Chapter 13

Surgical Management of Primary Hepatocellular Carcinoma

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/51418

1. Introduction

Hepatocellular carcinoma (HCC) is among the most common malignancy and cause of cancer related death worldwide, with a high prevalence in Asia and south Africa as well as an increasing incidence in the western country. Patients with liver cirrhosis are at highest risk of developing this malignant disease, and the majority of HCC patients will develop the disease on the background of preexisting hepatitis virus infection. It is estimated 50–70% associated with hepatitis C virus in North America and Europe and 70% associated with hepatitis B virus in Asia and Africa [1], and the incidence of HCC is significantly higher in men than in women. However, surveillance programs for HCC in patients with cirrhosis and chronic hepatitis, and the advancement of diagnostic tools are likely to further increase the incidence of HCC and the detection of small lesions in the liver that prompted the proportion of patients diagnosed at a potentially curative stage of disease.

Several staging systems have so far been proposed for aiding assessment of treatment planning for HCC patients, but an overall consensus remains not exist for any of these staging systems.The Tumor-Node-Metastasis staging (TNM) system of the American Joint Committee on Cancer/Committee of the International Union Against Cancer (AJCC/UICC) has been widely used for numerous cancer staging in order to stratify patients into prognostic groups [2], but it is not perfectly applicable for HCC in terms of treatment assessment as the TNM staging does not consider the underlying liver functional reserve and seems only applicable to patients undergoing liver resection or liver transplantation. The Cancer of the Liver Italian Program (CLIP) classifications and the Okuda staging system were introduced not only considering tumor features but also liver functional reserve.The CLIP scoring system considers cirrhotic status in terms of Child-Turcotte-Pugh (CTP) class and several factors related to tumor features including tumor morphology, Alphafeto protein (AFP) level, and

portal vein thrombosis [3]. Although the CLIP scoring system is probably helpful to identify patients with a poor prognosis, it might be inadequate to identify patients at early stages of disease. The Okuda system has also been found unsuitable for prognostic stratification of patients at an early stage of disease [4]. Therefore, the Japan Integrated Staging score that combines the CTP class with the Liver Cancer Study Group of Japan TNM stage was formulated to provide better stratification of patients with early HCC than that achieved by the CLIP score and Okuda system [5]. Additionally, the Barcelona Clinic Liver Cancer(BCLC) staging system was suggested as a modification of the Okuda system, and has been validated superior for prognostic stratification of patients with HCC than other staging systems [6-8]. The BCLC staging system involves factors related to underlying liver function, tumor characteristics, and patients' performance status, and was proposed as a means of predicting prognosis and as a guide to selecting appropriate therapy for HCC patients.

Generally, these staging systems was developed aiming to stratify patients into groups with similar prognoses and to serve as a guiding choice of therapy. Current popular treatments for HCC include liver resection, percutaneous ethanol injection (PEI) or radiofrequency ablation (RFA), transcatheter arterial chemoembolization (TACE), liver transplantation, and targeted therapy with novel biologic agent such as sorafenib. The selection of treatment modality for HCC patients should be based on the patient's prognosis, which is complex to assess, as it depends on three factors, namely, the tumor characteristics, the underlying liver functional reserve and the patient's physical condition. At present, only liver resection and liver transplantation are considered the best potential curative therapies. Nonetheless, because of underlying liver dysfunction, lack of liver donor availability, and/or late detection at advanced cancerous stage, only a small proportion of patients are eligible for these curative treatments. This chapter reviews the importance and clinical impact of surgical management in terms of liver resection and transplantation for patients with primary HCC and highlights their relative strengths and weakness.

2. Liver Resection

Liver resection remains the mainstay curative treatment for patients with HCC. However, the majority of HCC patients are often associated with liver cirrhosis due to hepatitis B or C viral infection, which might prohibit from liver resection because of impaired liver function. Moreover, many HCC patients present with advanced tumor stage and only approximately 20–30% of patients are candidates for liver resection on presentation [9-11]. In spite of this situation, the advancement in anesthetic and surgical techniques, as well as a thorough understanding of the liver anatomy, and better perioperative care, have contributed dramatically to the safety and effectiveness of liver resection for HCC.

Since the proposal of the finger fracture technique for hepatic lobectomy in 1953, transection of the hepatic parenchyma has evolved during the last 50 years. By finger fracture technique, the liver tissue is fractured and crushed by the thumb and index finger followed by isolating and ligating the resistant intrahepatic vascular and ductal structures [12]. Howev-

http://dx.doi.org/10.5772/51418

er, there is some troublesome bleeding from the resection line which makes the surgeons fear for the safety of the finger fracture technique. To overcome this short coming of the finger fracture technique, many special instruments were invented to increase the successful rate and safety of liver resection ever since (Figure 1). Currently, Kelly clamp crushing technique is still one of the most widely used techniques for liver resection. However, in many centers, including the author's center, ultrasonic dissection using the Cavitron Ultrasonic Surgical Aspirator (CUSA) has become the standard technique of liver resection. Today, laparoscopic liver resection has become feasible in experienced centers due to improvement in instruments [13-15]. Additionally, modern concepts including the use of vascular inflow occlusion, anatomic resection, and low central venous pressure anesthesia, and surgical approaches such as the anterior approach and liver hanging maneuver have been developed along with using more effective instruments for transection of hepatic parenchyma [16-18]. As a result, liver resections are increasingly being performed and accepted as a safety procedure.

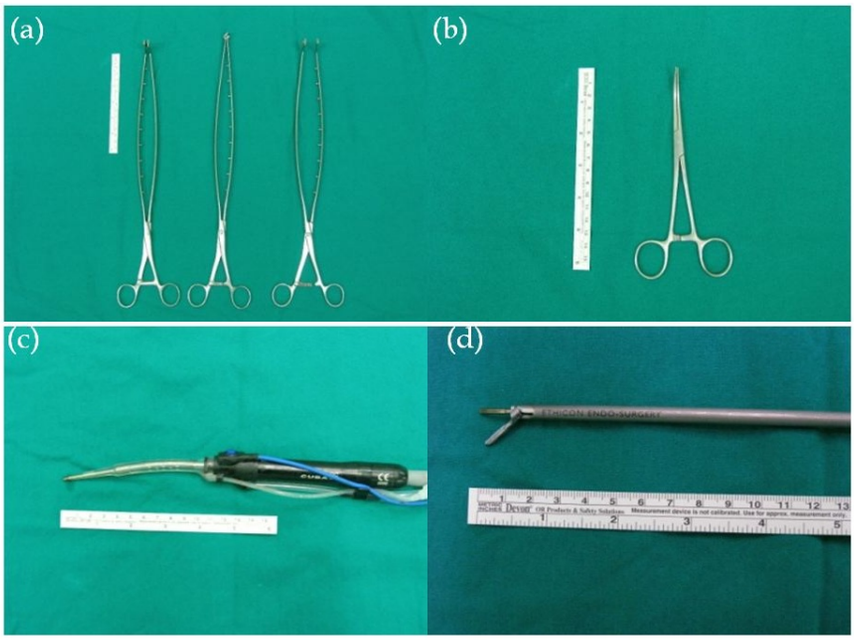

Figure 1. Liver resection instruments. (a). Lin's clamp designed by T.Y. Lin. (b). Kelly clamp. (c). Cavitron Ultrasonic Surgical Aspirator (CUSA). (d). Harmonic scalpel for laparoscopic liver resection.

2.1. Preoperative assessment

The major concern of liver resection in HCC patients is postoperative liver failure, which is particularly worrisome in patients requiring major resections and/or diseased background of cirrhotic liver. Therefore, a thorough evaluating of patients in terms of tumor features of radiologic examination, underlying liver function, and the patient's physical status is very important. Theoretically, a successful liver resection for HCC patients should be weighed against the balance of these three factors.

