

Review Article

Surgical Resection of Hepatocellular Carcinoma in Compensated Cirrhotic Liver: The Benefits and Selection Criteria

Wael Mohialddin Ahmed Doush and Juhaina Ahmed Elzein

¹Faculty of Medicine and Health Sciences, Omdurman Islamic University, Department of Gastroenterological Surgery, Ibn Sina Specialized Hospital, Khartoum, Sudan

²Department of Family Medicine, Sudan Medical Specialization Board, Khartoum, Sudan

Corresponding Author:

Wael Mohialddin Ahmed
Doush;
MBBS, MSc, MD, MRCSEd,
Assistant Professor of
General Surgery, Faculty of
Medicine and Health
Sciences, Omdurman Islamic
University, Department of
Gastroenterological Surgery,
Ibn Sina Specialized Hospital,
P.O.Box 7597, Khartoum
11123, Sudan.
Mobile
phone:+249124529752;
email:
dr.wael.doush@gmail.com

Received 23 August 2019

Accepted 14 December 2019

Published 30 December 2019

Production and Hosting by
Knowledge E

© Wael Mohialddin Ahmed
Doush and Juhaina Ahmed
Elzein. This article is
distributed under the terms of
the [Creative Commons
Attribution License](#), which
permits unrestricted use and
redistribution provided that
the original author and
source are credited.

Editor-in-Chief:

Prof. Mohammad A. M. Ibnouf

 OPEN ACCESS

Abstract

Background: Hepatocellular carcinoma (HCC) represents a fifth of common malignancies, with an annual diagnosis of 750,000 new cases. It is the third cause of cancer deaths worldwide. The cirrhotic liver is a leading cause of HCC with the annual conversion rate to HCC in the range of 2–6 %. The underlying liver cirrhosis limits certain treatment modalities that potentially further aggravates liver dysfunction. Over the past decade, there were substantial improvements in the HCC resection techniques that has resulted in the reduction of operative mortality. This allowed doing major hepatectomy in cirrhotic patients who are suitable for liver transplantation but lacking availability of cadaveric or living donors. Also, patients who have multi-focal HCC underlying cirrhosis which render them unsuitable for liver transplantation due to its extension beyond Milan criteria.

Objective: The objective of this study was to assess the benefits and selection criteria of HCC surgical resection within child–Turcotte–Pugh score (CTP) A and B liver cirrhosis to achieve the best surgical outcomes.

Methods: We performed a literature search within English written trials using PubMed and MEDLINE reviews databases from 1986 to 2017. One hundred fifty studies are included in this review evaluating various parameters including HCC and compensated cirrhosis prevalence, pathogenesis, clinical presentation, and diagnostic methods. Furthermore, we have compared oncological hepatic resection with other modalities like transarterial chemoembolization, liver transplantation, embolization of the portal vein, laparoscopic hepatic resection, and ALPPS technique. Principles of surgical hepatectomy and postoperative complications are also presented in this review.

Conclusion: This review has demonstrated that hepatic cirrhosis complicated by portal hypertension is not an absolute contraindication for HCC resection. Furthermore, elective surgery must not be directed exclusively to CTP A cirrhosis but it can be applied to highly selected patients who had suffered from advanced hepatic cirrhosis. If multifocal HCC underlying hepatic cirrhosis was unsuitable for liver transplantation, hepatectomy can be carried out to increase the tumor cure chances, prevent it's recurrences, and lead to significant survival rate improvement. The degree of cirrhosis significantly affects the decision of primary hepatic carcinoma treatment and it's prognosis. The interdisciplinary assessment of liver function by surgeons, hepatologists, anesthesiologists, and specialists of critical care are essential for maximum critical stabilization of the patients.

Keywords: Child-Turcotte-Pugh score; hepatocellular carcinoma; hepatectomy; liver cirrhosis; portal hypertension

1. Introduction

A significant increase in CTP A and CTP B cirrhotic patients complicated by portal hypertension who requiring surgical resection was observed. This is due to several reasons. First, cirrhosis is relatively common. During 2012, more than three million and 14.1 million new cases were diagnosed in Europe and globally respectively [1]. Over the past decades, significant progress in liver disease management was obtained but liver cirrhosis is still a major health disease belong to annually about 14-26 per 100,000 suffered from cirrhosis of which 170,000 died of its complications [2, 3]. Second, liver cirrhosis is a leading cause of hepatocellular carcinoma (HCC) [4, 5]. Finally, liver cirrhosis and HCC share certain risk factors such as alcohol abuse, smoking and metabolic diseases [6–9].

2. Methods

2.1. The pathogenesis of HCC in underlying cirrhotic liver

Liver cirrhosis represents a wound healing response to chronic liver injury and shows a prevalence of 250 patients per 100,000 persons [10, 11]. It's characterized by liver parenchymal distortion and is associated with nodular formation, fibrous septae and blood flow alterations [12]. The fibrosis natural course starts with a long-lasting asymptomatic compensated phase followed by rapidly progressive decompensated cirrhotic phase characterized by liver function impairment [13, 14]. The median survival time of decompensated cirrhosis is significantly shorter than compensated cirrhosis (2 years vs >12 years) [13, 15]. In cirrhotic patients, about 5-30% develop HCC within a cumulative five years [16, 17]. The annual conversion rate to HCC arising in cirrhotic patients is two to six percent [18]. HCC represents the third cause of cancer deaths worldwide and the fifth common malignancy with an annual diagnosis of 750,000 new cases. In Asia, the risk is 35-117 per 100,000 annually, where in the USA the risk is only 7 per 100,000 persons per year [19]. In addition, 75-80% of HCC cases were due to infection by long-term hepatitis B virus (50-55%) or hepatitis C virus (25-30%) [20–23]. Primary biliary

cirrhosis, hereditary hemochromatosis, chronic alcohol abuse, diabetes and obesity were also recognized as important risk factors [24–29].

2.2. Clinical presentation of compensated liver cirrhosis and HCC

Compensated cirrhosis defined as detection of clinical hepatic complications without a possibility to be reversed in patients not having symptoms that indicate cirrhosis. These complications include HCC, portal hypertension, esophageal varices, ascites, jaundice and hepatic encephalopathy. It can be discovered clinically through hepatomegaly, palpable left liver lobe and the enlarged spleen [30–33]. HCC prevalence was found to be dominated by males within all etiologies, with an average age of 50 years. Symptoms of HCC appear in the form of vague right hypochondrial pain, unidentified fever origin, lethargy, anorexia, weight loss and nausea. Clinically HCC related signs are obstructive jaundice and hepatomegaly [24–29, 34].

2.3. Diagnosis of compensated liver cirrhosis and HCC

Nowadays, the continuous improvements of diagnostic techniques using laboratory tests in combination with radiological images, permits early diagnosis of liver cirrhosis prior to the development of portal hypertension and HCC [35]. The laboratory findings which help in the diagnosis of compensated cirrhosis are bilirubin >1.1 mg/dL, elevated AST/ALT ratio, serum albumin <2.5 g/dL, platelet count $<150,000/L$, prothrombin time $<100\%$ and increased alkaline phosphatase level [33]. OGD must be done to assess the size and severity of esophageal varices and prevent their bleeding in future [32]. Furthermore, HCC diagnosis often depends on serological tumor marker alpha-fetoprotein (AFP) which is sensitive by 25% in a malignant lesion less than 3 cm in diameter to fifty percent for tumors more than 3 cm as shown by radiological images [36]. In suspected patients with cirrhosis, abdominal ultrasound shows the nodular surface of the liver and the portal vein mean velocity less than 12 cm/second. Other signs which suggest cirrhosis are left lobe with caudate hypertrophy, segment IV atrophy, gallbladder fossa expansion, the presence of portosystemic collaterals, perihepatic minimal ascites, dilated portal vein above or equal to 13 mm, dilated splenic vein and superior mesenteric vein above or equal to 11 mm and enlarged splenic diameter above 12 cm. Moreover, because abdominal ultrasound is associated with low sensitivity, these signs cannot allow a full exclusion of cirrhosis in patients with chronic compensated liver disease [37, 38]. Fibroscan (elastography) is another test which helps in the assessment

of hepatic stiffness and exclusion of cirrhosis caused by multiple different causes. A score of more than 12.5 kPa has an accuracy of more than 90% to diagnose liver cirrhosis [39, 40]. The previously mentioned ultrasound signs of hepatic cirrhosis can be revealed by cross-sectional imaging including contrast-enhanced computed tomography scan (CT) in portal venous phase and magnetic resonance imaging (MRI) which are precise in the diagnosis of cirrhosis with a variable success rate [41, 42]. Also, imaging studies are requested for planning oncological treatment and follow-up of metastatic recurrence [43]. American Association for the Study of Liver Disease (AASLD) and European Association for the Study of Liver (EASL) guidelines recommend abdominal ultrasound as surveillance study. If the ultrasound image shows suspicious nodules in cirrhotic liver below 1 cm then these nodules are re-examined two times per year. In the absence of nodular changes over two years, annual surveillance was recommended [44, 45]. Some authors recommended that a screening strategy of combined abdominal ultrasound and serum alfa-fetoprotein measurement every 6-months reduced HCC mortality rate by forty percent [46]. If HCC with a size between 1-2 cm discovered in hepatic cirrhosis by enhanced CT or MRI, images will show a high arterial contrast uptake followed by rapid washout in the late stage (Figures 1, 2) [47].

