many centers the Child-Pugh score may be supplemented by specialized investigations such as the indocyaninegreen (ICG) retention test, especially in marginal cases (e.g. Child-Pugh B, possible mild portal hypertension). ICG retention of 14% at 15 min is widely accepted (in Asia Pacific area) as a reflection of adequate functional reserves for major resection (defined as resection of > 2 Couinaud segments) (figure 2).

Figure 2. Couinaud liver segments

Assessment of the volume and function of residual liver should also be addressed by CT volumetry, particularly since portal vein embolization can be a valuable tool to increase the liver remnant volume and function prior to major hepatic resection, particularly for right sided tumors.

1.5. Portal vein embolization

Preoperative portal vein embolization (PVE) is a valuable adjunct to major liver resection. PVE can initiate hypertrophy of the anticipated future liver remnant to enable an extended resection in a patient with normal liver or major resection in a well compensated cirrhotic patient that would otherwise leave a remnant liver insufficient to support life following partial hepatectomy.

There are potential benefits to use of PVE:

- Reduce post-operative morbidity and mortality,
- Convert unresectable tumor due insufficient future liver remnant to resectable for potential cure.
- Subclinical disease or rapid progression may be detected prior to definitive surgery on post-embolization imaging studies, thus sparing the patient an unnecessary operation.
- The absence of compensatory hypertrophy identify patient with impaired liver regeneration, for that decrease post liver resection failure by preclude them from major liver resection.

The success of PVE was addressed by *Abulkhir A et al*, in a meta-analysis of data from 37 published series of PVE prior to liver resection. Four weeks after PVE, there was an overall increase in liver volume of between 10 and 12 % that was independent of technique, and 85 % of patients underwent planned laparotomy for attempted major hepatectomy. Following resection, only 23 patients had transient liver failure (2.5 %), and seven patients died of acute liver failure (0.8 %).

Liver regeneration usually peaks within the first 2 weeks after PVE. Studies in swine have shown that regeneration peaks within 7 days of PVE, with 14% of hepatocytes undergoing replication. Regeneration rates reported for humans are comparable to those found in animals. Non-cirrhotic livers demonstrate the fastest regeneration: 12–21 cm³/day at 2 weeks after PVE, approximately 11 cm³/day at 4 weeks, and 6 cm³/day at 32 days. Livers in patients with cirrhosis or diabetes regenerate more slowly (approximately 9 cm³/day at 2 weeks). Biliary obstruction, diabetes, chronic ethanol consumption, nutritional status, male gender, old age, and hepatitis all limit regeneration. Controlling these factors where possible is essential to maximize liver hypertrophy.

Two techniques can be utilized for PVE:

- The TIPE procedure is performed via a minilaparotomy and requires general anesthesia.
- The percutaneous approach (PTPE), which is more commonly used, can be performed in the radiology suite with local anesthesia and conscious sedation.

Volumetric assessment of the liver volume with CT imaging should be done before PVE and again before surgery. A standardized technique for measuring the future liver remnant, to select patients for PVE prior to a planned extended hepatectomy (trisegmentectomy) or hemihepatectomy in the setting of underlying liver disease, is strongly recommended. In considering the need for PVE, the ratio of future liver remnant and total estimated liver volume should be calculated. If the future liver remnant is $< 20\%$ in a patient with a normal liver or 40% in a patient with a cirrhotic liver, PVE should be considered.

Some reports have shown accelerated tumor growth in the liver after PVE. Problems with tumor growth are not seen when all of the tumor-bearing areas of the liver are embolized.

Transarterial chemoembolization (TACE) has been proposed as a complementary procedure prior to PVE in patients with HCC. TACE not only eliminates the arterial blood supply to the tumor, but it also embolizes potential arteriportal shunts in cirrhotic livers that attenuate the effects of PVE. Most reserve the "double embolization" procedure for patients with HCC in patients with liver disease who require right hepatectomy.

2. Surgery

Liver resection is a potentially curative therapy for patients with early-stage HCC (solitary tumor ≤ 5 cm in size, or ≤ 3 tumors each ≤ 3 cm in size and no evidence of gross vascular invasion) in a Child-Pugh class A score and no evidence of portal hypertension (although a minor resection could be considered in some patients with portal hypertension) ^{Table 4}. However, in highly selected cases, patients with a Child-Pugh class B score may be considered for limited liver resection, particularly if liver function tests are normal and no portal hypertension.

Optimal tumor characteristics for liver resection are solitary tumors without major vascular invasion. Although no limitation on the size of the tumor is specified for liver resection, the risk of vascular invasion and dissemination increases with size. However, in one study by *Pawlik TM*, no evidence of vascular invasion was seen in approximately one-third of patients with single HCC tumors of 10 cm or larger. Nevertheless, the presence of macro- or microscopic vascular invasion is considered to be a strong predictor of HCC recurrence.

Liver resection is controversial in patients with limited and multifocal disease as well as those with major vascular invasion. Multifocality is associated with lower survival, but does not exclude a good outcome in selected patients. In several studies, resection of multifocal HCC is associated with five-year survival rates of approximately 24 %. Patients with multinodular HCC who appear to benefit from resection are those with sufficient liver reserve to tolerate resection, without extrahepatic disease and without major vascular invasion. Liver resection in patients with major vascular invasion should only be performed in highly selected situations by experienced teams.

Despite even aggressive surgical approaches, most patients have HCC or liver disease too advance to permit treatment with "curative" intent. In high-incidence regions of the world, only 10 to 15 % of newly diagnosed patients are candidates for standard resection, whereas in

low incidence areas, between 15 and 30 % of patients are potentially resectable. Furthermore, only one-half of patients referred for surgery actually have resectable tumors. Among the reasons for unresectability are the extent of intrahepatic disease, extrahepatic extension, inadequate functional hepatic reserve, and involvement of the confluence of the portal or hepatic veins.