2.1.1. Evaluation of tumor status

The assessment of tumor status is the essential step for determining resectability and the appropriate type of liver resection. The routine radiologic imaging examination prior to liver resection should include a dynamic liver computed tomography (CT) scan, hepatic angiography, and/or magnetic resonance imaging (MRI) to confirm the diagnosis of HCC as well as tumor status in terms of size, number and location. Additionally, a chest X-ray or contrast CT scan of chest and abdomen could be performed to exclude lung or other extrahepatic metastasis. The CT scan provides important information not only on the tumor size, number, location, and any vascular invasion but also on the relationship between the tumor and major vasculature. Generally, pre-operative biopsy is not necessary as may risk needle track related tumor seeding.

Large HCC—Solitary HCC with diameter of less than 5 cm is the best candidate for liver resection because of favorable patients' outcome in terms of HCC recurrent-free survival [19, 20]. However, numerous patients continue to be diagnosed HCC at an advanced stage that sometimes presented with large tumor with diameter exceed 10 cm. Although liver resection for patients with large tumor can be a great challenge for liver surgeons, liver resection for large HCCs has been shown to be safe and reasonable long-term survival results can be achieved that appear to be much better than any other nonsurgical treatments [21-23]. The 5-year survival rate in patients with tumors larger than 10 cm after liver resection is approximately 21–27.5% [23-25]. Additionally, since liver transplantation and local ablation are not indicated for these patients, surgical resection remains the only treatment of choice that provides potential cure of patients with large HCC.

Multiple HCCs—Multiple HCCs may represent as a manifestation of advanced disease with intrahepatic metastasis or independent tumors that derived from multiple foci of hepatocarcinogenesis, which could be an event associated with a poor prognosis. Patients with multiple HCCs more than 3 nodules have been considered unsuitable for resection. However, it had been shown that liver resection still can provide survival benefits even for patients with multiple tumors in a background of CTP class A cirrhosis, and the overall survival rates can up to 58% at 5 years [26]. Additionally, combined resection and radiofrequency ablation is considered a new strategy to increase the chance of curative treatment for patients with bilobar multiple HCCs. For example, resection of the large tumor in one lobe and ablation of smaller tumors in the other lobe can be performed, or resection of peripheral lesions and ablation of central lesions for patients with multifocal tumors associated with cirrhosis and borderline liver function can be performed [27, 28]. The results showed patients who underwent surgical resection for multiple HCCs had better survival outcomes as compared with those who received nonsurgical therapy. Hence, when clearance of all tumor nodules is feasible and liver function permits, surgical resection or plus effective local ablative therapy should be considered for patients with bilobar or multiple HCCs.

HCC involving major portal and hepatic veins—HCCs with major portal or hepatic veins involvement represent an aggressive tumor behavior and frequently associated with multifocal tumors. Although HCCs with vascular invasion are not considered as favorable surgical candidates, studies from experienced liver surgical groups have shown that surgical resec-

tion for such tumors seems justified as it still results in better survival rates as compared with that of nonsurgical treatment [29, 30]. The overall survival rates at 5 years were ranged from 23% to 42% in selected patient who has no liver cirrhosis or impaired liver function.

2.1.2. Evaluation of liver function

Preoperative proper assessment of liver function is fundamental to the safe of liver resection for HCC patients, but there is no individual test accurately predicting liver function.The CTP classification is the most common measure to assess liver function, and it combines different parameters and provides a rough evaluation of the gross synthetic and excretory capacity of the liver. Generally, patients with CTP class A are considered good candidates for liver resection. Patients with CTP class B may be only suitable for minor liver resection such as wedge resection or single segmentectomy [31], whereas patients with CTP class C are contraindicated for resection. The risk of death after liver resection increases with each CTP class. However, this classification is a crude measure and has proven insufficient to stratify the surgical risk of patient with liver cirrhosis.

Portal hypertension is usually defined by that the portal venous pressure is greater than 10 mmHg, in which the normal value ranges from 5 to 8 mmHg. Patients with portal hypertension undergoing liver resection may lead to severe complications, such as variceal bleeding, endotoxemia, and even hepatic failure in the postoperative period [32]. However, measurement of portal venous pressure prior to liver resection is difficult, and portal hypertension could only be roughly assessed by clinical and radiologic signs including splenomegaly, abdominal collaterals, thrombocytopenia with platelet count less than 100,000/mm^3, or esophagogastric varices. Although portal hypertension is considered a relatively contraindication of liver resection, study had shown that liver resection is also capable of providing survival benefits to patients with a background of portal hypertension [26]. Additionally, patients with abnormal elevation of liver function tests in terms of serum aspartate and alanine aminotransferase levels might have a higher risk of postoperative complication and mortality rates, and are considered to be poor candidates for major liver resection [33, 34]. Therefore, patients with abnormal liver function tests should be carefully assessed and selected prior to liver resection.

Additionally, several hepatobiliary centers have employed more sophisticated quantitative liver function tests, such as the lidocaine monoethylglycinexylidide test, aminopyrine breath test, galactose elimination capacity, and indocyanine green (ICG) clearance test to evaluate the hepatic metabolic function and to predict the risk of postoperative liver failure [35-37]. However, these specific tests reflect the function of the whole liver, whereas the risk of postoperative liver failure relies on the liver function reserve of the remnant liver. Among the various methods, the ICG test is the most widely used to assess liver function prior to liver resection. The ICG is an organic dye that is taken up by the hepatocytes and excreted via the bile in an adenosine triphosphate (ATP) dependent manner without been metabolized and undergoing enterohepatic circulation. Thus, the clearance of ICG from systemic circulation

is merely a measure of hepatic blood flow and function. This test evaluates the retention ratio of ICG from the peripheral blood at definitive time point after injection of 0.5 mg ICG/kg (usually 15 minutes, ICG-15), and Makuuchi et al. have incorporated the ICG-15 and two clinical features in terms of serum bilirubin level and the presence of ascites into an algorithm of liver resection (Figure 2) [38]. In patients with bilirubin levels less than 1.0mg/dL and the absence of ascites, ICG-15 is used to predict the extent of liver segments that can be safely removed. In general, an ICG-15 of 10–20% is usually considered a safety upper limit for major liver resection. Accordingly, the algorithm has been validated toward zero surgical mortality after liver resection by several hepatobiliary centers [39, 40].

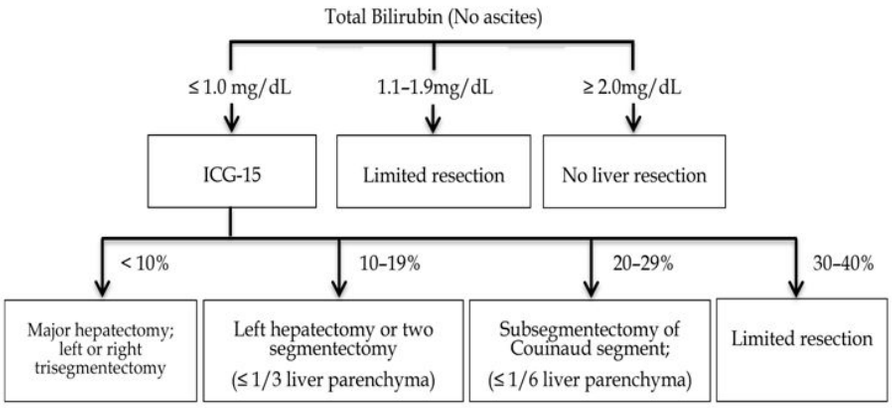

Figure 2. Makuuchi's algorithm for liver resection in patients with HCC [38]. Limited resection means enucleation of the tumor (usually ≤ 5cm) and less than 1 cm of liver tissue surrounding the tumor was removed.

ICG-15 (%)	Safe resection ratio of liver volume
0	< 63.3%
~ 5	< 53.4%
~ 10	<43.5%
~ 15	<33.6%
~ 20	<23.7%
~ 25	<13.8%
~ 30	<3.9%
≥ 32	0%

Table 1. The safe resection ratio of liver volume based on the ICG test [43].