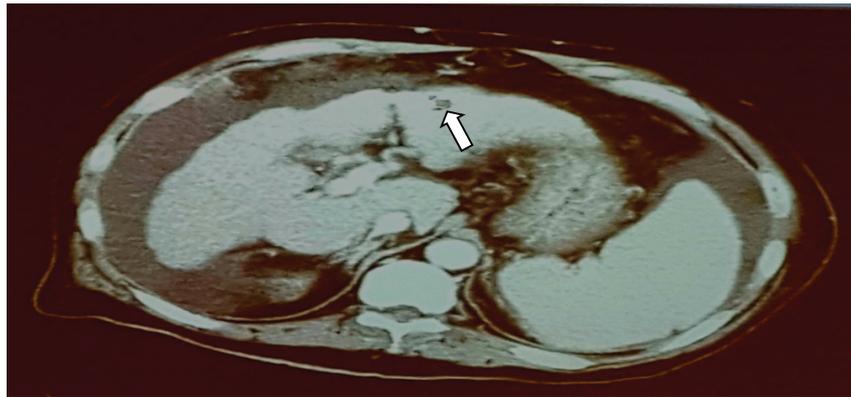


Figure 1: Contrast-enhanced CT scan image of small HCC nodule in cirrhotic liver.

Currently, the HCC diagnosis often depends on cross-sectional imaging rather than angiography [48]. The EASL recommended histological biopsy is not mandatory in HCC diagnosis if HCC nodule on MRI or CT angiography is found to be more than 2 cm in diameter with AFP elevation in sequential measurements or more than 400 ng/mL [45, 49]. On the other hand, liver biopsy is commonly requested for hepatic cirrhosis of unknown etiology [50]. In the early diagnostic phase of HCC, the positron emitting tomography (PET) scan is not suitable except in suspicion of extra-hepatic metastases that are not seen on CT or MRI images [51].

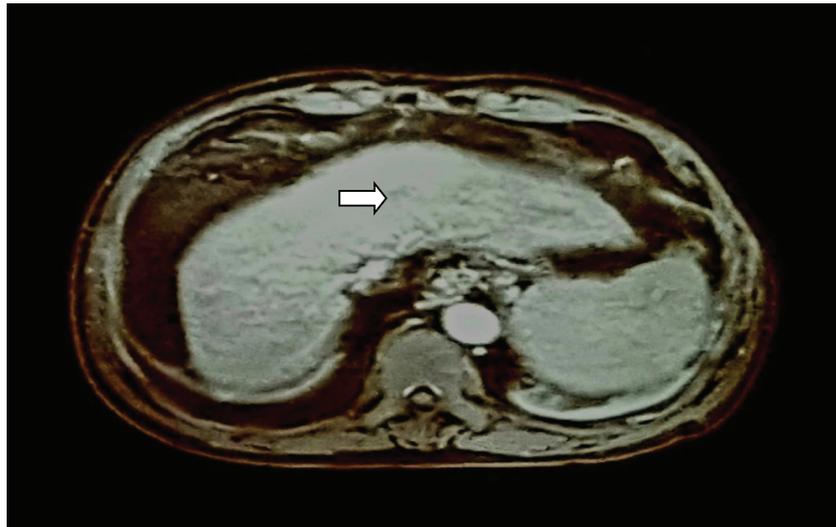


Figure 2: MRI image of small HCC nodule in hepatic cirrhosis.

2.4. Surgical management of HCC in a compensated cirrhotic liver

2.4.1. Management overview

The nature of underlying liver cirrhosis limits certain treatment modalities. Hence, the oncological staging of HCC must include cancer prognosis and liver function values when selecting patients for surgical resection [52, 53]. Currently, the American and European Liver Associations use the Barcelona Clinic Liver Cancer (BCLC) staging system [28]. In the 1980s, Surgical removal of HCC within cirrhosis was a major surgery with a mortality rate of 15-30% and was limited largely to segmental or sub-segmental hepatectomy [54, 55]. Later, the operative mortality rate declined to 15% due to improvements in major hepatectomy techniques [56–58].

2.4.2. Benefits of oncological hepatic resection

HCC resection aimed at radical removal of the tumor and morbidity reduction. Therefore, patient selection is crucial [13]. After hepatic resection, operative mortality range between three to eight percent and the five years survival rate reached thirty to fifty percent [59]. In a large series of 22800 of hepatectomy cases, 22% were free from HCC recurrence over ten years [60].

Hepatic resection for HCC has several advantages:

1. Compared to liver transplantation it requires no waiting time and is performed in any well prepared medical centers.

2. The resected tumor can be diagnosed histopathologically. Hence, it determines the prognosis [61].
3. Hepatic resection can be performed as rescue therapy for HCC recurrence and/or liver failure while waiting for future liver transplantation [62–64].

A current study of 2046 hepatectomy patients performed in ten large liver centers, revealed that 50% of operated patients had BCLC stage A without portal hypertension, while 36% and 14% had hepatectomy in BCLC stage B and C, respectively [65]. The overall 5-years survival post-hepatectomy in BCLC stages including A, B and C cirrhosis were 61%, 57% and 38% and five years free of recurrence were 21%, 27% and 18% respectively. Thus, HCC resection had reasonable long-term outcome in advanced cirrhotic stages [66, 67].

2.4.3. Selection of candidates for oncological hepatic resection

Hepatectomy is frequently performed within cirrhosis in presence or absence of portal hypertension in spite of metastatic risk reduction by cirrhosis [68, 69]. Hepatectomy has been indicated for non-portal hypertensive patients with single tumor nodule and normal bilirubin measurement according to EASL and AASLD HCC guidelines treatment [70]. Furthermore, BCLC suggests HCC curative hepatectomy only in non-portal hypertensive CTP A cirrhosis and in tumor in early stages [76]. In contrast, multiple publications worldwide revealed that hepatectomy for HCC within cirrhotic liver with portal hypertension can give a good life span expectancy [67, 71, 72]. Torzilli et al. showed that about 50% of hepatectomies with cirrhotic liver done beyond BCLC criteria is associated with overall five years survival of 57% and 38% for stage B and stage C patients respectively [65]. Also, gives an excellent long-term survival rate compared to transarterial chemoembolization (TACE) and HCC resection can be offered to cases beyond BCLC criteria [73–76]. Yin et al. revealed in a study of 173 patients that suffered from HCC beyond the Milan criteria, liver resection patients have a significant better long-term survival rate of 51.5% for three years, vs 18.1% when compared to TACE. Hence, complicated liver cirrhosis with portal hypertension must not be denied HCC hepatectomy [76]. Furthermore, neoadjuvant TACE therapy has been failed in improvement of survival rate for HCC underlying cirrhotic cases despite its initial promising results [77]. Ishizawa et al. showed excellent predictors of HCC resectability in spite of portal hypertension depending on a combination of bilirubin, ascites and indocyanine green clearance [71].

The followings are the criteria for selecting the candidates for liver resection:

1. Rule out of extrahepatic metastases

The performance of chest CT scan prior to resection is desirable, due to lymph nodes, lungs or bone metastasis [78].

2. Evaluation of HCC extent

HCC site, size, account and proximity to major vessels all influence the respectability. CTP A cirrhotic patients may tolerate major hepatic resection, while CTP B patients tolerate a safe minor resections. Tumor size precisely may not indicate safe hepatectomy and some authors reported that tumors above ten centimeters had more than 45% five years survival [79]. HCC invasion of a biliary tree or main vessels might be a contraindication for resection, except portal vein involvement or hepatic segmental thrombosis [80]. Multinodular tumors have a poor prognostic ratio, reoccur within 80–100% of patients and thirty percent of them survive for five years. If hepatic transplantation is not feasible multinodular tumors might be respectable [81, 82].