Indication for liver resection:
Indicated:
- Solitary tumor ≤ 5 cm in size or ≤ 3 tumors each ≤ 3 cm in size and no evidence of gross vascular invasion.
- Solitary tumors (any size) without major vascular invasion.
Patient should be in a Child-Pugh class A and no evidence of portal hypertension
Controversial:
- Multifocal disease
- Major vascular invasion
- Child-Pugh class B score and no portal hypertension

Table 4. Indications for liver resection in hepatocellular carcinoma

2.1. Intraoperative staging

Laparoscopy and intraoperative ultrasound (IOUS) may improve the selection of patients for potentially curative resection. IOUS can accurately determine the size of the primary tumor and detect portal or hepatic vein involvement, which precludes curative resection. Another benefit of IOUS is the identification of major intrahepatic vascular structures, which can be used to guide segmental or non-anatomic resections.

2.2. Technique

In non-cirrhotic liver, an anatomical resection should be performed. Up to two-thirds of the functional parenchyma can be removed safely depending upon the age of the patient and his liver's regenerative capacity. However, for cirrhotic patients, because the capacity for liver regeneration is impaired in these patients, resection is generally limited to less than 25% of functional parenchyma. to maintain postoperative liver function. However, some patients maintain adequate functional hepatic reserve even after a formal hemi-hepatectomy, particularly if preoperative portal vein embolization (PVE) is used to induce compensatory hypertrophy in the future liver remnant. Both anatomic and wedge resection are acceptable, though some studies suggest portal-oriented resections enable longer overall and disease-free survival when feasible which might be because of the pattern of intrahepatic spread of liver cancer cells along segmental portal vein pedicle, so segmental resection may improve the chance of tumor clearance compared with a non-anatomical wedge resection.

Surgical outcomes in cirrhotic patients have improved over the past decade as a result of advances in surgical techniques, in particular the techniques that help to reduce bleeding during liver parenchyma transection and perioperative support. One of the most important advances is the thorough understanding of the segmental anatomy of the liver, which can be delineated using intraoperative ultrasound during operation. The delineation of a proper transaction plane is important not only for adequate tumor-free margin in resection of liver tumors but also to avoid inadvertent injuries to major intrahepatic vessels or bile duct pedicles. Use of the Pringle maneuver for vascular inflow occlusion as an alternative to total vascular occlusion has decrease deleterious effect on liver. Intermittent Pringle occlusion is well tolerated by cirrhotic patients for up to 60 minutes and is better tolerated than continuous clamping. The use of low CVP (less than 5mm Hg) anesthesia and newer instruments such as the ultrasonic dissector, hydrojet and vascular stapling devices has also significantly improved visualization, limited blood loss and decreased operative times.

2.3. Anterior technique

Some surgeons have advocated an anterior or "no touch" technique to resection of these tumors. This approach utilizes initial transection of the liver parenchyma to the inferior vena cava (IVC), and ligation of the inflow and outflow vessels before mobilization of the right liver lobe. The advocates of this technique hypothesize that separation of the right liver and the tumor from the IVC before mobilization avoids prolonged rotation and displacement of the hepatic lobes, therefore reducing the risk of vascular rupture. In addition, division of the vessels before tumor manipulation theoretically minimizes the potential for tumor cell dissemination caused by tumor compression.

2.4. Centrally located tumors

Surgical management of centrally located tumors (i.e., those in segments IV, V, and VIII) is especially problematic. Extended right or left hemi-hepatectomy is the treatment of choice if potentially curative surgery can be undertaken safely. An alternative segment-oriented approach, meso-hepatectomy (also called central hepatectomy), has been proposed in which the central liver segments IV and/or V, and VIII (with or without segment I) are removed and the lateral sectors remain intact.

While randomized trials have not been conducted, the available data suggest that meso-hepatectomy is a reasonable alternative to extended resection for centrally located tumors, providing acceptable oncologic outcomes with less hepatic parenchymal loss. However, in some centers, meso-hepatectomy is seldom used, partly because it is a complex and technically demanding procedure that requires two hepatic resection planes and bilateral biliary reconstruction. This results in a higher risk of bile leak and bleeding as well as long-term biliary stricture and biliary dysfunction. In addition, some data suggest that portal vein embolization followed by major hepatectomy might be safer.

2.5. Minimally invasive surgery

The success of minimally invasive resection of benign hepatic tumors has led to interest in laparoscopic approaches to surgery for HCC. The available literature is limited by the lack of prospective trials and the paucity of information on long-term oncologic outcomes.

Looking to the available literature, laparoscopic resection is feasible and safe in experienced hands. It is also highly technically demanding and should be undertaken only in high volume centers.

2.6. Tumor rupture

Approximately 10% of HCC spontaneously rupture. The clinical picture is that of acute abdominal pain and distension with drop in the hematocrit and hypotension. Initially, these patients' hemodynamic should be stabilized followed by trans-arterial embolization for control of bleeding. If unsuccessful, emergency surgery may be required.

Although the presence of a tumor rupture suggests a high likelihood of peritoneal seeding and usually a poor outcome from resection, this is not inevitable. If bleeding can be controlled (arterial embolization is recommended), a formal staging evaluation should be undertaken, followed by laparoscopic exploration and a subsequent attempt at resection, if feasible. Several retrospective series suggest a low, but defined long-term survival rate following resection in such situations.

In the largest series from Hong Kong by *Liu CL et al*, 154 of 1716 patients who were newly diagnosed with HCC between 1989 and 1998 presented with spontaneous rupture. The 30-day mortality rate following tumor rupture was 38 %. After initial stabilization and clinical evaluation, 33 underwent hepatic resection. Although the median survival after hepatectomy was worse in ruptured as compared to non-ruptured cases (26 *versus* 49 months) and the rate of extra-hepatic recurrence was higher (46 *versus* 26 %), 8 patients (24 %) remained alive without recurrent disease after a median follow-up period of 45 months.

2.7. Postoperative management

Postoperative management is primarily supportive. Those patients should be monitored in ICU with great attention to hydration status, not over or under hydrated with CVP monitor. The extent of postoperative morbidity is related to the extent of operative resection. Major postoperative complications include bile leak in 8% and pleural effusion in 7%, which are usually treated conservatively.