Although the assessment of hepatic function and liver volume to be resected is crucial for a safe liver resection, volumetric analysis of the future liver remnant (FLR) has also been suggested. The FLR can be measured directly by computer-assisted models of contrast-en-

hanced spiral CT. However, it remains controversial regarding which index of the FLR volume should be used. Some surgeons use the actual total liver volume minus liver volume to be removed on CT images as the FLR volume, while others use the estimated ideal liver volume that is calculated by a formula based on body surface area as a standard for calculation of the FLR. Nonetheless, the exactly number of the adequate FLR volume in cirrhotic patients is also no consensus, and at least an FLR of 40% is recommended in patients with chronic liver disease [41, 42]. In the authors' center, we have established an equation to reveal the relationship between the ratio of FLR volume and ICG-15 values as well as references for determining a safe resection ratio of the liver volume (Table 1)[43].

2.2. Preoperative therapy

Since not all patients with HCC are amenable to surgical resection, several strategies such as preoperative TACE that might be used to downsize large HCC or portal vein embolization (PVE) to increase the FLR have been suggested. However, the efficacy of these preoperative approaches in terms of HCC oncologic viewpoint remains the subject of debate.

2.2.1. Portal vein embolization

The concept of PVE was introduced on the basis of the idea that an increase in the FLR will reduce the risk of liver failure after major liver resection for hilar bile duct carcinoma in 1982 [44]. By occluding portal venous branch of the tumor-bearing liver, PVE induces atrophy of the resection part and hypertrophy of the FLR. Although the ability of liver regeneration in cirrhotic liver is impaired, PVE may induce clinically sufficient hypertrophy in these patients as well.Currently, PVE could be considered for patients with liver cirrhosis when the FLR is expected less than 40% of the total liver volume [45, 46]. PVE may also be used as a dynamic liver function test, in which inadequate hypertrophy of the FLR or intolerance of the patient after PVE indicate that major liver resection is contraindicated. In general, PVE is a relatively safe procedure, and it may increase the resectability of initial unresectable HCC and reduce the risk of post hepatectomy liver failure. Additionally, it seems no adverse effect on the oncologic outcome of HCC patients undergoing major liver resection [47, 48]. However, the potential for progression of the primary tumor after PVE remains a major concern, whereas a combination of TACE as a complementary procedure to PVE could be considered in order to improve the outcome of HCC patients [49].

2.2.2. Preoperative transcatheter arterial chemoembolization (TACE)

The use of TACE as a neoadjuvant treatment for HCC was proposed in a variety of settings such as palliative treatment for unresectable HCC, to improve the resectability of intial unresectable HCC, to downstage the primary tumor for liver transplantation or for delay surgery. The major goal of TACE is aimed at inducing tumor necrosis and shrinkage as well as preventing the dissemination of the primary tumor (Figure 3). Theroretically, the use of neoadjuvant TACE in the setting of resectable HCC might be capable of improving survival by

reducing tummor recurrences. Nonethelesss, the fact is that most studies show conflict outcomes of TACE as a neoadjuvant therapy and do not support routine use of preoperative TACE before liver resection [50-53]. Moreover, preoperative TACE for resectable large HCC is not recommended because it does not provide complete necrosis of the large tumor andmay actually result in progression of the primary tumor owing to delay surgery and complicate the operation during the process of liver mobilization due to the presence of perihepatic adhesions after TACE.

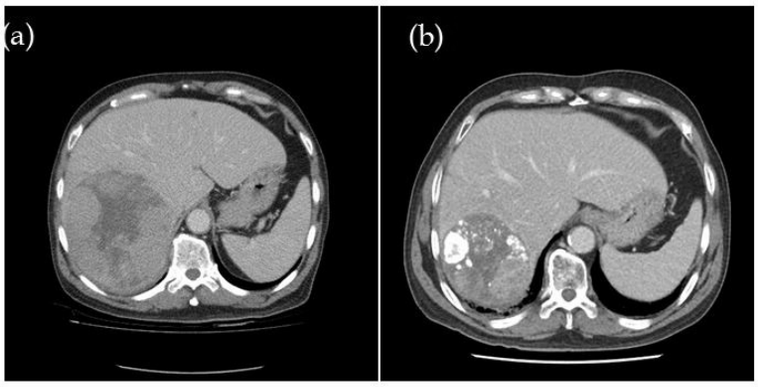

Figure 3. TACE induces remarkable shrinkage of tumor mass. (a) A huge liver tumor around 15 cm in size located at right lobe liver. (b) The tumor was decreased by half in size after three courses of TACE. (4 months after HCC diagnosed)

Clinically, spontaneous tumor rupture accompanied by hemorrhaging has been seen in small portion of patients with HCC at initial presentation, which might lead to a life-threatening condition depending on the severity of hemorrhage. Transcatheter arterial embolization (TAE) should be performed for ruptured HCC to control tumor bleeding as well as stabilizing clinical condition of patients. Liver resection then can be evaluated after the patient has recovery from shock status and post-TAE damage of the liver according to the criteria of liver resection. Generally, TAE followed by staged liver resection of tumor seems to be a rational treatment strategy for patients with ruptured HCC and hemorrhage if the lesion is resectable, and long-term survival could be expected [54, 55].

2.3. Outcome of liver resection

The operative mortality of liver resection has been reduced to less than 5% with some centers approaching to zero mortality in recent years [39, 40, 56]. The improvement is primarily resulting from advances in surgical techniques, perioperative management, and more cautious patient selection. However, the postoperative morbidity rate remains high that ranges from 25 to 50% even in experienced centers [11, 57, 58]. Ascites and pulmonary complications are the most common complications, but serious complications such as liver failure, postoperative hemorrhage, bile leakage, and intra-abdominal sepsis are less frequent nowadays. Apart from that, the long-term survival after resection of HCC have much improvedlately, but HCC recurrence remains a major concern for patients undergoing liver resection.

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2.3.1. HCC recurrence

The high incidence of postoperative recurrence, estimated excess of 70% at 5 years, is the greatest frustration in treating patient with HCC. Recurrent HCCs are mostly intrahepatic that accounts for approximately 80–90% of cases after liver resection. There are two peaks of HCC recurrence after liver resection:The first peak occurs at approximately 1 year posthepatectomy and about 40% of recurrence within the period, in which metastatic dissemination of the primary tumor is mainly responsible for this early peak. The second peak is observed at the 4th postoperative year with a 35% of recurrent rate per year, and the majority of the second peak is more likely attributable to new tumors development related to the carcinogenic effect of underlying chronic liver disease [59].

Currently, there is no well-established adjuvant therapy to reduce the risk of recurrence after curative liver resection. Although numerous studies have demonstrated the efficacy of some new modalities including acyclic retinoid, polyprenoic acid [60], intra-arterial iodine-131-labelled lipiodol [61], and adoptive immunotherapy [62] as adjuvant therapy in the prevention of HCC recurrence after liver resection, the sample size of these individual studies was rather small and further validated by randomized trials with large sample size is required. Additionally, interferon has been proposed as adjuvant therapy in patients with HCC and viral hepatitis after liver resection and shown beneficial for reducing recurrence and prolonging survival [63, 64]. Nonetheless, a more recent cohort study based on a phase III randomized trial of adjuvant interferon alfa-2b in HCC after curative resection does not support the benefit of interferon in reducing postoperative recurrence of viral hepatitis-related HCC [65]. Apart from that, another potential approach is to use molecular targeted therapy such as sorafenib that is applied for advanced HCC and may inhibit HCC cell proliferation and angiogenesis. However, further trial is indicated to test the efficacy of these targeting drugs as adjuvant therapy after resection of HCC.

Compared with the development of postoperative adjuvant therapy, the risk factors for HCC recurrence after liver resection have been extensively explored and established. The risk factors for tumor recurrence can be categorized into three core groups, related to host factors, tumor factors, and surgical factors [66]. The tumor factors including vascular invasion, satellite nodules, large tumor, elevation of AFP, poor differentiated histologic grade, tumor rupture, and advanced tumor stage are frequently reported risk factor for HCC recurrence after liver resection. The host factors are the patient's characteristics and underlying liver diseases such as cirrhosis and viral hepatitis. Both tumor and host factors are determined before operation, and the surgeon can only control surgical factors including negative resection margin, anatomic resection, meticulous liver mobilization, and less blood transfusion.