3. The liver functional reserve estimation

• *Determining of functional residual liver volume after oncological resection*

The least residual hepatic volume in non-chronic liver disease patients needed for the avoidance of advanced hepatic dysfunction postoperatively was twenty to thirty percent [82]. In the 1990s, very few studies analyzed cirrhotic patients for the role of future remnant hepatic volume prognosis. Shirabe et al. have studied chronic liver disease in 80 patients and fifty percent of them suffered from cirrhosis did a major hepatectomy and revealed that liver failure deaths happened when a remnant hepatic volume less than 250 mL/m² body surface and concluded that safe limit of major hepatectomy depending on functioning residual volume of the liver. Currently, highly resolution CT volumetry scan can measure residual volume that is accepted for safe hepatectomy which is 30% in non-cirrhotic liver disease and 40% in CTP A cirrhosis not complicated by portal hypertension [83, 84]. In 2012, the associating liver partition and portal vein ligation for staged hepatectomy (ALPPS) technique was first published for raising the resection chances of inoperable HCC through rapid hypertrophy of the future liver remnant (FLR) which reduces postoperative liver failure risk. This technique was indicated when FLR reached up to 30% or 40 % in case of chemotherapy complicated by hepatic injury, colorectal liver metastases,

hilar cholangiocarcinoma, gallbladder cancer, primary hepatic lymphoma and 18% of surgeons suggested this technique for CTP A cirrhotic patients. The disadvantages of ALPPS technique are perioperative morbidity is 68% and postoperative mortality is 12% at 6 months. Biliary fistula and adhesions can complicate the ALPPS first stage. Moreover, it was contraindicated in extra-hepatic distant metastases, patients beyond 75 years old, macrovesicular steatosis above 50% and CTP B or C cirrhosis is considered as an absolute contraindication especially if combined with HCC as chronic liver damage has less cellular regeneration [85].

- *Assessment of liver function*

For more than forty years the Child-Turcotte-Pugh score known as a gold standard grading system for the liver function to select candidates for hepatectomy and predict prognosis after surgeries for portal hypertension like portocaval shunt and transection of the esophagus in cirrhotic patients. There is general agreement that surgical resection can be performed safely and should be considered as a beginning treatment for solitary tumors within CTP A cirrhosis [85–88]. Alternative therapies including liver transplantation must be sought for CTP B or C hepatic cirrhosis not suitable for major hepatectomy [89–91]. Hence, according to the BCLC algorithm current version, HCC treatment depends on the underlying cirrhotic severity graded by CTP classes [28, 92]. The original score was slightly modified later using the INR, serum bilirubin, serum albumin, hepatic encephalopathy and ascites which classifies the patients into compensated CTP A, mild CTP B and severely decompensated CTP C cirrhosis. The survival rate of one year for CTP A is 95%, CTP B is 80% and CTP C account forty-four percent [13, 93]. The model for end-stage liver disease (MELD) score has been established for candidates selection into liver transplantation and survival prediction of transjugular intrahepatic portosystemic shunt (TIPS) patients. It's measured from bilirubin, INR and creatinine [89, 94]. Currently, it is correlated with postoperative resection outcomes and hepatectomy candidates selection. If the score was more than nine, this generally was associated with higher postoperative liver failure rates [89, 91]. Other studies revealed if the score is equal or less than ten, this means patients are suitable for partial hepatectomy [87, 95, 96]. In Asia, the clearance test of indocyanine green (ICG) is an acceptable test for the liver function. After intravenous dye injection, the rate of retention at 15 minutes (ICGR15) for the normal liver function is 10%. Safe major hepatectomy is

allowed when ICGR15 is equal to or less than fourteen percent [57]. The cut-off ICGR15 for minor hepatectomy is 22% and ICGR15 values up to 40% were suitable for limited resection [97–99]. Sixty-five percent of patients with CTP B showed an ICGR15 less than twenty-two percent. This test is most applicable to a small hepatectomy; therefore, it is perfect for patients with CTP B who require segmental hepatectomy. A recent study compared the prognosis of MELD score with ICGR15 in 395 patients suffering from cirrhosis did not have surgery revealed the ICGR15 was more precise in survival prediction [100]. Furthermore, the Japanese HCC clinical guidelines recently recommended a preoperative ICGR15 usage for evaluation of the liver function [101].

- *Assessment of portal hypertension*

Portal hypertension clinical signs reflect a deterioration of liver disease following hepatectomy, and also poor long-term outcome. In other words, portal hypertension determines the success rate of surgical resection. The BCLC guidelines had recommended hepatectomy only for non-clinical significant portal hypertension patients which can be assessed by hepatic vein-portal gradient (HVPG) less than 10 mmHg [28]. This invasive direct method may not be available everywhere. Also, the BCLC determines portal hypertension signs clinically by many indirect clinical tests: endoscopic esophageal varices or enlarged spleen described as more than 12 cm in diameter with platelets count less than $100,000/\text{mm}^3$. Some authors recommended that hepatectomy was contraindicated if these signs appear [92, 102]. Currently, portal hypertension must not be considered as an absolute contraindication for hepatectomy within well-compensated CTP A cirrhosis or MELD score below ten [67, 103]. Complications of portal hypertension like variceal rupture bleeding and hemostatic disorders due to thrombocytopenia can safely be treated [104, 105].

4. Comorbidities of other organs

Severe comorbidity like congestive cardiac failure and chronic renal failure must be considered as contraindications for surgical removal of HCC. Diabetes mellitus is common in patients that suffer from cirrhosis and recently a report showed post-hepatectomy morbidity and mortality in these patients [106, 107].

Hence, the guidelines in western countries currently recommend resection exclusively for cirrhotic cases have well-preserved liver function determined by normal bilirubin levels in serum associated with HVPG ≤ 10 mmHg or platelets number $\geq 100 \times 10^9$ per liter. By following these strict criteria, the liver resection can be

applied only in 5–10% of all patients with HCC [108]. Moreover, patients who had liver resection with normal serum bilirubin levels and non-clinical significant portal hypertension (CSPH) can reach 70% of five years survival, while those with CSPH reach about fifty percent. Prognosis is worse in CSPH patients who have elevated bilirubin [71, 109].

2.4.4. Preoperative therapy of oncological hepatic resection

1. Antiviral therapy of chronic hepatitis B virus (HBV)-related HCC patients:

The preoperative antiviral therapy of chronic hepatitis B virus-related HCC patients is essential, leading to improved liver function and reduce progression chances into cirrhosis. It decreased HCC incidence in these patients, prolonging overall survival after curative and palliative modalities which delay HCC recurrence in patients treated for 3 years (1.5% vs 4.0%) and 5 years (5.1% vs 12%) rather than those without treatment [110]. If HBV-DNA was detected, then 1-3 months preoperative therapy must begin. Entecavir and tenofovir disoproxil are recommended as first-line anti-HBV drugs with high efficacy. Also, a combination of α -interferon and ribavirin had reduced occurrence of HCC significantly. Administration of lamivudine, dipivoxil or entecavir postoperatively had a significant reduction in HCC death and its recurrence with an improvement of hepatic function six months later [110].

2. Embolization of the portal vein (EPV):

Before hepatic resection EPV is helpful in increasing residual volume of the liver when extended hepatectomy is mandatory and when liver remnant volume is inadequate [111–112]. Prospective studies revealed that an early outcome improvement in patients who had right HCC hepatectomy with portal vein embolization preoperatively. The complication rate of EPV is 10–20% and accelerated portal hypertension can appear in 1% of cirrhotic patients [112–113]. EPV is relatively contraindicated if there are segmental portal occlusion/invasion, biliary obstruction, coagulopathy and renal failure [114, 115].

2.4.5. Principles of surgical hepatectomy

Intraoperative bleeding is a major risk that determines the perioperative mortality.

The following are some points on the principles of surgical resection:

1. Cooperative work with the anesthetic staff is mandatory throughout hepatectomy. During parenchymal dissection, the blood loss is risky and is controlled by reduction of central venous pressure up to 5 mmHg by options including diuretics, volume restriction, positive end-expiratory pressure, decreased tidal volume and reverse Trendelenburg position [116, 117].
2. The hepatic hilar vascular occlusion (Pringle maneuver) may not be recommended in cirrhosis. However, it is urgently used for prevention of extensive bleeding during parenchymal dissection by intermittent occlusion for fifteen minutes then five minutes of releasing (Figures 3, 4) [118, 121].