2.8. Perioperative mortality

The 30-day operative mortality rate in modern series of HCC resection ranges widely from 1 -24 %. Fewer than 10 % of perioperative deaths are due to uncontrolled intraoperative hemorrhage; most are due to postoperative liver failure. The presence of cirrhosis is the most important predictor of post-resection liver failure and death. The 30-day postoperative mortality for cirrhotic patients ranges from 14 -24 %, compared to 0.8 -7 % for non-cirrhotics.

Two additional factors influence the development of postoperative liver failure in cirrhotic patients are intraoperative blood loss of >1500 ml and postoperative infection of any type. Mortality can also be reduced by appropriate selection of patients and meticulous surgical technique, with the inclusion of preoperative volumetry and portal vein embolization when appropriate.

Consensus is growing that 30-day operative mortality is an inadequate indicator of risk, particularly of postoperative hepatic insufficiency and failure. Using an approach similar to liver transplantation reporting, 90-day mortality reporting appears to be a more valuable indicator of outcome of liver resection, especially in the cases of extended resection and resection in patients with diseased livers. This relates to the late development of slowly progressive jaundice, ascites, and eventual death, which typically occurs outside the hospital and well after 30 postoperative days in patients with marginal or inadequate liver remnants (post resection liver failure will be discussed in detail at end of this chapter).

2.9. Fast track surgery

Surgical pathway and 'fast-track' (FT) programs are structured interdisciplinary strategies that have been introduced to optimize perioperative care and accelerate post-operative recovery. The main aim of the FT protocol is to reduce the metabolic and inflammatory response to surgical stress and preserve vital functions. A review done by *Lidewij et al* showed primary hospital stay was significantly reduced after FT care in two out of the three studies. In one study, median hospital stay was 6 days in the FT group compared with 8 days in the control group ($P < 0.001$). In the other study, primary hospital stay was reduced from 11 days to 7 days ($P < 0.01$). There were no significant differences in rates of readmission, morbidity and mortality between FT and control groups. One trial found a significantly shorter time to successful resumption of a normal diet in the FT group (1 post-operative day for FT patients vs. 3 days for the control group).

3. Long-term outcomes

Results of large retrospective studies have shown 5-year survival rates of over 50% for patients undergoing liver resection for HCC, and some studies suggest that in carefully selected patients having no vascular invasion by tumor, solitary lesions without intrahepatic metastasis, tumor diameter ≤ 5 cm, and a negative surgical margin of >1 cm, five-year survival rates up to 78 %. However, HCC tumor recurrence rates at 5 years following liver resection have been reported up to 70%.

Palavecino M et al reported series of 54 patients with advanced HCC and significant tumor burden who were treated with PVE plus major hepatectomy, the five-year overall survival was 72 % and the five-year disease-free survival was 56 %.

3.1. Tumor-related prognostic factors

The most important tumor-related prognostic factors are presence and degree of vascular invasion, tumor number and size, and surgical margin status. Other poor prognostic indicators are absence of a tumor capsule, preoperative alpha fetoprotein (AFP) levels >10,000 ng/ml, and poor histologic grade of differentiation.

Both intrahepatic and extra-hepatic spread of HCC is more common with tumors >5 cm, particularly when associated with venous invasion. In a report by Zhou XD compared 1000 patients with tumors ≤5 cm and 1366 patients having tumors >5 cm, all of whom underwent hepatectomy over the same period, five-year survival rates were significantly better for patients with smaller tumors (63 % versus 37 %, respectively). Nevertheless, several series indicate five year survival rates ranging from 25 to 35 percent in selected patients undergoing resection for single HCC ≥10 cm. However, although increasing tumor size is associated with increased risk for vascular invasion, large, solitary tumors without vascular invasion have the same prognosis as small solitary tumors without vascular invasion.

The importance of wide resection margins is debated. In study by Ozawa K of 225 patients with HCC who underwent resection, three-year survival was significantly better when a >1 cm tumor-free margin was achieved (77 % versus 21%, respectively). However, larger series by Poon RT suggest that a negative margin of <1 cm is acceptable.

Gross or microscopic invasion of branches of the portal or hepatic veins is associated with a lower probability of survival following resection.

3.2. Underlying liver dysfunction

Preoperative liver dysfunction and cirrhosis are important negative prognostic factors. Yamanaka N reported a series of 295 patients undergoing resection of HCC, the four-year survival was more than twofold higher for non-cirrhotic compared to cirrhotic patients (81% versus 35 %). This difference in outcome may be related in part to the higher frequency of multicentric HCC in cirrhotic patients.

In patients with cirrhosis related to HBV infection, active hepatitis is also a poor prognostic factor. As a general rule, the severity of cirrhosis, rather than the presence of a small, early stage HCC, limits long-term survival in cirrhotic patients with HCC. Chronic liver disease provides a field that contributes to the development of second primary HCCs and a persisting risk of HCC-related death beyond five years.

3.3. Recurrences

Treatment of recurrence is a poorly investigated area. Solitary recurrence might benefit from repeat resection, but in most patients recurrence will be multifocal. It has been suggested, retrospective analyses, that patients with recurrence might be candidates for salvage transplantation. Most of the recurrences and specially those that appear early during follow-up are due to tumor dissemination and have a more aggressive biological pattern as compared to primary tumors. Hence, only those patients in whom recurrence is due to de novo oncogenesis

can be expected to benefit from salvage transplantation or repeated resection. While the most accurate predictors of recurrence due to dissemination (vascular invasion, satellites) may be identified on pathology, and since the results of transplantation in these patients is good, some authors have proposed that this category of patients should be listed immediately after resection. This might be more effective than waiting for recurrence to develop with excessive tumor burden possibly excluding liver transplantation. Organ allocation policies might have to be modified to take these findings into account. Other treatment modalities can provide disease control (i.e., trans-arterial arterial embolization of chemoembolization, radiofrequency ablations, sorafenib).