The treatment strategy for HCC recurrence after liver resection should be the same as that for primary HCC. Although repeat hepatectomy could be a difficulty owing to perihepatic adhesion related to first operation, surgical resection remains a preferred treatment whenever the tumor is considered to be resectable [67-69].

2.3.2. Survival of patients

Despite the high incidence of postoperative HCC recurrence, current strategy of aggressive multimodality treatments for recurrent tumors using TACE, RFA, or liver transplantation has largely improved the overall outcomes of patients even after the development of recurrent HCC. Moreover, surgical resection of recurrent HCC presenting as extrahepatic metastases could be considered in selected patients who are with isolated extrahepatic metastases and has otherwise good performance status, good hepatic functional reserve, and well-treated intrahepatic HCC, and a survival benefit can be expected from this aggressive approach [70]. Generally, the overall 5-year survival after resection of HCC reported in the literature from large series is mostly near 50% or even better in recent years (Table 2).

Authors (Years)	Study period	Subgroups	No. of patients	5-year RFS/OS
Hanazaki et al. (2000) [71]	1983–1997		386	23.3%/34.4%
Zhou et al. (2001) [58]	1967–1998	size≤5cm	1000	—/62.7%
		size>5cm	1366	—/37.1%
Wang et al. (2010) [72]	1991–2004		438	—/43.3%
Fan et al. (2011) [73]	1989–2008	1989–1998	390	24%/42.1%
		1999–2008	808	34.8%/54.8%
Sakamoto et al. (2011) [74]	1988–2010	Caudate lobe	46	44%/76%
		Other sites	737	40%/64%
Nara et al. (2012) [75]	1990–2007	SM>1mm	374	40.0%/72.2%
		SM≤1mm	165	28.1%/63.5%
		SM-postive	31	7.4%/36%
Chan et al. (2012) [76]	2001–2005		651	33.9%/51.7%
Giuliante et al. (2012) [77]	1992–2008	Tumor ≤3cm	588	32.4%/52.8%
Shrager et al. (2012) [78]	1992–2008	Non-cirrhosis	206	39%/46.3%
		cirrhosis	462	—/—
Altekruse et al. (2012) [79]	1998–2008	SEER–13	1348	—/47%

Table 2. Long-term survival of patients undergoing liver resection for HCC reported from large series in recent years. RFS, recurrence-free survival; OS, overall survival; SM, surgical margin; SEER-13, Surveillance Epidemiology and End Results of USA.

3. Liver transplantation

Recurrence remains a major problem after liver resection for HCC even after margin-negative resection. Most of the patients with HCC have underlying cirrhosis that provides potential field for development of hepatocellular carcinoma. Since majority hepatic malignancies are HCC and almost 80% of them have underlying cirrhosis, resection is option in only

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small number of patients and in such patients, recurrence rate is high after resection. Liver transplantation practically offers greater chance of cure by removing underlying liver cirrhosis and HCC. Also, HCC is multifocal especially with hepatitis C, and total hepatectomy removes the source of potential possibility of later-developing tumors whereas partial hepatic resection does not.

However, liver transplantation for HCC did not yield satisfactory results initially. Recurrence rates were up to 80% and long term survival rates were unacceptably below that of patients who underwent liver transplantation for non-malignant causes. These recurrences usually appeared within 2 years of transplant, most common site being liver allograft that led to a decline in enthusiasm and a serious concern about using precious donor livers for treatment [80].It was Bismuth who initially reported good outcomes with liver transplantation for small HCC [81] and subsequently, Mazzaferro et al introduced the Milan criteria reporting liver transplantation for HCC with equivalent outcomes to non-HCC patients[82].

Liver transplantation has become now potential curative treatment and it is presently the treatment of choice for patients with CTP class B or C cirrhosis and early hepatocellular carcinoma. Compared with surgical resection, liver transplantation is associated with better overall and recurrence-free survival in well selected patients [83-85]. The improved overall-results after liver transplantation are thought to be due to better patient selection and the emergence of various locoregional therapies for HCC that prevent tumor progression while patient is waitlisted for liver transplantation, thus preventing drop out.

3.1. Patient selection criteria

A major goal of liver transplant team is to select the patients with HCC and cirrhosis at earlier stage of their disease in order to achieve survival duration comparable with that of other patients with benign liver disease receiving transplants, so as to justify or prioritize the allocation of a liver graft. Liver transplant candidates with HCC must meet the Milan criteria to qualify for exceptional HCC waiting list consideration. Also, several other extended criteria such as UCSF (University of California at San Francisco) criteria are used for patient selection in highly specialized transplant centres.

3.1.1. Milan's criteria

In 1996, a prospective cohort study defined restrictive selection criteria that led to superior survival for transplant patients in comparison with any other previous experience with transplantation or other options for HCC. Since then, these selection criteria have become universally known as the Milan criteria in recognition of their origin (Table 3) [82]. These criteria have been widely applied in the selection of patients with HCC for liver transplantation.In North America as well as in many other world regions, patients within Milan criteria HCC are given priority to liver transplantation. Generally, a 4-year overall and recurrence-free survival rates of 85% and 92%, respectively, can be achieved using this selection criteria.

Criteria of liver transplantation for patients with HCC
Single lesion ≤5 cm.
Up to three separate lesions, none larger than 3 cm.
No evidence of gross vascular invasion.
No regional nodal or distant metastases.

Table 3. Milan's criteria for liver transplantation.

3.1.2. Extended Criteria

Considerable interest has arisen in expansion of usual transplant criteria in highly specialized centres to offer liver transplantation to broader group of patients with HCC as investigators argued that Milan's criteria are too restrictive and limit liver transplantation at the time when incidence of HCC is on the rise. Using explant pathologic data, Yao and co-workers at the University of California, San Francisco (UCSF) reported 5-year post-transplantation survival of 75% in patients with tumors as large as 6.5 cm and cumulative tumor burden ≤8 cm (Table 4)[86].

Extended criteria of liver transplantation for patients with HCC
Solitary tumor up to 6.5 cm.
A maximum of 3 tumor nodules each up to 4.5 cm.
A total tumor diameter not exceeding 8 cm.
No regional nodal or distant metastases.

Table 4. UCSF criteria for liver transplantation.

The UCSF criteria have been shown to be associated with long -term survival similar to Milan criteria when based on explant pathology [87, 88]. However, because of the small sample size and use of retrospective explant tumor pathology, the results of these studies were challenged and also several groups advised caution in expanding the criteria.

Additionally, a recent multicentre study led by the Milan's group had retrospectively reviewed patients who underwent transplantation for HCC in order to explore the survival of patients with tumors that exceed the Milan criteria. Accordingly, a prognostic model of overall survival based on tumor characteristics in terms of size and number was derived, and an expanded criterion termed "up-to-seven criteria" was introduced [89]. Patients who fell within the criteria that the sum of the largest tumor size and the number of tumors does not exceed seven could achieve a 5-year overall survival of 71.2% after liver transplantation enabling more patients to qualify as transplant candidates.

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3.2. Prognostic Indicators

Several studies have identified patient and tumor-related variables associated with prognosis following liver transplantation for HCC. The majority of prognostic factors are similar to that of liver resection for patients with HCC.

3.2.1. Tumor related factors

Important prognostic factors in most of scientific studies include tumor number, size, and location (especially bilobar distribution). The most consistent association is with tumor size. Other factors are histologic grade of differentiation, stage of disease according to the American Liver Tumor Study Group (ALTSG) modification of the TNM staging criteria, the presence of macrovascular and microvascular invasion, absolute level of serum AFP, and extrahepatic spread. Tumor size predicts both the likelihood of vascular invasion and tumor grade, but the relationship is nonlinear and a significant proportion of small tumors have unfavourable histology, whereas some larger ones do not [90, 91].