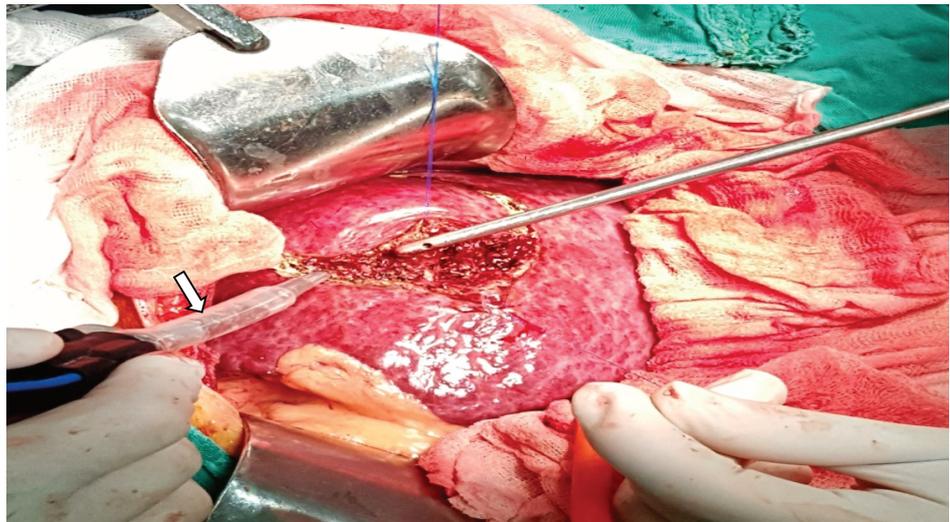


Figure 3: Intraoperative CUSA circumferential HCC resection in cirrhotic liver using intermittent hilar vascular occlusion.

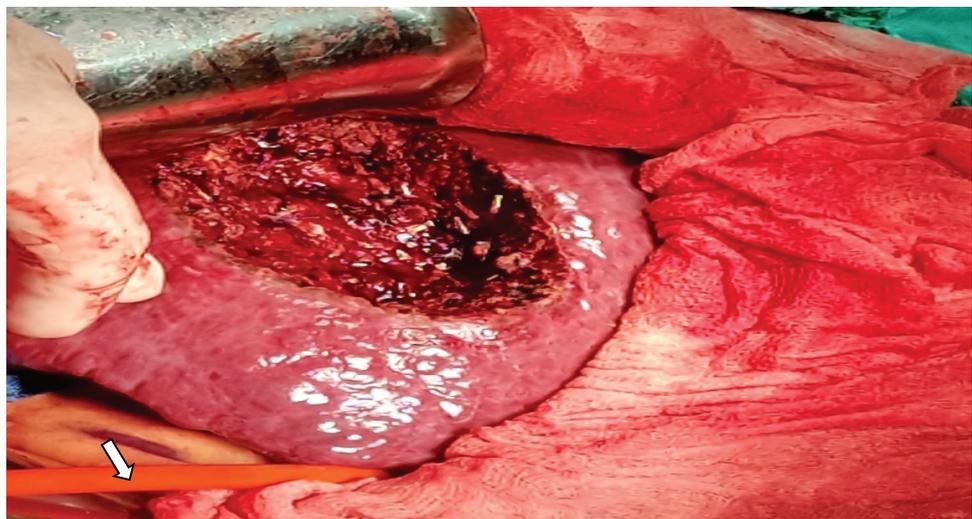


Figure 4: Adequate HCC resection margins within the cirrhotic liver using intermittent hilar vascular occlusion.

3. Hepatectomy that depends on anatomic Couinaud segments is not important, but high care should be given to vascularized parenchyma preservation for prevention of postoperative liver failure [122]. In particular, this maneuver might be useful in cases with mild portal hypertension and advanced CTP B cirrhosis [123].
4. One centimeter wide margin is generally adequate. However, two centimeters wide margin produces greater survival rate (Figures 5, 6) [122, 124, 125].

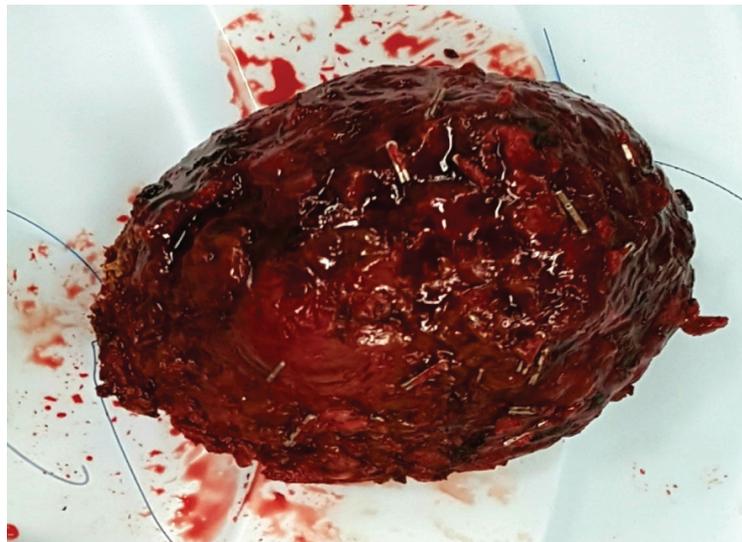


Figure 5: Postoperative circular hepatic tissue contained HCC mass.

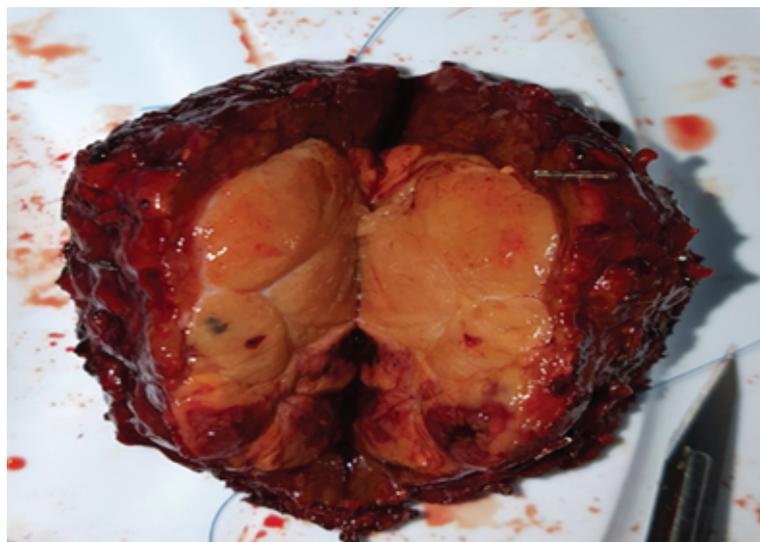


Figure 6: Postoperative adequate resection margins of HCC mass.

5. Liver transection maneuvers that depend on a high tissue resistance discrimination of bile ducts and blood vessels compared to the liver tissues include crushing dissector instrument, water jet dissection, stapler dissection and cavitory ultrasound suction aspirator (CUSA) (Figure 3) [126–129].

6. The anterior approach may be beneficial in large tumors, where caval vein mobilization may need traction or pressure on the tumor has a capability to cause bleeding, rupture and tumor cells dissemination [130, 131]. This technique has been helped by the hanging maneuver through blunt dissection to pass a band between the right and middle hepatic veins and in front of the inferior vena cava. Band traction makes a straight transection with bleeding control in its depths [132, 133]. Furthermore, fibrin glue application following hepatic resection is not beneficial in controlling of blood loss and in a reduction of blood transfusion requirements [134].
7. Current standards of liver resection describe 2-3% mortality rate and five-year survival rate around sixty percent [135].

When comparing open hepatic resection and laparoscopic resection, 90% of laparoscopic resections were minor resections [136]. Because of the underlying liver disease, post-HCC hepatectomy complications occur in fifty percent of cases [137]. Laparoscopic hepatectomy advantages are minimal peritoneal dissection, less aggressive technique, reduced ascitic fluid and liver failure [138, 139]. Furthermore, reduced laparoscopic post-operative adhesions help in future liver transplantation salvage with less morbidity when compared to open hepatectomy [140]. Major disadvantages which reduce widespread of laparoscopic liver resection are difficulties in the transection of parenchyma and tissue mobilization that may be associated with massive bleeding risk. In addition to greater difficulty in performing anatomical resections and wide margin resection [141, 142].

2.4.6. Postoperative complications of oncological hepatic resection in compensated cirrhosis

The hepatic resection in cirrhotic portal hypertension showed increased morbidity with a range from twenty-two percent to fifty percent [67, 71, 72, 143]. These complications arranged in the following points:

1. Postoperative life-threatening liver failure, which can be managed by remnant liver optimal perfusion, prophylactic antibiotics and intensive care of electrolytes, fluid balance, renal function, and coagulation [144, 145].
2. Ascites reduced after 5-7 days with the support of fluid volume restriction, diuretics and albumin infusion. Ascitic fluid persistence needs microbiological test, early detection and treatment of any infections [146].

3. Suspected postoperative infection, mainly from chest pneumonia. Also, superinfected ascites can be treated by third generation cephalosporins like ceftriaxone or cefotaxime, or carbapenems alternatively. Furthermore, sampling and microbiologic culture of ascitic fluid is advised before the start of antibiotic treatment [147–149].
4. Disorders of wound healing noticed rather commonly due to malnutrition and for postoperative ascites. A running suture during abdominal closure gives protection against wound dehiscence. Also, a drainage system prevents fluid accumulation with reduction of intra-abdominal pressure which leads to wound healing improvement [150].
5. Postoperative hemorrhage in cirrhotic patients may include superficial wound bleeding, resection site bleeding and gastrointestinal bleeding. Therapies that include coagulation products supplementation are highly important [150].