Fewer than 20 % of disease recurrences have an extra-hepatic with overall poor prognosis, and the benefit of systemic therapy is modest, at best.

3.4. Surveillance

Although data on the role of surveillance in patients with resected HCC are very limited, recommendations are based on the consensus that earlier identification of disease may facilitate patient eligibility for investigational studies or other forms of treatment. The NCCN panel recommends high-quality cross-sectional imaging every 3-6 months for 2 years, then every 6-12 months. AFP levels, if initially elevated, should be measured every 3 months for 2 years, then every 6-12 months. Re-evaluation according to the initial work-up should be considered in the event of disease recurrence.

3.5. Survival

Liver resection is a potentially curative therapy for patients with early-stage HCC (solitary tumor ≤ 5 cm in size, or ≤ 3 tumors each ≤ 3 cm in size and no evidence of gross vascular invasion). 5-year survival rates of over 50% for patients undergoing liver resection for HCC, and some studies suggest that for selected patients with preserved liver function and early stage HCC, liver resection can achieve a 5-year survival rate of about 70%. However, HCC tumor recurrence rates at 5 years following liver resection have been reported to exceed 70%.

3.6. Post-Resection Liver Failure (PRLF)

PRLF is a devastating complication that is resource intensive and carries with it considerable morbidity and mortality. The reported incidence of PRLF ranges between 0.7 - 9.1%. An inadequate quantity and/or quality of residual liver mass are key events in its pathogenesis. Major risk factors are the presence of comorbid conditions, pre-existent liver disease and small Remnant Liver Volume (RLV). It is essential to identify these risk factors during the pre-operative assessment that includes evaluation of liver volume, anatomy and function.

There is no uniformity concerning the definition of PRLF. In general, PRLF is characterized as failure of one or more of the hepatic synthetic and excretory functions that include hyperbilirubinemia, hypo-albuminemia, prolonged prothrombin time, elevated serum lactate and/or different grades of hepatic encephalopathy (HE). PRLF is defined by the so-called 50-50 criteria, which describe PRLF as prothrombin index less than 50% (equal to an international

standardized ratio more than 1.7) and serum bilirubin more than 50 mmol/L (2.9 mg/dL) on post-operative day 5. When these 50–50 criteria were fulfilled, patients had a 59% risk of mortality compared with 1.2% when they were not met (sensitivity 69.6% and specificity 98.5%). This rarely occurs in isolation and is often coupled with failure of multiple organs and/or features of sepsis.

3.7. Pathophysiology of PRLF

After resection of various amounts of functional liver mass, both death and regeneration of the remaining hepatocytes occur. Physiologically, regeneration outweighs hepatocyte death and both liver mass and function are restored rapidly. For example, during the first 10 days after right hepatectomy for living donor liver transplantation, restoration of liver mass up to 74% of the initial volume has been reported. This regeneration is triggered by an increased metabolic demand placed upon remnant hepatocytes. The ability of the liver remnant to surmount the effect of surgical resection depends on its capacity to limit hepatocyte death, to resist metabolic stress, to preserve or recover an adequate synthetic function and to enhance its regenerative power. These factors rely on both the quality and the quantity of remaining liver parenchyma. A variety of intraoperative as well as post-operative hits identified that may attribute to the development of PRLF. These include hepatic parenchymal congestion, ischemia–reperfusion injury (IRI) and reduced phagocytosis capacity. Liver failure could be defined as either “cholestatic” (characterized by regeneration of hepatocytes and fibrosis) or “non-regenerative” (characterized by pronounced apoptosis of hepatocytes).

3.8. Hepatic parenchymal congestion

Partial liver resection leads to a relatively augmented sinusoidal perfusion, leading to shear–stress and congestion of hepatic parenchyma and resulting in vascular and parenchymal damage similar to small-for-size syndrome after liver transplantation, although less severe. Moreover, inadequate venous drainage of the liver remnant induces hepatic venous congestion and functional hepatic volume loss. Hepatic parenchymal congestion may be less severe in patients with cirrhosis of the liver with preexisting portacaval collaterals.

3.9. Hepatic ischemia–reperfusion injury

Hepatic ischemia–reperfusion injury follows massive bleeding or hepatic in- or outflow occlusion during liver surgery. Although the resistance of the liver to warm ischemia is relatively high, hepatic ischemia and reperfusion activate a complex cascade that triggers the innate immune response by recruitment and activation of Kupffer cells, endothelial cells and the complement system. These express pro-inflammatory proteins [nuclear factor κ B, tumour necrosis factor- α , interleukin-6], reactive oxygen species, chemokines, complement factors and vascular cell adhesion molecules. Subsequently, polymorphonuclear neutrophils are activated, which aggravate hepatic injury. Although these processes are primarily intended to maintain homeostasis, unrestrained activation may become destructive.

3.10. Reduced phagocytosis capacity

Infection complicates the course of PLF either as a precipitant or during later stages. Partial hepatectomy reduced the phagocytosis capacity of the hepatic reticuloendothelial system. Nevertheless, the liver remnant has to clear bacteria and their products following bacterial translocation or intra-abdominal infection. Diminished hepatic clearance of bacteria might enhance the susceptibility for the development infections and PRLF.

3.11. Risk factors of PRLF

The extent of resection correlates most closely with rates of PRLF and death; and the incidence increases with the number of segments resected. The incidence of PLF is < 1 % in patients with no underlying parenchymal disease when 1-2 segments are resected, around 10 % when 4 segments are resected, and 30 % when 5 segments or more are resected. However, the exact amount of residual liver mass required to preserve sufficient liver function is unknown. In general, an RLV ≥ 25 –30% in otherwise healthy livers is consistent with a good post-resectional outcome. RLV below 25% in normal livers predicted PRLF with a positive predictive value of 90% (95% CI 68–99%) and a specificity of 98% (95% CI 92–100%). When liver function is restricted, RLV should be as high as 40% to guarantee adequate remnant liver function.