3.2.2. Patient related factors

Patients with HCV infection tend to have severe underlying liver disease and more advanced HCC at presentation as compared to HBV infection and underlying alcoholic cirrhosis. Hence, the recurrence of HCC is more common among the HCV recipients and thus reduced survival [92]. The immunosuppressive treatment after liver transplantation is associated with increased risk of tumor recurrence. Thus, immunosuppressant should be reduced to minimum effective levels. Several studies have shown lower recurrence with sirolimus which is attributed to its anti-proliferative effects on HCC [93-95]. But there is need for large randomized controlled trials to conclude sirolimus as most appropriate immunosuppressant for patients undergoing liver transplantation for HCC.

3.3. Deceased Donor Liver Transplantation (DDLT)

3.3.1. Graft Allocation

The shortage of donor livers has necessitated the development of allocation system, whereby priority for donor organs is given to the most severely ill patients. The prolonged waiting period frequently results in tumor progression to an extent beyond the transplantable criteria, leading to a patient's removal or dropout from the waiting list [96]. Allocation of deceased donor livers for both adults and children is based upon the "model for end stage liver disease" or MELD score, a statistical model based upon predicted survival in patients with cirrhosis.As a result of the high dropout rate for patients with HCC, the Organ Procurement and Transplantation Network (OPTN) of the U.S. has reconsidered the priority of liver graft allocation. While waiting list priority was determined primarily by liver disease severity based on the Model for End-Stage Liver Disease (MELD) score, patients with HCC that fulfilled the Milan criteria were registered with an adjusted score and were subsequently as-

signed additional scores at regular intervals to reflect their risk for dropout as a result of tumor progression.

3.3.2. Listing Criteria of transplantation candidates

In an attempt to ensure that preoperative assessment is as accurate as possible, UNOS provides a set of specific requirements for listing patients with HCC for orthotopic liver transplantation.

I. The diagnosis must be confirmed by thorough assessment by imaging modalities such as ultrasound, dynamic CT and /or MRI. Tumor numbers, size, presence or absence of extrahepatic disease and major vascular disease must be documented.

II. Patient must have one of the following:

1. An Alfa fetoprotein level > 200 ng/mL.

2. Celiac angiography showing tumor blush corresponding to the site shown by CT/MRI/ultrasonography.

3. A biopsy confirming HCC

4. History of RFA, TACE or other locoregional therapy.

III. Must be within Milan's criteria.

IV. Continued documentation of the tumor is required every three months by CT or MRI to ensure continued eligibility for liver transplantation.

Patients will be given priority MELD score depending upon the state of underlying disease. Prioritization scores for patients with HCC are based upon tumor size and number. With this new organ allocation policy, waiting time for the patients with HCC to receive a deceased-donor liver has decreased significantly.

3.4. Living Donor Liver Transplantation (LDLT)

The shortage of organs from deceased donors has curtailed the adoption of living donor liver transplantation. Living donors can potentially provide an essentially unlimited source of liver grafts for a planned transplant operation as soon as the diagnosis of HCC is made, thus decreasing the uncertainty of long waiting periods and reducing possibility of tumor progression [97]. The living donor can be from adult-to-adult or adult-to-child. In children mostly left lateral segment of the liver harvested and donors are usually ABO-compatible parents. While in adult-to-adult, right or left liver can be harvested that depends upon pretransplant evaluation of donor and CT volumetry of liver. The GRWR (graft to recipient weight ratio) must be more than 0.8%. Donor not meeting these criteria is rejected for the fear of small-for-size syndrome and subsequent graft failure [98, 99].

Because a live donor graft is a dedicated gift that is directed exclusively to a particular recipient, there is no need for an objective allocation system based on a prioritization scheme. Presently LDLT comprises almost >90% of liver transplants in Asia as compared to <5% in

http://dx.doi.org/10.5772/51418

US. Unlike in the U.S., where recipients with malignancies receive extra prioritization in the deceased donor organ allocation scheme, HCC patients in Asia do not. HCC patients in Asia have a dismal chance of receiving a deceased donor graft and LDLT is often the only option.

3.5. Pretransplant locoregional therapies

Pretransplant locoregional therapy has been adopted by the liver transplant community worldwide. This concept, known as "bridging therapy" is meant to limit tumor progression and dropout rate while patients are on the transplant wait list. The most popular techniques include TACE, transarterial drug-eluting beads, transarterial radio-embolizationand RFA.In the transplant setting, TACE is currently the most popular neo-adjuvant treatment. It is indicated in Child–Pugh A or B cirrhotic patients to downstage tumors into the Milan criteria or to prevent tumor progression. For patients with small HCC confined to the liver, recent data also indicate that transplantation when used with multimodal therapy using locoregional procedures and neoadjuvant systemic chemotherapy, results in improved recurrence-free survival [100, 101]. Apart from that, it is also important to know the wait list dropout rate and bridging therapy-associated complication rate, because the benefit of preventing wait list dropout should outweigh the risk of bridging therapy.Patient-individualized treatment strategy should be based on the performance status, hepatic reserve, tumor burden, and tumor vascularity pattern.

3.6. Outcome of liver transplantation

To date, orthotopic liver transplantation is no doubt the best therapeutic option for early, unresectable HCC, although it is limited by graft shortage and the need for appropriate patient selection. Since the introduction of the milan's criteria, the liver transplantation for primary HCC is on rise with promising recurrence-free survival and overall survival. Excellent 5-year post-transplant patient survival of at least 70% has been reported from many centers [102]. Furthermore, better definition of the prognostic factors and more rigorous patient selection have resulted in significant improvement in 5-year survival for patients receiving transplants for HCC in the past decade.

However, a tendency for higher HCC recurrence has been reported for patients who underwent LDLT than patients who underwent DDLT [103, 104]. The reasons for this difference are not completely answered by current studies. Possible explanations can be related to the selection bias for clinical characteristics associated with aggressive tumor behavior, elimination of natural selection during the waiting period, and enhancement of tumor growth and invasiveness by small-for-size graft injury and regeneration [105, 106]. Additionally, more clinical studies with long-term follow-up are needed to evaluate the role of LDLT for early HCC. At present, if a suitable and willing donor is identified, LDLT is a reasonable alternative to waiting 6 to 12 months for a deceased donor graft in patients with HCC who are otherwise eligible for liver transplantation.

Although liver transplantation is the only option for the cure in majority of the patients with HCC complicated by underlying cirrhosis precluding resection, identification of prognostic

factors and refinement of selection criteria will improve the outcomes of liver transplantation for this otherwise fatal disease. Nonetheless, liver transplantation may also pose a risk of post transplant lymphoproliferative disorders and other de novo malignacy associated with long term immunosuppression.

4. Conclusion

The management of patients with HCC remains complex and challenging. Although liver resection and liver transplantation are the curative treatments for HCC at present, there is considerable controversy as to whether patients with HCC are better served with liver transplantation versus liver resection. Liver transplantation removes HCC with underlying cirrhosis and thus sounds best option; however, technical challenges associated with transplantation and/or immunosuppression should be taken into consideration for selecting transplant cadidates. Currently, most studies suggest that liver resection should be a priority in patients who are candidates for either liver resection or transplantation [102, 107]. Despite a better cancer cure rate for liver transplatation, liver resection remains superior for patients in terms of limited organ availability and transplantation-associated morbidity and mortality. Therefore, the optimal treatment for patients with preservd liver function should always be resection whenever the tumor is resectable, and liver transplantation could be reserved as a salvage therapy for patients who encounter HCC recurrence after primary liver resection. Theoretically, this strategy will not only improve patient survival but relieve the growing demand of available donor livers.

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References

[1] Forner, A., Llovet, J. M., & Bruix, J. (2012). Hepatocellular Carcinoma. *Lancet*, 379(9822), 1245-1255.

[2] Sobin, L. H., Gospodarowicz, M. K., & wittekind, C. (2009). Tnm Classification of Malignant Tumours. *John Wiley & Sons.*

[3] Anonymous. (1998). NewA.PrognosticSystem.forHepatocellular.CarcinomaA Retrospective Study of 435 Patients: The Cancer of the Liver Italian Program (Clip) Investigators. *Hepatology*, 28(3), 751-755.