In conclusion, this review has demonstrated that hepatic cirrhosis complicated by portal hypertension is not an absolute contraindication for HCC resection. Furthermore, elective surgery must not be directed exclusively to CTP A cirrhosis but it can be applied to highly selected patients who had suffered from advanced hepatic cirrhosis. If multifocal HCC underlying hepatic cirrhosis was unsuitable for liver transplantation, hepatectomy can be carried out to increase the tumor cure chances, prevent its recurrences and lead to significant survival rate improvement. The degree of cirrhosis significantly affects the decision of primary hepatic carcinoma treatment and its prognosis. The interdisciplinary assessment of liver function by surgeons, hepatologists, anesthesiologists and specialists of critical care are essential for maximum critical stabilization of the patients.

Authors Contributions

Manuscript writing, critical revision of contents: Wael M. Doush

Data collection, data analysis and manuscript design: Wael M. Doush and Juhaina A. Elzein

Manuscript drafting and revision: Juhaina A. Elzein

All authors read and gave the final approval of the manuscript to be published.

Financial Support and Sponsorship

This review article did not receive financial support and sponsorship from any institute.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

The authors would like to thank Prof. Wei-Chen Lee, Prof. Mohammed Hassan Abdulgalil, Chen Fang Lee, and Omar Alkarouri for their kind suggestions and unlimited support.

References

- [1] Torre, L. A., Bray, F., Siegel, R. L., et al. (2015). Global cancer statistics 2012. *CA: A Cancer Journal for Clinicians*; vol. 65, pp. 87–108.
- [2] Blachier, M., Leleu, H., Peck-Radosavljevic, M., et al. (2013). The burden of liver disease in Europe: a review of available epidemiological data. *Journal of Hepatology*, vol. 58, pp. 593–608.
- [3] Zatonski, W. A., Sulkowska, U., Manczuk, M., et al. (2010). Liver cirrhosis mortality in Europe with special attention to Central and Eastern Europe. *European Addiction Research*, vol. 16, pp. 193–201.
- [4] European Association for the Study of the Liver; European Organisation for Research and Treatment of Cancer. (2012). EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *Journal of Hepatology*, vol. 56, pp. 908–943.
- [5] Bridgewater, J., Galle, P. R., Khan, S. A., et al. (2014). Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *Journal of Hepatology*, vol. 60, pp. 1268–1289.
- [6] Molina, J. R., Yang, P., Cassivi, S. D., et al. (2008). Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship. *Mayo Clinic Proceedings*, vol. 83, pp. 584–594.
- [7] Dam, M. K., Flensburg-Madsen, T., Eliassen, M., et al. (2013). Smoking and risk of liver cirrhosis: a population-based cohort study. *Scandinavian Journal of Gastroenterology*, vol. 48, pp. 585–591.

- [8] Poschl, G. and Seitz, H. K. (2004). Alcohol and cancer. *Alcohol and Alcoholism*, vol. 39, pp. 155–165.
- [9] Bugianesi, E. (2005). Steatosis, the metabolic syndrome and cancer. *Alimentary Pharmacology & Therapeutics*, vol. 22, pp. 40–43.
- [10] Schuppan, D. and Afdhal, N. H. (2008). Liver cirrhosis. *Lancet*, vol. 371, pp. 838–851.
- [11] Sorensen, H. T., Thulstrup, A. M., Mellekjar, L., et al. (2003). Long-term survival and cause-specific mortality in patients with cirrhosis of the liver: a nationwide cohort study in Denmark. *Journal of Clinical Epidemiology*, vol. 56, pp. 88–93.
- [12] Jiao, J., Friedman, S. L., and Aloman, C. (2009). Hepatic fibrosis. *Current Opinion in Gastroenterology*, vol. 25, pp. 223–229.
- [13] D'Amico, G., Garcia-Tsao, G., and Pagliaro, L. (2006). Natural history and prognostic indicators of survival in cirrhosis: A systematic review of 118 studies. *Journal of Hepatology*, vol. 44, pp. 217–231.
- [14] De Franchis, R. (2000). Updating consensus in portal hypertension: report of the baveno III consensus workshop on definitions, methodology and therapeutic strategies in portal hypertension. *Journal of Hepatology*, vol. 33, pp. 846–852.
- [15] D'Amico, G., Morabito, A., Pagliaro, L., et al. (1986). Survival and prognostic indicators in compensated and decompensated cirrhosis. *Digestive Diseases and Sciences*, vol. 31, pp. 468–475.
- [16] El-Serag, H. B. (2011). Hepatocellular carcinoma. *The New England Journal of Medicine*, vol. 365, pp. 1118–1127.
- [17] Bruno, S., Stroffolini, T., Colombo, M., et al. (2007). Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: A retrospective study. *Hepatology*, vol. 45, pp. 579–587.
- [18] Liaw, Y. F., Tai, D. I., Chu, C. M., et al. (1986). Early detection of hepatocellular carcinoma in patients with chronic type B hepatitis: a prospective study. *Gastroenterology*, vol. 90, pp. 263–267.
- [19] Cheng, E., Zarrinpar, A., Geller, D., et al. (2015). Liver. In: Brunicaardi F (ed.) *Principles of Surgery* (tenth edition), p. 1291. New York, NY: McGraw Hill.
- [20] Bosch, F. X., Ribes, J., Diaz, M., et al. (2004). Primary liver cancer: Worldwide incidence and trends. *Gastroenterology*, vol. 127, pp. S5–S16.
- [21] But, D. Y., Lai, C. L., and Yuen, M. F. (2008). Natural history of hepatitis related hepatocellular carcinoma. *World Journal of Gastroenterology*, vol. 14, pp. 1652–1656.
- [22] Fattovich, G., Stroffolini, T., Zagni, I., et al. (2004). Hepatocellular carcinoma in cirrhosis: incidence and risk factors. *Gastroenterology*, vol. 127, pp. S35–S50.

- [23] Lok, A. S., Seeff, L. B., Morgan, T. R., et al. (2009). Incidence of hepatocellular carcinoma and associated risk factors in hepatitis C-related advanced liver disease. *Gastroenterology*, vol. 136, pp. 138–148.
- [24] O'shea, R. S., Dasarathy, S., and McCullough, A. J. (2010). Alcoholic liver disease. *Hepatology*, vol. 51, pp. 307–328.
- [25] Velazquez, R. F., Rodriguez, M., Navascues, C. A., et al. (2003). Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology*, vol. 37, pp. 520–527.
- [26] Calle, E. E., Rodriguez, C., Walker-Thurmond, K., et al. (2003). Overweight, obesity, and mortality from cancer in a prospectively studied cohort of US adults. *The New England Journal of Medicine*, vol. 348, pp. 1625–1638.
- [27] Veldt, B. J., Chen, W., Heathcote, E. J., et al. (2008). Increased risk of hepatocellular carcinoma among patients with hepatitis C cirrhosis and diabetes mellitus. *Hepatology*, vol. 47, pp. 1856–1862.
- [28] Bruix, J. and Sherman, M. (2011). Management of hepatocellular carcinoma: An update. *Hepatology*, vol. 53, pp. 1020–1022.
- [29] Erez, A., Shchelochkov, O. A., Plon, S. E., et al. (2011). Insights into the pathogenesis and treatment of cancer from inborn errors of metabolism. *American Journal of Human Genetics*, vol. 88, pp. 402–421.
- [30] Walker, M., El-Serag, H. B., Sada, Y., et al. (2016). Cirrhosis is under-recognised in patients subsequently diagnosed with hepatocellular cancer. *Alimentary Pharmacology & Therapeutics*, vol. 43, pp. 621–630.
- [31] Muir, A. J. (2015). Understanding the complexities of cirrhosis. *Clinical Therapeutics*, vol. 37, pp. 1822–1836.
- [32] Garcia-Tsao, G., Sanyal, A. J., Grace, N. D., et al. (2007). Prevention and management of gas-troesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*, vol. 46, pp. 922–938.
- [33] Grattagliano, I., Ubaldi, E., Portincasa, P., et al. (2009). Liver disease: Early signs you may be missing. *Journal of Family Practice*, vol. 58, pp. 514–521.
- [34] Valla DC. (2003). The diagnosis and management of the budd-chiari syndrome: consensus and controversies. *Hepatology*, vol. 38, pp. 793–803.
- [35] Ripoll, C., Croszmann, R., Gracia-Tesoa, G., et al. (2007). Hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. *Gastroenterology*, vol. 133, pp. 481–488.