The use of vascular occlusive techniques and significant intraoperative blood loss can exacerbate the level of dysfunction. Vascular occlusive techniques induce ischemia in the liver remnant. These effects are greatest following total vascular exclusion (inflow + outflow occlusion), but also occur after prolonged intermittent inflow occlusion.

Intraoperative blood loss (> 1–1.2 liters) and the need for blood transfusion increase the risk of PLF and sepsis. This may relate to the immunosuppressive effects of blood transfusion or the initiation of the inflammatory response that accompanies significant hemorrhage.

Vascular reconstruction following *in situ en bloc* liver and inferior vena cava resection or *ex vivo* liver resection is associated with increased rates of PRLF. *Ex vivo* resection and reimplantation is associated with an unacceptably high mortality rate. Biliary reconstruction is associated with increased morbidity and mortality after liver resection but does not independently predict PRLF.

Underlying parenchymal disease reduces the functional and regenerative capacity of the liver remnant. In patients with cirrhosis but no functional impairment or portal hypertension, resection of up to 50 % is safe. In patients with Child–Pugh grade B or C disease, even small resections can result in PRLF. The high risk of developing PLF in patients with cirrhosis can be explained by the wide range of comorbid conditions like portal hypertension, diabetes mellitus, jaundice, malnutrition, hypersplenism and coagulopathy as well as frequent impaired preoperative liver function and hepatic functional reserve. Furthermore, patients with cirrhosis have an impaired hepatic regenerative capacity. NAFLD (non alcoholic fatty liver disease) represents a spectrum of disease ranging from steatosis to steatohepatitis (non-alcoholic steatohepatitis, NASH), fibrosis and cirrhosis. The grade of steatosis, correlates with rates of PRLF and death following major Resection. The presence of steatosis is hypothesized

to be associated with impaired hepatic microcirculation, decreased resistance to ischemia–reperfusion injury, increased intrahepatic oxidative stress and dysfunction in mitochondrial adenosine triphosphate synthesis. Chemotherapy-induced liver injury is increasingly prevalent as more patients receive chemotherapy for colorectal liver metastases before liver resection. Cholestasis reduces both hepatic metabolic and regenerative capacities, and increases rates of liver dysfunction after major resection.

Other patient-based factors that predict PRLF are age, malnutrition, diabetes mellitus and male sex. Elderly patients (≥ 65) suffer frequently from comorbid conditions and have reduced regenerative capacity of hepatocytes. Approximately 65–90% of patients with advanced liver disease suffer from protein–calorie malnutrition. Malnutrition is associated with an altered immune response, reduced hepatic protein synthesis and a reduction in hepatocyte regenerative capacity. Diabetes mellitus is associated with increased morbidity and mortality after liver resection. This may be due to immune dysfunction or because insulin absence or resistance reduces regenerative capacity. PRLF is more common in males as testosterone may have immune-inhibitory effects, predisposing to septic complications.

3.12. Prevention of PRLF

Diabetes mellitus should be screened for and treated before surgery. Nutrition should be evaluated and consideration given to preoperative oral carbohydrate loading in order to reduce postoperative insulin resistance. There is no evidence to support delaying liver resection for a period of nutritional optimization, unless the patient is severely malnourished. It has been hypothesized that the nutritional status of depleted patients should be corrected via oral, enteral or parenteral methods before surgery. A meta-analysis on the effect of total parenteral nutrition compared with enteral nutrition on morbidity and mortality after liver resection revealed no superiority of either form of nutrition. However, a beneficial effect of additional parenteral nutrition has been demonstrated in a subgroup of patients who had cirrhosis and underwent major hepatectomy.

The risk of PRLF may be reduced by strategies to increase parenchymal volume and protect against parenchymal damage. Strategies available for volume manipulation for HCC patients include portal vein embolization alone or in combined with locoregional treatment (RFA or TAE). Portal vein embolization induces apoptosis in the ipsilateral lobe, and proliferation and growth of the contralateral lobe. This increases the functional capacity of the liver remnant, limits the effects of hepatic hyperperfusion that may occur in a small-for-size remnant, and predicts the regenerative response in the future remnant. Failure to proliferate after portal vein embolization can be used to select patients with impaired regenerative capacity in which major resection would not be tolerated. The primary concern over portal vein embolization is that it may increase tumor growth owing to an ipsilateral surge in hepatic arterial flow. Locoregional treatment can be used in combination with Portal vein embolization to control tumor load before resection.

In order to limit parenchymal damage and optimize regenerative capacity, a series of hepatoprotective measures may be employed (intermittent portal clamping, ischemic precondition-

ing and hypothermic liver preservation). Total vascular occlusion should be avoided unless resection cannot be undertaken without it (for example a tumor at the cavohepatic intersection). If resection without vascular occlusion is not possible, inflow occlusion is preferable to total vascular exclusion. Intermittent portal clamping with intervals allowed for reperfusion is preferred to continuous clamping, usually applying a 15-min clamp–5-min release regimen. Ischemic preconditioning increases tolerance to prolonged hepatic ischemia and adenosine 5'-triphosphate depletion by exposing the parenchyma to short intervals of ischemia and reperfusion intraoperatively before resection. This downregulates ischemia–reperfusion injury and results in less hepatic injury. Ischemic preconditioning reduces the histological effects of ischemia–reperfusion injury, however, without improving clinical outcome. Hypothermic liver preservation in conjunction with total vascular exclusion attenuates ischemia–reperfusion injury. The future remnant is infused with a preservative fluid and surrounded by crushed ice to maintain the liver at 4 °C.

Data from living liver donors suffering from biopsy proven moderate steatosis revealed that a body weight reduction of 5% or intervention with a low-fat, high protein diet and exercise significantly improved hepatic steatosis. However, weight reduction before surgery may not be feasible because of time deficit and the often pre-existent malnutrition.