[4] Okuda, K., Ohtsuki, T., Obata, H., Tomimatsu, M., Okazaki, N., Hasegawa, H., Nakajima, Y., & Ohnishi, K. (1985). Natural History of Hepatocellular Carcinoma and Prognosis in Relation to Treatment. Study of 850 Patients. *Cancer*, 56(4), 918-928.

[5] Kudo, M., Chung, H., & Osaki, Y. (2003). Prognostic Staging System for Hepatocellular Carcinoma (Clip Score): Its Value and Limitations, and a Proposal for a New Staging System, the Japan Integrated Staging Score (Jis Score). *J Gastroenterol*, 38(3), 207-215.

[6] Llovet, J. M., Bru, C., & Bruix, J. (1999). Prognosis of Hepatocellular Carcinoma: The Bclc Staging Classification. *Semin Liver Dis*, 19(3), 329-338.

[7] Marrero, J. A., Fontana, R. J., Barrat, A., Askari, F., Conjeevaram, H. S., Su, G. L., & Lok, A. S. (2005). Prognosis of Hepatocellular Carcinoma: Comparison of 7 Staging Systems in an American Cohort. *Hepatology*, 41(4), 707-16.

[8] Bruix, J., & Llovet, J. M. (2009). Major Achievements in Hepatocellular Carcinoma. *Lancet*, 373(9664), 614-616.

[9] Cance, W. G., Stewart, A. K., & Menck, H. R. (2000). The National Cancer Data Base Report on Treatment Patterns for Hepatocellular Carcinomas: Improved Survival of Surgically Resected Patients, 1985-1996. *Cancer*, 88(4), 912-920.

[10] Liu, C. L., & Fan, S. T. (1997). Nonresectional Therapies for Hepatocellular Carcinoma. *Am J Surg*, 173(4), 358-365.

[11] Fong, Y., Sun, R. L., Jarnagin, W., & Blumgart, L. H. (1999). An Analysis of 412 Cases of Hepatocellular Carcinoma at a Western Center. *Ann Surg*, 229(6), 790-799, discussion 9-800.

[12] Lin, T. Y. (1974). A Simplified Technique for Hepatic Resection: The Crush Method. *Ann Surg*, 180(3), 285-290.

[13] Buell, J. F., Thomas, M. T., Rudich, S., Marvin, M., Nagubandi, R., Ravindra, K. V., Brock, G., & Mc Masters, K. M. (2008). Experience with More Than 500 Minimally Invasive Hepatic Procedures. *Ann Surg*, 248(3), 475-486.

[14] Cherqui, D., Husson, E., Hammoud, R., Malassagne, B., Stephan, F., Bensaid, S., Rotman, N., & Fagniez, P. L. (2000). Laparoscopic Liver Resections: A Feasibility Study in 30 Patients. *Ann Surg*, 232(6), 753-762.

[15] Vibert, E., Perniceni, T., Levard, H., Denet, C., Shahri, N. K., & Gayet, B. (2006). Laparoscopic Liver Resection. *Br J Surg*, 93(1), 67-72.

[16] Lai, E. C., Fan, S. T., Lo, C. M., Chu, K. M., & Liu, C. L. (1996). Anterior Approach for Difficult Major Right Hepatectomy. World J Surg discussion 8., 20(3), 314-317.

[17] Wang, W. D., Liang, L. J., Huang, X. Q., & Yin, X. Y. (2006). Low Central Venous Pressure Reduces Blood Loss in Hepatectomy. *World J Gastroenterol*, 12(6), 935-939.

[18] Wu, T. J., Wang, F., Lin, Y. S., Chan, K. M., Yu, M. C., & Lee, W. C. (2010). Right Hepatectomy by the Anterior Method with Liver Hanging Versus Conventional Approach for Large Hepatocellular Carcinomas. *Br J Surg*, 97(7), 1070-1078.

[19] Dahiya, D., Wu, T. J., Lee, C. F., Chan, K. M., Lee, W. C., & Chen, M. F. (2010). Minor Versus Major Hepatic Resection for Small Hepatocellular Carcinoma (Hcc) in Cirrhotic Patients: A 20-Year Experience. *Surgery*, 147(5), 676-685.

[20] Wayne, J. D., Lauwers, G. Y., Ikai, I., Doherty, D. A., Belghiti, J., Yamaoka, Y., Regimbeau, J. M., Nagorney, D. M., Do, K. A., Ellis, L. M., Curley, S. A., Pollock, R. E., & Vauthey, J. N. (2002). Preoperative Predictors of Survival after Resection of Small Hepatocellular Carcinomas. *Ann Surg*, 235(5), 722-730, discussion 30-1.

[21] Ng, K. K., Vauthey, J. N., Pawlik, T. M., Lauwers, G. Y., Regimbeau, J. M., Belghiti, J., Ikai, I., Yamaoka, Y., Curley, S. A., Nagorney, D. M., Ng, I. O., Fan, S. T., & Poon, R. T. (2005). Is Hepatic Resection for Large or Multinodular Hepatocellular Carcinoma Justified? Results from a Multi-Institutional Database. *Ann Surg Oncol*, 12(5), 364-373.

[22] Regimbeau, J. M., Farges, O., Shen, B. Y., Sauvanet, A., & Belghiti, J. (1999). Is Surgery for Large Hepatocellular Carcinoma Justified? *J Hepatol*, 31(6), 1062-1068.

[23] Yeh, C. N., Lee, W. C., & Chen, M. F. (2003). Hepatic Resection and Prognosis for Patients with Hepatocellular Carcinoma Larger Than 10 Cm: Two Decades of Experience at Chang Gung Memorial Hospital. *Ann Surg Oncol*, 10(9), 1070-1076.

[24] Huang, J. F., Wu, S. M., Wu, T. H., Lee, C. F., Wu, T. J., Yu, M. C., Chan, K. M., & Lee, W. C. (2012). Liver Resection for Complicated Hepatocellular Carcinoma: Challenges but Opportunity for Long-Term Survivals. J Surg Oncol. (In press)

[25] Poon, R. T., Fan, S. T., & Wong, J. (2002). Selection Criteria for Hepatic Resection in Patients with Large Hepatocellular Carcinoma Larger Than 10 Cm in Diameter. *J Am Coll Surg*, 194(5), 592-602.

[26] Ishizawa, T, Hasegawa, K, Aoki, T, Takahashi, M, Inoue, Y, Sano, K, Imamura, H, Sugawara, Y, Kokudo, N, & Makuuchi, M. (2008). Neither Multiple Tumors nor Portal Hypertension Are Surgical Contraindications for Hepatocellular Carcinoma. *Gastroenterology*, 134(7), 1908-1916.

[27] Choi, D., Lim, H. K., Joh, J. W., Kim, S. J., Kim, M. J., Rhim, H., Kim, Y. S., Yoo, B. C., Paik, S. W., & Park, C. K. (2007). Combined Hepatectomy and Radiofrequency Ablation for Multifocal Hepatocellular Carcinomas: Long-Term Follow-up Results and Prognostic Factors. *Ann Surg Oncol*, 14(12), 3510-3518.

[28] Liu, C. L., Fan, S. T., Lo, C. M., Ng, I. O., Poon, R. T., & Wong, J. (2003). Hepatic Resection for Bilobar Hepatocellular Carcinoma: Is It Justified? *Arch Surg*, 138(1), 100-104.

[29] Pawlik, T. M., Poon, R. T., Abdalla, E. K., Ikai, I., Nagorney, D. M., Belghiti, J., Kianmanesh, R., Ng, I. O., Curley, S. A., Yamaoka, Y., Lauwers, G. Y., & Vauthey, J. N. (2005). Hepatectomy for Hepatocellular Carcinoma with Major Portal or Hepatic Vein Invasion: Results of a Multicenter Study. *Surgery*, 137(4), 403-410.

[30] Minagawa, M., Makuuchi, M., Takayama, T., & Ohtomo, K. (2001). Selection Criteria for Hepatectomy in Patients with Hepatocellular Carcinoma and Portal Vein Tumor Thrombus. *Ann Surg*, 233(3), 379-384.