- [36] Stefaniuk, P., Cianciara, J., and Wiercinska-Drapalo, A. (2010). Present and future possibilities for early diagnosis of hepatocellular carcinoma. *World Journal of Gastroenterology*, vol. 16, pp. 418–424.
- [37] Simonovsky, V. (1999). The diagnosis of cirrhosis by high resolution ultrasound of the liver surface. *British Journal of Radiology*, vol. 72, pp. 29–34.
- [38] Berzigotti, A., Abraldes, J., Tandon, P., et al. (2010). Ultrasonographic evaluation of liver surface and transient elastography in clinically doubtful cirrhosis. *Journal of Hepatology*, vol. 52, pp. 846–853.
- [39] EASL-ALEH. (2015). Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *Journal of Hepatology*, vol. 63, pp. 237–264.
- [40] Castera, L. (2012). Non-invasive methods to assess liver disease in patients with hepatitis B or C. *Gastroenterology*, vol. 142, pp. 1293–1302.
- [41] Brancatelli, G., Federle, M., Ambrosini, R., et al. (2007). Cirrhosis: CT and MR imaging evaluation. *European Journal of Radiology*, vol. 61, pp. 57–69.
- [42] Smith, A., Branch, C., Zand, K., et al. (2016). Liver surface nodularity quantification from routine ct images as a biomarker for detection and evaluation of cirrhosis. *Radiology*, vol. 280, pp. 771–781.
- [43] Ghanaati, H., Alavian, S. M., Jafarian, A., et al. (2012). Imaging and imaging guided interventions in the diagnosis and management of hepatocellular carcinoma (HCC)- review of evidence. *Iranian Journal of Radiology*, vol. 9, pp. 167–177.
- [44] Bruix, J. and Sherman, M. (2011). Management of hepatocellular carcinoma: An update. *Hepatology*, vol. 53, pp. 1020–1022.
- [45] Blum, H. (2011). Hepatocellular carcinoma: HCC. *Hepatitis Monthly*, vol. 11, pp. 69–70.
- [46] Bialecki, E., Ezenekwe, A., Brunt, E., et al. (2006). Comparison of liver biopsy and non-invasive methods for diagnosis of hepatocellular carcinoma. *Clinical Gastroenterology and Hepatology*, vol. 4, pp. 361–368.
- [47] Zhang, B. H., Yang, B. H., and Tang, Z. Y. (2004). Randomized controlled trial of screening for hepatocellular carcinoma. *Journal of Cancer Research and Clinical Oncology*, vol. 130, pp. 417–422.
- [48] Henedige, T. and Venkatesh, S. (2013). Imaging of hepatocellular carcinoma: diagnosis, staging and treatment monitoring. *Cancer Imaging*, vol. 12, pp. 530–547.
- [49] El-Serag, H., Marrero, J., Rudolph, L., et al. (2008). Diagnosis and treatment of hepatocellular carcinoma. *Gastroenterology*, vol. 134, pp. 1752–1763.
- [50] EASL. (2012). Management of alcoholic liver disease. *Journal of Hepatology*, vol. 57, pp. 399–420.

- [51] Ho, C., Chen, S., Yeung, D., et al. (2007). Dual-tracer PET/CT imaging in evaluation of metastatic hepatocellular carcinoma. *Journal of Nuclear Medicine*, vol. 48, pp. 902–909.
- [52] Russell, M. C. (2015). Complications following hepatectomy. *Surgical Oncology Clinics of North America*, vol. 24, pp. 73–96.
- [53] Durand, F. and Valla, D. (2008). Assessment of prognosis of cirrhosis. *Seminars in Liver Disease*, vol. 28, pp. 110–122.
- [54] Gozzetti, G., Mazziotti, A., Cavallari, A., et al. (1988). Clinical experience with hepatic resections for hepatocellular carcinoma in patients with cirrhosis. *Surgery, Gynecology & Obstetrics*, vol. 166, pp. 503–510.
- [55] Matsumata, T., Kanematsu, T., Shirabe, K., et al. (1990). Decreased morbidity and mortality rates in surgical patients with hepatocellular carcinoma. *British Journal of Surgery*, vol. 77, pp. 677–680.
- [56] Tjandra, J. J., Fan, S. T., and Wong, J. (1991). Peri-operative mortality in hepatic resection. *ANZ Journal of Surgery*, vol. 61, pp. 201–206.
- [57] Fan, S. T., Lai, E. C., Lo, C. M., et al. (1995). Hospital mortality of major hepatectomy for hepatocellular carcinoma associated with cirrhosis. *Archives of Surgery*, vol. 130, pp. 198–203.
- [58] Capussotti, L., Borgonovo, G., Bouzari, H., et al. (1994). Results of major hepatectomy for large primary liver cancer in patients with cirrhosis. *British Journal of Surgery*, vol. 81, pp. 427–431.
- [59] Belghiti, J. and Kianmanesh, R. (2005). Surgical treatment of hepatocellular carcinoma. *HPB*, vol. 7, pp. 42–49.
- [60] Eguchi, S., Kanematsu, T., Aii, S., et al. (2011). Recurrence-free survival more than 10 years after liver resection for hepatocellular carcinoma. *British Journal of Surgery*, vol. 98, pp. 552–557.
- [61] Landman, M. P., Feurer, I. D., Pinson, C. W., et al. (2011). Which is more cost effective under the MELD system: Primary liver transplantation, or salvage transplantation after hepatic resection or after locoregional therapy for hepatocellular carcinoma within Milan criteria? *HPB*, vol. 13, pp. 783–791.
- [62] Sala, M., Fuster, J., Llovet, J. M., et al. (2004). High pathological risk of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. *Liver Transplantation*, vol. 10, pp. 1294–1300.
- [63] Cucchetti, A., Vitale, A., Gaudio, M. D., et al. (2010). Harm and benefits of primary liver resection and salvage transplantation for hepatocellular carcinoma. *American Journal of Transplantation*, vol. 10, pp. 619–627.

- [64] Kishi, Y., Hasegawa, K., Sugawara, Y., et al. (2011). Hepatocellular carcinoma: current management and future development-improved outcomes with surgical resection. *International Journal of Hepatology*, vol. 2011, pp. 1–10.
- [65] Torzilli, G., Belghiti, J., Kokudo, N., et al. (2013). A snapshot of the effective indications and results of surgery for hepatocellular carcinoma in tertiary referral centers: Is it adherent to the EASL/AASLD recommendations? An observational study of the HCC east-west study group. *Annals of Surgery*, vol. 257, pp. 929–937.
- [66] Verloh, N., Haimerl, M., Zeman, F., et al. (2014). Assessing liver function by liver enhancement during the hepatobiliary phase with Gd-EOB-DTPA-enhanced MRI at 3 Tesla. *European Radiology*, vol. 24, pp. 1013–1019.
- [67] Cucchetti, A., Ercolani, G., Vivarelli, M., et al. (2009). Is portal hypertension a contraindication to hepatic resection? *Annals of Surgery*, vol. 250, pp. 922–928.
- [68] Dahl, E., Rumessen, J., and Gluud, L. L. (2011). Systematic review with metaanalyses of studies on the association between cirrhosis and liver metastases. *Hepatology Research*, vol. 41, pp. 618–625.
- [69] Cai, B., Liao, K., Song, X. Q., et al. (2014). Patients with chronically diseased livers have lower incidence of colorectal liver metastases: A meta-analysis. *Plos One*, vol. 9, e108618.
- [70] Berzigotti, A., Reig, M., Abraldes, J. G., et al. (2015). Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and metaanalysis. *Hepatology*, vol. 61, pp. 526–536.
- [71] Ishizawa, T., Hasegawa, K., Aoki, T., et al. (2008). Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology*, vol. 134, pp. 1908–1916.
- [72] Zhong, J. H., Ke, Y., Gong, W. F., et al. (2014). Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. *Annals of Surgery*, vol. 260, pp. 329–340.
- [73] Chang, W. T., Kao, W. Y., Chau, G. Y., et al. (2012). Hepatic resection can provide long-term survival of patients with non-early-stage hepatocellular carcinoma: Extending the indication for resection? *Surgery*, vol. 152, pp. 809–820.
- [74] Liu, P. H., Hsia, C. Y., Lee, Y. H., et al. (2015). Surgical resection versus transarterial chemoembolization for BCLC stage C hepatocellular carcinoma. *Journal of Surgical Oncology*, vol. 111, pp. 404–409.
- [75] Vitale, A., Burra, P., Frigo, A. C., et al. (2015). Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona clinic liver cancer stages: A multicentre study. *Journal of Hepatology*, vol. 62, pp. 617–624.