Patients with cirrhosis of the liver are more susceptible to the development of PRLF in case of resection of comparable tumor volumes. However, cirrhosis of the liver cannot be prevented and, therefore, prevention of PRLF in these patients can only be achieved by careful patient selection, adequate nutritional support and the use of an appropriate surgical technique.

3.13. Manifestation

PRLF reflects deregulation of the synthetic, excretory and detoxifying capacities of the liver remnant. In addition, the majority of patients suffering from PRLF will also meet the criteria of the systemic inflammatory response syndrome and experience multiple organ failure. Unfortunately, a substantial number of patients suffering from PRLF deteriorate, leading to a fatal outcome in approximately 80%. However, PRLF is a potentially reversible disorder because of the regenerative capacity of the liver remnant.

3.13.1. Liver

The clinical consequences of PRLF are jaundice, coagulopathy, ascites, edema and/or HE.

Ascites occurs as a result of surgery (portal hypertension, dissection, gross fluid overload), and may be difficult to assess it in the immediate postoperative period.

Data from Suc *et al.* and Balzan *et al.* concerning liver function on different days after uncomplicated hepatic resection showed an initial increase of serum bilirubin and a decrease of prothrombin time before normalization of these values on the seventh post-operative day.

3.13.2. Circulation

Circulatory failure occurring during PRLF resembles the circulatory failure of patients with sepsis. The pathophysiological changes usually observed are enhanced vascular permeability, diffuse intravascular coagulation and peripheral vasodilatation that are clinically represented by reduced peripheral resistance and hemodynamic instability.

3.13.3. Kidneys

Post-hepatic resection renal dysfunction can either result from perioperative disturbances in renal circulation inducing acute tubular necrosis or accompany PRLF. It is characterized by azotemia or oliguria and may cause ascites formation; pleural effusion and fluid overload requiring diuretics or hemofiltration. There is a distinct chance of reversibility of renal failure when there is recovery of PRLF. Furthermore, it can be hypothesized that the pivotal role of the kidney in ammonia excretion is impaired, leading to hyperammonemia and HE in patients suffering from PRLF.

3.13.4. Lung

Although moderate pulmonary edema seems to be a normal finding after partial hepatic resection owing to general hemodynamic alterations, this usually does not impair oxygen exchange. Severe remote lung injury, pulmonary edema and acute respiratory distress syndrome can develop as part of the multiple organ dysfunction syndromes that accompanies PRLF.

3.13.5. Hepatic encephalopathy

Hepatic encephalopathy is a potentially reversible neuropsychiatric disorder, characterized by varying degrees of confusion and disorientation. Hyperammonemia plays a central role in its development and has a direct toxic effect on neurotransmission and astrocyte function. Although hepatic encephalopathy are important markers for liver failure, altered mental state may occur in response to drugs such as opiates and may be difficult to assess it in the immediate postoperative period.

3.13.6. Treatment of PRLF

Large, randomized trials concerning the treatment of PRLF are lacking, and therefore, recommendations for treatment modalities are difficult to make. Management principles resemble those applied to patients with acute liver failure, acute-on-chronic liver failure or sepsis and focus on support of liver and end-organ function. Goal-directed therapy should be provided for circulatory disturbances, renal and ventilatory dysfunction, coagulopathy, malnutrition and HE (table 5). Patients should undergo clinical and laboratory assessment after liver resection, with the frequency of monitoring and level of care stratified according to risk.

It is normal for serum bilirubin levels and INR to rise in the first 48–72 h postresection. However, bilirubin concentration above 50 $\mu\text{mol/l}$ (3 mg/dl) or INR greater than 1.7 beyond 5 days is unusual and usually reflects liver dysfunction. Serum bilirubin remains the most sensitive predictor of outcome in PLF. PT and INR are also valuable, but interpretation may be compromised if the patient has received clotting factors. Serum albumin, although an indicator of hepatic synthetic function, will vary in response to inflammation and administration of intravenous fluids. Increased levels of liver enzymes are common after liver resection and do not predict outcome. C-reactive protein levels are dampened after major liver resection, and day 1 levels inversely correlate with PRLF indices. Serum lactate has a prognostic value in severe sepsis and ALF, with a serum lactate level above 3.0 mmol/l after fluid resuscitation predicting death in ALF.

The systemic inflammatory response syndrome (SIRS) is present in more than 50 % of patients with ALF and predicts a negative outcome. The incidence of SIRS in patients with PLF has not been evaluated formally, but as in ALF it is likely to be implicated in sepsis, encephalopathy and end-organ dysfunction. Several studies have examined the role of postoperative functional assessment of the liver. The ICG15 predicts PRLF, but its value diminishes once liver failure is established because changes in hepatic blood flow also influence ICG15. Although PRLF is a potentially reversible condition, mortality rates remain high and currently there is little scope for therapeutic intervention.

Management of PRLF must be undertaken in conjunction with critical care, hepatology, infectious disease and radiology services. The pattern of organ dysfunction that occurs as a result of PRLF is similar to that in sepsis. Cardiovascular failure is characterized by reduced systemic vascular resistance and capillary leak. Acute lung injury, pulmonary oedema and acute respiratory distress syndrome may ensue. Acute kidney injury can progress rapidly in PRLF. Fluid balance should be managed judiciously with avoidance of salt and water overload. Identifying and treating underlying sepsis is a key in managing patients with PRLF. Sepsis may exacerbate PRLF, and bacterial infection is present in 80 % of patients with PRLF and in 90 % of those with ALF. Any acute deterioration should be attributed to sepsis until proven otherwise. Management of sepsis should be in accordance with the surviving sepsis guidelines. A trial of prophylactic antibiotics after liver resection failed to show a reduction in liver dysfunction or infective complications. However, the administration of antibiotics in patients suffering from acute liver failure is associated with a significant decrease in infectious complications and this may also be advantageous in patients suffering from PRLF. In critically ill patients with PRLF, chest radiography and cultures of blood, urine, sputum and drain site/ascetic fluid should be performed. Current guidelines for ALF propose that broad spectrum antibiotics should be administered empirically to patients with progression to grade 3 or 4 hepatic encephalopathy, renal failure and/or worsening SIRS parameters.