[31] Kuroda, S., Tashiro, H., Kobayashi, T., Oshita, A., Amano, H., & Ohdan, H. (2011). Selection Criteria for Hepatectomy in Patients with Hepatocellular Carcinoma Classified as Child-Pugh Class B. *World J Surg*, 35(4), 834-841.

[32] Bruix, J., Castells, A., Bosch, J., Feu, F., Fuster, J., Garcia-Pagan, J. C., Visa, J., Bru, C., & Rodes, J. (1996). Surgical Resection of Hepatocellular Carcinoma in Cirrhotic Patients: Prognostic Value of Preoperative Portal Pressure. *Gastroenterology*, 111(4), 1018-1022.

[33] Noun, R., Jagot, P., Farges, O., Sauvanet, A., & Belghiti, J. (1997). High Preoperative Serum Alanine Transferase Levels: Effect on the Risk of Liver Resection in Child Grade a Cirrhotic Patients. World J Surg discussion 5., 21(4), 390-394.

[34] Poon, R. T., Fan, S. T., Lo, C. M., Liu, C. L., Ng, I. O., & Wong, J. (2000). Long-Term Prognosis after Resection of Hepatocellular Carcinoma Associated with Hepatitis B-Related Cirrhosis. *J Clin Oncol*, 18(5), 1094-1101.

[35] Ercolani, G., Grazi, G. L., Calliva, R., Pierangeli, F., Cescon, M., Cavallari, A., & Mazziotti, A. (2000). The Lidocaine (Megx) Test as an Index of Hepatic Function: Its Clinical Usefulness in Liver Surgery. *Surgery*, 127(4), 464-471.

[36] Merkel, C., Gatta, A., Zoli, M., Bolognesi, M., Angeli, P., Iervese, T., Marchesini, G., & Ruol, A. (1991). Prognostic Value of Galactose Elimination Capacity, Aminopyrine Breath Test, and Icg Clearance in Patients with Cirrhosis. Comparison with the Pugh Score. *Dig Dis Sci*, 36(9), 1197-21103.

[37] Redaelli, C. A., Dufour, J. F., Wagner, M., Schilling, M., Husler, J., Krahenbuhl, L., Buchler, M. W., & Reichen, J. (2002). Preoperative Galactose Elimination Capacity Predicts Complications and Survival after Hepatic Resection. *Ann Surg*, 235(1), 77-85.

[38] Makuuchi, M., Kosuge, T., Takayama, T., Yamazaki, S., Kakazu, T., Miyagawa, S., & Kawasaki, S. (1993). Surgery for Small Liver Cancers. *Semin Surg Oncol*, 9(4), 298-304.

[39] Imamura, H., Seyama, Y., Kokudo, N., Maema, A., Sugawara, Y., Sano, K., Takayama, T., & Makuuchi, M. (2003). One Thousand Fifty-Six Hepatectomies without Mortality in 8 Years. *Arch Surg*, 138(11), 1198-206, discussion 206.

[40] Torzilli, G., Makuuchi, M., Inoue, K., Takayama, T., Sakamoto, Y., Sugawara, Y., Kubota, K., & Zucchi, A. (1999). No-Mortality Liver Resection for Hepatocellular Carcinoma in Cirrhotic and Noncirrhotic Patients: Is There a Way? A Prospective Analysis of Our Approach. *Arch Surg*, 134(9), 984-992.

[41] Kubota, K., Makuuchi, M., Kusaka, K., Kobayashi, T., Miki, K., Hasegawa, K., Harihara, Y., & Takayama, T. (1997). Measurement of Liver Volume and Hepatic Functional Reserve as a Guide to Decision-Making in Resectional Surgery for Hepatic Tumors. *Hepatology*, 26(5), 1176-1181.

[42] Shirabe, K., Shimada, M., Gion, T., Hasegawa, H., Takenaka, K., Utsunomiya, T., & Sugimachi, K. (1999). Postoperative Liver Failure after Major Hepatic Resection for Hepatocellular Carcinoma in the Modern Era with Special Reference to Remnant Liver Volume. *J Am Coll Surg*, 188(3), 304-309.

[43] Lee, C. F., Yu, M. C., Kuo, L. M., Chan, K. M., Jan, Y. Y., Chen, M. F., & Lee, W. C. (2007). Using Indocyanine Green Test to Avoid Post-Hepatectomy Liver Dysfunction. *Chang Gung Med J*, 30(4), 333-338.

[44] Makuuchi, M., Thai, B. L., Takayasu, K., Takayama, T., Kosuge, T., Gunven, P., Yamazaki, S., Hasegawa, H., & Ozaki, H. (1990). Preoperative Portal Embolization to Increase Safety of Major Hepatectomy for Hilar Bile Duct Carcinoma: A Preliminary Report. *Surgery*, 107(5), 521-527.

[45] Farges, O., Belghiti, J., Kianmanesh, R., Regimbeau, J. M., Santoro, R., Vilgrain, V., Denys, A., & Sauvanet, A. (2003). Portal Vein Embolization before Right Hepatectomy: Prospective Clinical Trial. *Ann Surg*, 237(2), 208-217.

[46] Kokudo, N., & Makuuchi, M. (2004). Current Role of Portal Vein Embolization/ Hepatic Artery Chemoembolization. *Surg Clin North Am*, 84(2), 643-657.

[47] Seo, D. D., Lee, H. C., Jang, M. K., Min, H. J., Kim, K. M., Lim, Y. S., Chung, Y. H., Lee, Y. S., Suh, D. J., Ko, G. Y., Lee, Y. J., & Lee, S. G. (2007). Preoperative Portal Vein Embolization and Surgical Resection in Patients with Hepatocellular Carcinoma and Small Future Liver Remnant Volume: Comparison with Transarterial Chemoembolization. *Ann Surg Oncol*, 14(12), 3501-3509.

[48] Siriwardana, R. C., Lo, C. M., Chan, S. C., & Fan, S. T. (2012). Role of Portal Vein Embolization in Hepatocellular Carcinoma Management and Its Effect on Recurrence: A Case-Control Study. *World J Surg*, 36(7), 1640-6.

[49] Yoo, H., Kim, J. H., Ko, G. Y., Kim, K. W., Gwon, D. I., Lee, S. G., & Hwang, S. (2011). Sequential Transcatheter Arterial Chemoembolization and Portal Vein Embolization Versus Portal Vein Embolization Only before Major Hepatectomy for Patients with Hepatocellular Carcinoma. *Ann Surg Oncol*, 18(5), 1251-1257.

[50] Wu, C. C., Ho, Y. Z., Ho, W. L., Wu, T. C., Liu, T. J., & P'Eng, F. K. (1995). Preoperative Transcatheter Arterial Chemoembolization for Resectable Large Hepatocellular Carcinoma: A Reappraisal. *Br J Surg*, 82(1), 122-126.

[51] Yamasaki, S., Hasegawa, H., Kinoshita, H., Furukawa, M., Imaoka, S., Takasaki, K., Kakumoto, Y., Saitsu, H., Yamada, R., Oosaki, Y., Arii, S., Okamoto, E., Monden, M., Ryu, M., Kusano, S., Kanematsu, T., Ikeda, K., Yamamoto, M., Saoshiro, T., & Tsuzuki, T. (1996). A Prospective Randomized Trial of the Preventive Effect of Pre-Opera-

tive Transcatheter Arterial Embolization against Recurrence of Hepatocellular Carcinoma. *Jpn J Cancer Res*, 87(2), 206-211.

[52] Zhang, Z., Liu, Q., He, J., Yang, J., Yang, G., & Wu, M. (2000). The Effect of Preoperative Transcatheter Hepatic Arterial Chemoembolization on Disease-Free Survival after Hepatectomy for Hepatocellular Carcinoma. *Cancer*, 89(12), 2606-2612.

[53] Zhou, W. P., Lai, E. C., Li, A. J., Fu, S. Y., Zhou, J. P., Pan, Z. Y., Lau, W. Y., & Wu, M. C. (2009). A Prospective, Randomized, Controlled Trial of Preoperative Transarterial Chemoembolization for Resectable Large Hepatocellular Carcinoma. *Ann Surg*, 249(2), 195-202.