- [76] Yin, L., Li, H., Li, A. J., et al. (2014). Partial hepatectomy vs. transcatheter arterial chemoembolization for resectable multiple hepatocellular carcinoma beyond Milan Criteria: A RCT. *Journal of Hepatology*, vol. 61, pp. 82–88.
- [77] Chua, T., Liauw, W., Saxena, A., et al. (2010). Systematic review of neoadjuvant transarterial chemoembolization for resectable hepatocellular carcinoma. *Liver International*, vol. 30, pp. 166–174.
- [78] Young, A. L., Malik, H. Z., Abu-Hilal, M., et al. (2007). Large hepatocellular carcinoma: time to stop preoperative biopsy. *Journal of the American College of Surgeons*, vol. 205, pp. 453–462.
- [79] Ikai, I., Yamamoto, Y., Yamamoto, N., et al. (2003). Results of hepatic resection for hepatocellular carcinoma invading major portal and/or hepatic veins. *Surgical Oncology Clinics*, vol. 12, pp. 65–75.
- [80] Wang, B. W., Mok, K. T., Liu, S. I., et al. (2008). Is hepatectomy beneficial in the treatment of multinodular hepatocellular carcinoma? *Journal of the Formosan Medical Association*, vol. 107, pp. 616–626.
- [81] Ng, K. K., Vauthey, J. N., Pawlik, T. M., et al. (2005). Is hepatic resection for large or multinodular hepatocellular carcinoma justified? Results from a multi-institutional database. *Annals of Surgical Oncology*, vol. 12, pp. 364–373.
- [82] Guglielmi, A., Ruzzenente, A., Conci, S., et al. (2012). How much remnant is enough in liver resection? *Digestive Surgery*, vol. 29, pp. 6–17.
- [83] Shirabe, K., Shimada, M., Gion, T., et al. (1999). Postoperative liver failure after major hepatic resection for hepatocellular carcinoma in the modern era with special reference to remnant liver volume. *Journal of the American College of Surgeons*, vol. 188, pp. 304–309.
- [84] Schindl, M. J., Redhead, D. N., Fearon, K. C., et al. (2005). The value of residual liver volume as a predictor of hepatic dysfunction and infection after major liver resection. *Gut*, vol. 54, pp. 289–296.
- [85] Popescu, G. A., Alexandrescu, S. T., Grigorie, R. T., et al. (2017). Good to know: The ALPPS procedure - Embracing a new technique. *Chirurgia*, vol. 112, pp. 332–341.
- [86] Farges, O., Malassagne, B., Flejou, J. F., et al. (1999). Risk of major liver resection in patients with underlying chronic liver disease. *Annals of Surgery*, vol. 229, pp. 210–215.
- [87] Cucchetti, A., Ercolani, G., Vivarelli, M., et al. (2006). Impact of model for end-stage liver disease (MELD) score on prognosis after hepatectomy for hepatocellular carcinoma on cirrhosis. *Liver Transplantation*, vol. 12, pp. 966–971.

- [88] McCormack, L., Petrowsky, H., Jochum, W., et al. (2007). Hepatic steatosis is a risk factor for postoperative complications after major hepatectomy: A matched case-control study. *Annals of Surgery*, vol. 245, pp. 923–930.
- [89] The, S. H., Christein, J., Donohue, J., et al. (2005). Hepatic resection of hepatocellular carcinoma in patients with cirrhosis: Model of End-Stage Liver Disease (MELD) score predicts perioperative mortality. *Journal of Gastrointestinal Surgery*, vol. 9, pp. 1207–1215.
- [90] Hsu, K. Y., Chau, G. Y., Lui, W. Y., et al. (2009). Predicting morbidity and mortality after hepatic resection in patients with hepatocellular carcinoma: The role of model for end-stage liver disease score. *World Journal of Surgery*, vol. 33, pp. 2412–2419.
- [91] Forner, A., Reig, M. E., de Lope, C. R., et al. (2010). Current strategy for staging and treatment: The BCLC update and future prospects. *Seminars in Liver Disease*, vol. 30, pp. 61–74.
- [92] Llovet, J. M., Bru, C., and Bruix, J. (1999). Prognosis of hepatocellular carcinoma: The BCLC staging classification. *Seminars in Liver Disease*, vol. 19, pp. 329–338.
- [93] Durand, F. and Valla, D. (2008). Assessment of prognosis of cirrhosis. *Seminars in Liver Disease*, vol. 28, pp. 110–122.
- [94] Malinchoc, M., Kamath, P. S., Gordon, F. D., et al. (2000). A model to predict poor survival in patients undergoing transjugular intrahepatic portosystemic shunts. *Hepatology*, vol. 31, pp. 864–871.
- [95] Delis, S. G., Bakoyiannis, A., Dervenis, C., et al. (2009). Perioperative risk assessment for hepatocellular carcinoma by using the MELD score. *Journal of Gastrointestinal Surgery*, vol. 13, pp. 2268–2275.
- [96] Cescon, M., Cucchetti, A., Grazi, G. L., et al. (2009). Indication of the extent of hepatectomy for hepatocellular carcinoma on cirrhosis by a simple algorithm based on preoperative variables. *Archives of Surgery*, vol. 144, pp. 57–63.
- [97] Yamazaki, S. and Takayama, T. (2008). Surgical treatment of hepatocellular carcinoma: evidence-based outcomes. *World Journal of Gastroenterology*, vol. 14, pp. 685–692.
- [98] Fan, S. T. (2010). Liver functional reserve estimation: state of the art and relevance for local treatments: The eastern perspective. *Journal of Hepato-biliary-pancreatic Sciences*, vol. 17, pp. 380–384.
- [99] Zipprich, A., Kuss, O., Rogowski, S., et al. (2010). Incorporating indocyanin green clearance into the model for end stage liver disease (MELD-ICG) improves prognostic accuracy in intermediate to advanced cirrhosis. *Gut*, vol. 59, pp. 963–968.

- [100] Lau, H., Man, K., Fan, S. T., et al. (1997). Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. *British Journal of Surgery*, vol. 84, pp. 1255–1259.
- [101] Kudo, M., Izumi, N., Kokudo, N., et al. (2011). Management of hepatocellular carcinoma in Japan: Consensus-based clinical practice guidelines proposed by the Japan society of hepatology (JSH) 2010 updated version. *Digestive Diseases*, vol. 29, pp. 339–364.
- [102] Earl, T. M. and Chapman, W. C. (2011). Conventional surgical treatment of hepatocellular carcinoma. *Clinics in Liver Disease*, vol. 15, pp. 353–370.
- [103] Capussotti, L., Ferrero, A., Vigano, L., et al. (2006). Portal hypertension: Contraindication to liver surgery? *World Journal of Surgery*, vol. 30, pp. 992–999.
- [104] Kawano, Y., Sasaki, A., Kai, S., et al. (2008). Short- and long-term outcomes after hepatic resection for hepatocellular carcinoma with concomitant esophageal varices in patients with cirrhosis. *Annals of Surgical Oncology*, vol. 15, pp. 1670–1676.
- [105] Sugimachi, K., Ikeda, Y., Tomikawa, M., et al. (2008). Appraisal of hepatic resection in the treatment of hepatocellular carcinoma with severe thrombocytopenia. *World Journal of Surgery*, vol. 32, pp. 1077–1081.
- [106] Matsumata, T., Taketomi, A., Kawahara, N., et al. (1994). Morbidity and mortality after hepatic resection in the modern era. *Hepato-gastroenterology*, vol. 42, pp. 456–460.
- [107] Poon, R. T., Fan, S. T., and Wong, J. (2002). Does diabetes mellitus influence the perioperative outcome or long term prognosis after resection of hepatocellular carcinoma? *American Journal of Gastroenterology*, vol. 97, pp. 1480–1488.
- [108] Forner, A., Llovet, J. M., and Bruix, J. (2012). Hepatocellular carcinoma. *Lancet*, vol. 379, pp. 1245–1255.
- [109] Llovet, J. M., Fuster, J., and Bruix, J. (1999). Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. *Hepatology*, vol. 30, pp. 1434–1440.
- [110] Zhang, Y. Q. and Guo, J. S. (2015). Antiviral therapies for hepatitis B virus related hepatocellular carcinoma. *World Journal of Gastroenterology*, vol. 21, pp. 3860–3866.
- [111] Sugawara, Y., Yamamoto, J., Higashi, H., et al. (2002). Preoperative Portal embolization in patients with hepatocellular carcinoma. *World Journal of Surgery*, vol. 26, pp. 105–110.
- [112] Farges, O., Belghiti, J., Kianmanesh, R., et al. (2003). Portal vein embolization before right hepatectomy: Prospective clinical trial. *Annals of Surgery*, vol. 237, pp. 208–217.