Coagulopathy may occur transiently after major resections and is found in all patients with PRLF. As in ALF, coagulation parameters can be used to chart the progress of PRLF, provided blood products have not been given. In a multinational review of fresh frozen

plasma given for transient coagulopathy after resection, there was no consensus for its use. In the absence of bleeding it is not necessary to correct clotting abnormalities, except for invasive procedures or when coagulopathy is profound. The level at which a coagulopathy should be corrected before an interventional procedure in ALF has yet to be defined (the commonly used threshold for correction is an INR above 1.5). Vitamin K may be given, but this is not supported by clinical trials. Thrombocytopenia may complicate liver failure. Indications for platelet transfusion in ALF include bleeding, profound thrombocytopenia ($< 20 \times 10^6 / L$), or when an invasive procedure is planned. A platelet count above $70 \times 10^6 / L$ is deemed safe for interventional Procedures. Recombinant factor VIIa (rFVIIa) has been used to treat coagulopathy in patients with ALF. In a large controlled trial of rFVIIa following major liver resection, no reduction in bleeding events was observed. Its role in PRLF is yet to be defined.

Gastrointestinal hemorrhage is a recognized complication of liver failure. In ALF, H_2 -receptor blockers and proton pump inhibitors (PPIs) reduce gastrointestinal hemorrhage in mechanically ventilated patients. In the non-ventilated patient an oral or sublingual PPI or oral H_2 -receptor blocker is likely to protect against gastrointestinal hemorrhage. High risk patients or patients with established PRLF should therefore receive prophylaxis. Large-volume ascites may also complicate PRLF. As in ALF, when this causes severe abdominal discomfort and/or respiratory compromise, consideration should be given to therapeutic paracentesis with simultaneous volume replacement with a plasma expander (ideally 20 % salt-poor albumin solution). The ratio for replacement is 6-8 gram 20% albumin per liter ascites drained. Nutrition is important and supplementation should be established early in patients with liver failure. Enteral nutrition is the preferred route as it improves gut function and restores normal intestinal flora. Parenteral nutrition can be used when enteral feeding is not tolerated, but should be introduced with caution owing to the risk of infection. In critically ill patients ensuring euglycemia improves survival and reduces morbidity.

The role of imaging in PRLF is to assess hepatic blood flow, identify reversible causes of liver failure and locate sites of infection. Hepatic blood flow can be evaluated using non-invasive imaging. Doppler ultrasonography may identify portal vein, hepatic artery and hepatic vein thrombosis. Contrast CT or MRI can be used to establish hepatic blood flow, provide more details of vascular abnormalities and identify sites of infection. If patency of hepatic vessels is still in doubt on cross-sectional imaging, angiography is the 'gold standard'. Vascular disorders may complicate liver resection and induce PRLF, but are rare. Longitudinal exposure of hepatic veins and the use of ultrasonic dissection may lead to hepatic vein thrombosis. Portal vein thrombosis has also been implicated in the development of PRLF. In these rare cases of inflow and outflow thrombosis with PRLF, a decision must be made regarding the benefit of surgical or radiological thrombectomy or dissolution *versus* anticoagulation.

Cerebral edema and intracranial hypertension may occur as a result of PRLF. Cerebral edema is unlikely in patients with grade 1 or 2 hepatic encephalopathy. With progression

to grade 3, a head CT should be performed to exclude intracranial hemorrhage or other causes of declining mental status. In patients with established ALF and encephalopathy, enteral lactulose might prevent or treat cerebral edema, although the benefits remain unproven. Progression to grade 3/4 encephalopathy warrants ventilation and may require intracranial pressure monitoring.

Stress ulcer	Proton pump inhibitor
Nutrition	Enteral energy supply of 2000 kcal/day Enteral preferred over total parenteral nutrition Maintain euglycemia
Sepsis	Serial chest X-ray, sputum, urine and blood culture Ascetic fluid from drain site Consider CT abdomen Broad spectrum antibiotic if progression of encephalopathy, renal failure or worsening SIRS parameters
Circulatory disturbances	CVP 8–12 mmHg MAP 70 mmHg Hematocrit >30% Pulmonary capillary wedge pressure ≤ 12–15 mmHg
Ventilatory dysfunction	Arterial oxygen saturation > 93% Central venous oxygen saturation > 70%
Renal dysfunction	Urine output > 0.5 mL/kg/hour
Coagulopathy	Correct if bleeding or interventional procedure (INR<1.5)
Thrombocytopenia	Correct if bleeding, profound thrombocytopenia (<20 × 10 ⁶ /L) or interventional procedure planned (<70 × 10 ⁶ /L)
Vascular inflow/outflow (thrombosis)	Doppler ultrasound CT/MR angiography If evidence of inflow/outflow occlusion consider anticoagulation/revascularization
Ascites	Paracentesis if severe pain/respiratory impairment
Encephalopathy	Lactulose If progression to grade 3–4 encephalopathy, CT head, ventilate and consider ICP monitoring

** ICP: IntraCranial Pressure, INR: International Normalized Ratio, MAP: Mean Arterial Pressure MR: Magnetic Resonance CT: Computed Tomography, CVP: Central Venous Pressure, SIRS: Systemic Inflammatory Response Syndrome

Table 5. Management of post resection liver failure.

The concept of hepatocyte transplantation has been investigated as a strategy to boost residual liver function. Intrahepatic hepatocyte transplantation has been used successfully to treat

patients with metabolic disorders of the liver. The efficacy of orthotopic liver transplantation for PRLF has only recently been reported. However, no criteria are available for the selection of patients who will benefit from emergency liver transplantation for PRLF. Patient who have favorable tumor characteristics (i.e. R0 resection, low T and negative N status, HCC within Milan criteria and absence of extra-hepatic disease), without comorbid conditions and without a limited life expectancy because of other medical conditions considered to be good candidate for emergency transplantation.

Extracorporeal liver support (ELS) devices fall into two categories: artificial and bioartificial systems. Artificial devices use combinations of hemodialysis and adsorption over charcoal or albumin to detoxify plasma. Bioartificial devices use human or xenogenic hepatocytes maintained within a bioreactor to detoxify and provide synthetic function. These systems have not been evaluated extensively in patients with PRLF. A recent meta-analysis and systematic review showed that ELS might improve survival in patients with ALF, but not acute-on-chronic liver failure, in comparison with standard medical therapy.

Abbreviation

ALF Acute liver failure

ICG Indocyaninegreen

HCC Hepatocellular carcinoma

FT Fast Track

RFA Radiofrequency ablation

PEI Percutaneous ethanol injection

SIRS Systemic Inflammatory Response Syndrome

PLRF Post-resection liver failure

TACE Transarterial chemoembolization

Author details

Mazen Hassanain*, Faisal Alsaif, Abdulsalam Alsharaabi and Ahmad Madkhali

*Address all correspondence to: mhassanain@ksu.edu.sa

Department of surgery, College of Medicine, Liver Disease Research Centre, King Saud University, Riyadh, Saudi Arabia

References

- [1] Jordi Bruix, and Morris Sherman. Management of Hepatocellular Carcinoma: An Update. *HEPATOLOGY*, (2011). , 53(3)
- [2] Peter Abrams, J. Wallis Marsh. Current Approach to Hepatocellular Carcinoma. *Surg Clin N Am* (2010). , 90(2010), 803-816.
- [3] Erwin Kuntz. Malignant liver tumor. *HEPATOLOGY TEXTBOOK AND ATLAS* (2008). Part DOI:, 4, 795-835.
- [4] Khan, M. A, Combs, C. S, Brunt, E. M, et al. Positron emission tomography scanning in the evaluation of hepatocellular carcinoma. *J Hepatol* (2000). , 32, 792-7.
- [5] Hepatobiliary Cancers. National comprehensive cancer network 2.(2012). www.nccn.org
- [6] Steven Curley, Carlton Barnett, Eddie Abdalla. Surgical resection for hepatocellular carcinoma. *uptodate Feb.2.* (2012). www.uptodate.com
- [7] Pierce Kah-Hoe Chow Resection for hepatocellular carcinoma: Is it justifiable to restrict this to the American Association for the Study of the Liver/Barcelona Clinic for Liver Cancer criteria? *REVIEW. Journal of Gastroenterology and Hepatology* (2012). , 27(2012), 452-457.
- [8] Pawlik, T. M, Delman, K. A, Vauthey, J. N, et al. Tumor size predicts vascular invasion and histologic grade: Implications for selection of surgical treatment for hepatocellular carcinoma. *Liver Transpl.* (2005). Sep; , 11(9), 1086-92.
- [9] Yokoyama, Y, Nagino, M, & Nimura, Y. Mechanisms of Hepatic Regeneration Following Portal Vein Embolization and Partial Hepatectomy: A Review. *World J Surg* ((2007).
- [10] Abdalla, E, Hicks, M, & Vauthey, J. Portal vein embolization: rationale, technique and future prospect. *British Journal of Surgery* (2011). , 2011(88), 165-175.
- [11] Eddie, K. Abdalla. Portal Vein Embolization Prior to Major Hepatectomy: The Evidence. *Venous Embolization of the Liver*. (2011). part , 6, 293-305.
- [12] David, C. Transhepatic Portal Vein Embolization: Anatomy, Indications, and Technical Considerations. *RadioGraphics* (2002). , 22, 1063-1076.
- [13] Abulkhir, A, Limongelli, P, Healey, A. J, et al. Preoperative portal vein embolization for major liver resection: a meta-analysis. *Ann Surg.* (2008).
- [14] Liu, C. L, Fan, S. T, Lo, C. M, et al. Management of spontaneous rupture of hepatocellular carcinoma: single-center experience. *J Clin Oncol.* (2001).
- [15] Lidewij Spelt *et al* Fast-track programmes for hepatopancreatic resections: where do we stand?. *Review. HPB* (2011). , 2011(13), 833-838.

- [16] De-Xin Lin *et al* Implementation of a Fast-Track Clinical Pathway Decreases Postoperative Length of Stay and Hospital Charges for Liver Resection. *Cell Biochem Biophys* ((2011)).
- [17] Zhou, X. D, Tang, Z. Y, Yang, B. H, et al. Experience of 1000 patients who underwent hepatectomy for small hepatocellular carcinoma. *Cancer*. (2001).
- [18] Ozawa, K, Takayasu, T, Kumada, K, et al. Experience with 225 hepatic resections for hepatocellular carcinoma over a year period. *Am J Surg*. (1991). , 4.
- [19] Poon, R. T, Fan, S. T, Ng, I. O, & Wong, J. Significance of resection margin in hepatectomy for hepatocellular carcinoma: A critical reappraisal. *Ann Surg*. (2000).
- [20] Poon, R. T, Fan, S. T, Ng, I. O, & Wong, J. Significance of resection margin in hepatectomy for hepatocellular carcinoma: A critical reappraisal. *Ann Surg*. (2000).
- [21] Giuseppe Garcea G. J. Maddern. Liver failure after major hepatic resection. *J Hepatobiliary Pancreat Surg* ((2009)).
- [22] Hammond, J. S. *et al*. Prediction, prevention and management of postresection liver failure. *British Journal of Surgery* (2011). , 98, 1188-1200.
- [23] Maartje, A. J. van den Broek. Liver failure after partial hepatic resection: definition, pathophysiology, risk factors and treatment. *Liver International* ((2008)).
- [24] Suc, B, Panis, Y, Belghiti, J, & Fekete, F. Natural history' of hepatectomy. *Br J Surg* (1992). , 79, 39-42.
- [25] Balzan, S, Belghiti, J, Farges, O, et al. The "50-50 criteria" on postoperative day 5: an accurate predictor of liver failure and death after hepatectomy. *Ann Surg* (2005). , 242, 824-8.