- [113] Abulkhir, A., Limongelli, P., Healey, A. J., et al. (2008). Preoperative portal vein embolization for major liver resection: A meta-analysis. *Annals of Surgery*, vol. 247, pp. 49–57.
- [114] Hwang, S., Lee, S. G., Ko, G. Y., et al. (2009). Sequential preoperative ipsilateral hepatic vein embolization after portal vein embolization to induce further liver regeneration in patients with hepatobiliary malignancy. *Annals of Surgery*, vol. 249, pp. 608–616.
- [115] Yoo, H., Kim, J. H., Ko, G. Y., et al. (2011). Sequential transcatheter arterial chemoembolization and portal vein embolization versus portal vein embolization only before major hepatectomy for patients with hepatocellular carcinoma. *Annals of Surgical Oncology*, vol. 18, pp. 1251–1257.
- [116] Jones, R., Moulton, C., and Hardy, K. (1998). Central venous pressure and its effect on blood loss during liver resection. *British Journal of Surgery*, vol. 85, pp. 1058–1060.
- [117] Huntington, J., Royall, N., and Schmidt, C. (2014). Minimizing blood loss during hepatectomy: A literature review. *Journal of Surgical Oncology*, vol. 109, pp. 81–88.
- [118] Belghiti, J., Noun, R., Zante, E., et al. (1996). Portal triad clamping or hepatic vascular exclusion for major liver resection: A controlled study. *Annals of Surgery*, vol. 224, pp. 155–161.
- [119] Brooks, A., Hammond, J., Girling, K., et al. (2007). The effect of hepatic vascular inflow occlusion on liver tissue pH, carbon dioxide, and oxygen partial pressures: defining the optimal clamp/release regime for intermittent portal clamping. *Journal of Surgical Research*, vol. 141, pp. 247–251.
- [120] Capussotti, L., Nuzzo, G., Polastri, R., et al. (2003). Continuous versus intermittent portal triad clamping during hepatectomy in cirrhosis. Results of a prospective, randomized clinical trial. *Hepato-gastroenterology*, vol. 50, pp. 1073–1077.
- [121] Lesurtel, M., Lehmann, K., De Rougemont, O., et al. (2009). Clamping techniques and protecting strategies in liver surgery. *HPB*, vol. 11, pp. 290–295.
- [122] Dahiya, D., Wu, T. J., Lee, C. F., et al. (2010). Minor versus major hepatic resection for small hepatocellular carcinoma (HCC) in cirrhotic patients: A 20-year experience. *Surgery*, vol. 147, pp. 676–685.
- [123] Duan, Y. F., Li, X. D., Sun, D. L., et al. (2015). A preliminary study on surgery for hepatocellular carcinoma patients with portal hypertension. *American Journal of Surgery*, vol. 210, pp. 129–133.

- [124] Shi, M., Guo, R. P., Lin, X. J., et al. (2007). Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: A prospective randomized trial. *Annals of Surgery*, vol. 245, pp. 36–43.
- [125] Poon, R. T., Fan, S. T., Ng, I. O., et al. (2000). Significance of resection margin in hepatectomy for hepatocellular carcinoma: A critical reappraisal. *Annals of Surgery*, vol. 231, pp. 544–551.
- [126] Rau, H. G., Duessel, A. P., and Wurzbacher, S. (2008). The use of water-jet dissection in open and laparoscopic liver resection. *HPB*, vol. 10, pp. 275–280.
- [127] Rau, H. G., Wichmann, M. W., Schinkel, S., et al. (2001). Surgical techniques in hepatic resections: Ultrasonic aspirator versus jet-cutter: A prospective randomized clinical trial. *Zentralbl Chir*, vol. 126, pp. 586–590.
- [128] Cannon, R. M., Saggi, B., and Buell, J. F. (2014). Evaluation of a laparoscopic liver resection in the setting of cirrhosis. *HPB*, vol. 16, pp. 164–169.
- [129] Hoffmann, K., Mueller-Buetow, V., Franz, C., et al. (2014). Factors predictive of survival after stapler hepatectomy of hepatocellular carcinoma: A multivariate, single-center analysis. *Anticancer Research*, vol. 34, pp. 767–776.
- [130] Liu, C. L., Fan, S. T., Cheung, S. T., et al. (2006). Anterior approach versus conventional approach right hepatic resection for large hepatocellular carcinoma: A prospective randomized controlled study. *Annals of Surgery*, vol. 244, pp. 194–203.
- [131] Lai, E. C., Fan, S. T., Lo, C. M., et al. (1996). Anterior approach for difficult major right hepatectomy. *World Journal of Surgery*, vol. 20, pp. 314–317.
- [132] Wu, T. J., Wang, F., Lin, Y. S., et al. (2010). Right hepatectomy by the anterior method with liver hanging versus conventional approach for large hepatocellular carcinomas. *British Journal of Surgery*, vol. 97, pp. 1070–1078.
- [133] Belghiti, J. (2010). Editorial perspective: Resection of large hepatocellular carcinoma using combination of liver hanging maneuver and anterior approach. *World Journal of Surgery*, vol. 34, pp. 1879–1880.
- [134] Hoots, W. K., Buchanan, G. R., Parmley, R. T., et al. (1991). Comprehensive care for patients with hemophilia: An expanded role in reducing risk for human immunodeficiency virus. *Texas Medicine*, vol. 87, pp. 73–75.
- [135] Jarnagin, W., Chapman, W. C., Curley, S., et al. (2010). Surgical treatment of hepatocellular carcinoma: Expert consensus statement. *HPB*, vol. 12, pp. 302–310.
- [136] Chung, C. D., Lau, L. L., Ko, K. L., et al. (2010). Laparoscopic liver resection for hepatocellular carcinoma. *Asian Journal of Surgery*, vol. 33, pp. 168–172.
- [137] Nguyen, K. T., Gamblin, T. C., and Geller, D. A. (2009). World review of laparoscopic liver resection—2,804 patients. *Annals of Surgery*, vol. 250, pp. 831–841.

- [138] Rao, A., Rao, G., and Ahmed, I. (2012). Laparoscopic or open liver resection? Let systematic review decide it. *American Journal of Surgery*, vol. 204, pp. 222–231.
- [139] Buell, J. F., Cherqui, D., Geller, D. A., et al. (2009). The international position on laparoscopic liver surgery: The Louisville statement, 2008. *Annals of Surgery*, vol. 250, pp. 825–830.
- [140] Laurent, A., Tayar, C., Andreoletti, M., et al. (2009). Laparoscopic liver resection facilitates salvage liver transplantation for hepatocellular carcinoma. *Journal of Hepato-biliary-pancreatic Sciences*, vol. 16, pp. 310–314.
- [141] Ramos, F. M., Loinaz, S. C., Fernandez, C. J., et al. (2011). Laparoscopic and hand-assisted liver resection: Preliminary results at a mid-sized hospital. *Hepato-gastroenterology*, vol. 58, pp. 492–496.
- [142] Cho, J. Y., Han, H. S., Yoon, Y. S., et al. (2008). Feasibility of laparoscopic liver resection for tumors located in the posterosuperior segments of the liver with a special reference to overcoming current limitations on tumor location. *Surgery*, vol. 144, pp. 32–38.
- [143] Capussotti, L., Muratore, A., Amisano, M., et al. (2005). Liver resection for hepatocellular carcinoma on cirrhosis: Analysis of mortality, morbidity and survival—A European single centre experience. *European Journal of Surgical Oncology*, vol. 31, pp. 986–993.
- [144] Balzan, S., Belghiti, J., Farges, O., et al. (2005). The “50-50 criteria” on postoperative day 5: An accurate predictor of liver failure and death after hepatectomy. *Annals of Surgery*, vol. 242, pp. 824–829.
- [145] Rahbari, N. N., Garden, O. J., Padbury, R., et al. (2011). Posthepatectomy liver failure: A definition and grading by the international study group of liver surgery (ISGLS). *Surgery*, vol. 149, pp. 713–724.
- [146] Pessaux, P., Msika, S., Atalla, D., et al. (2003). Risk factors for postoperative infectious complications in noncolorectal abdominal surgery: a multivariate analysis based on a prospective multicentre study of 4718 patients. *Archives of Surgery*, vol. 138, pp. 314–324.
- [147] Gomez-Jimenez, J., Ribera, E., Gasser, I., et al. (1993). Randomized trial comparing ceftriaxone with cefonicid for treatment of spontaneous bacterial peritonitis in cirrhotic patients. *Antimicrobial Agents and Chemotherapy*, vol. 37, pp. 1587–1592.
- [148] Rimola, A., Navasa, M., and Arroyo, V. (1995). Experience with cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis. *Diagnostic Microbiology and Infectious Disease*, vol. 22, pp. 141–145.

- [149] Peck, K. R., Cheong, H. S., Kang, C. I., et al. (2009). Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. *Clinical Infectious Diseases*, vol. 48, pp. 1230–1236.
- [150] De Goede, B., Klitsie, P. J., Hagen, S. M., et al. (2013). Meta-analysis of laparoscopic versus open cholecystectomy for patients with liver cirrhosis and symptomatic cholecystolithiasis. *British Journal of Surgery*, vol. 100, pp. 209–216.