[54] Hwang, T. L., Chen, M. F., Lee, T. Y., Chen, T. J., Lin, D. Y., & Liaw, Y. F. (1987). Resection of Hepatocellular Carcinoma after Transcatheter Arterial Embolization. Reevaluation of the Advantages and Disadvantages of Preoperative Embolization. *Arch Surg*, 122(7), 756-759.

[55] Liu, C. L., Fan, S. T., Lo, C. M., Tso, W. K., Poon, R. T., Lam, C. M., & Wong, J. (2001). Management of Spontaneous Rupture of Hepatocellular Carcinoma: Single-Center Experience. *J Clin Oncol*, 19(17), 3725-3232.

[56] Grazi, G. L., Ercolani, G., Pierangeli, F., Del Gaudio, M., Cescon, M., Cavallari, A., & Mazziotti, A. (2001). Improved Results of Liver Resection for Hepatocellular Carcinoma on Cirrhosis Give the Procedure Added Value. *Ann Surg*, 234(1), 71-78.

[57] Wei, A. C., Tung-Ping, Poon. R., Fan, S. T., & Wong, J. (2003). Risk Factors for Perioperative Morbidity and Mortality after Extended Hepatectomy for Hepatocellular Carcinoma. *Br J Surg*, 90(1), 33-41.

[58] Zhou, X. D., Tang, Z. Y., Yang, B. H., Lin, Z. Y., Ma, Z. C., Ye, S. L., Wu, Z. Q., Fan, J., Qin, L. X., & Zheng, B. H. (2001). Experience of 1000 Patients Who Underwent Hepatectomy for Small Hepatocellular Carcinoma. *Cancer*, 91(8), 1479-1486.

[59] Imamura, H., Matsuyama, Y., Tanaka, E., Ohkubo, T., Hasegawa, K., Miyagawa, S., Sugawara, Y., Minagawa, M., Takayama, T., Kawasaki, S., & Makuuchi, M. (2003). Risk Factors Contributing to Early and Late Phase Intrahepatic Recurrence of Hepatocellular Carcinoma after Hepatectomy. *J Hepatol*, 38(2), 200-207.

[60] Muto, Y., Moriwaki, H., Ninomiya, M., Adachi, S., Saito, A., Takasaki, K. T., Tanaka, T., Tsurumi, K., Okuno, M., Tomita, E., Nakamura, T., & Kojima, T. (1996). Prevention of Second Primary Tumors by an Acyclic Retinoid, Polyprenoic Acid, in Patients with Hepato cellular Carcinoma. Hepatoma Prevention Study Group. *N Engl J Med*, 334(24), 1561-1567.

[61] Lau, W. Y., Leung, T. W., Ho, S. K., Chan, M., Machin, D., Lau, J., Chan, A. T., Yeo, W., Mok, T. S., Yu, S. C., Leung, N. W., & Johnson, P. J. (1999). Adjuvant Intra-Arterial Iodine-131-Labelled Lipiodol for Resectable Hepatocellular Carcinoma: A Prospective Randomised Trial. *Lancet*, 353(9155), 797-801.

[62] Takayama, T., Sekine, T., Makuuchi, M., Yamasaki, S., Kosuge, T., Yamamoto, J., Shimada, K., Sakamoto, M., Hirohashi, S., Ohashi, Y., & Kakizoe, T. (2000). Adoptive Immunotherapy to Lower Postsurgical Recurrence Rates of Hepatocellular Carcinoma: A Randomised Trial. *Lancet*, 356(9232), 802-807.

[63] Huang, J. F., Yu, M. L., Huang, C. F., Chiu, C. F., Dai, C. Y., Huang, C. I., Yeh, M. L., Yang, J. F., Hsieh, M. Y., Hou, N. J., & LinChenWangChuang, Z. Y.S. C.L. Y.W. L. (2011). The Efficacy and Safety of Pegylated Interferon Plus Ribavirin Combination Therapy in Chronic Hepatitis C Patients with Hepatocellular Carcinoma Post Curative Therapies- a Multicenter Prospective Trial. *J Hepatol*, 54(2), 219-26.

[64] Shen, Y. C., Hsu, C., Chen, L. T., Cheng, C. C., Hu, F. C., & Cheng, A. L. (2010). Adjuvant Interferon Therapy after Curative Therapy for Hepatocellular Carcinoma (Hcc): A Meta-Regression Approach. *J Hepatol*, 52(6), 889-894.

[65] Chen, L. T., Chen, M. F., Li, L. A., Lee, P. H., Jeng, L. B., Lin, D. Y., Wu, C. C., Mok, K. T., Chen, C. L., Lee, W. C., Chau, G. Y., Chen, Y. S., Lui, W. Y., Hsiao, C. F., Whang-Peng, J., & Chen, P. J. (2012). Long-Term Results of a Randomized, Observation-Controlled, Phase Iii Trial of Adjuvant Interferon Alfa-2b in Hepatocellular Carcinoma after Curative Resection. *Ann Surg*, 255(1), 8-17.

[66] Tung-Ping, Poon. R., Fan, S. T., & Wong, J. (2000). Risk Factors, Prevention, and Management of Postoperative Recurrence after Resection of Hepatocellular Carcinoma. *Ann Surg*, 232(1), 10-24.

[67] Itamoto, T., Nakahara, H., Amano, H., Kohashi, T., Ohdan, H., Tashiro, H., & Asahara, T. (2007). Repeat Hepatectomy for Recurrent Hepatocellular Carcinoma. *Surgery*, 141(5), 589-597.

[68] Lee, P. H., Lin, W. J., Tsang, Y. M., Hu, R. H., Sheu, J. C., Lai, M. Y., Hsu, H. C., May, W., & Lee, C. S. (1995). Clinical Management of Recurrent Hepatocellular Carcinoma. *Ann Surg*, 222(5), 670-676.

[69] Wu, C. C., Cheng, S. B., Yeh, D. C., Wang, J., & P'Eng, F. K. (2009). Second and Third Hepatectomies for Recurrent Hepatocellular Carcinoma Are Justified. *Br J Surg*, 96(9), 1049-1057.

[70] Chan, K. M., Yu, M. C., Wu, T. J., Lee, C. F., Chen, T. C., Lee, W. C., & Chen, M. F. (2009). Efficacy of Surgical Resection in Management of Isolated Extrahepatic Metastases of Hepatocellular Carcinoma. *World J Gastroenterol*, 15(43), 5481-5488.

[71] Hanazaki, K., Kajikawa, S., Shimozawa, N., Mihara, M., Shimada, K., Hiraguri, M., Koide, N., Adachi, W., & Amano, J. (2000). Survival and Recurrence after Hepatic Resection of 386 Consecutive Patients with Hepatocellular Carcinoma. *J Am Coll Surg*, 191(4), 381-388.

[72] Wang, J., Xu, L. B., Liu, C., Pang, H. W., Chen, Y. J., & Ou, Q. J. (2010). Prognostic Factors and Outcome of 438 Chinese Patients with Hepatocellular Carcinoma Underwent Partial Hepatectomy in a Single Center. *World J Surg*, 34(10), 2434-2441.

[73] Fan, S. T., Mau, Lo. C., Poon, R. T., Yeung, C., Leung, Liu. C., Yuen, W. K., Ming, Lam. C., Ng, K. K., & Ching, Chan. S. (2011). Continuous Improvement of Survival Outcomes of Resection of Hepatocellular Carcinoma: A 20-Year Experience. *Ann Surg*, 253(4), 745-758.

[74] Sakamoto, Y., Nara, S., Hata, S., Yamamoto, Y., Esaki, M., Shimada, K., & Kosuge, T. (2011). Prognosis of Patients Undergoing Hepatectomy for Solitary Hepatocellular Carcinoma Originating in the Caudate Lobe. *Surgery*, 150(5), 959-967.

[75] Nara, S., Shimada, K., Sakamoto, Y., Esaki, M., Kishi, Y., Kosuge, T., & Ojima, H. (2012). Prognostic Impact of Marginal Resection for Patients with Solitary Hepatocellular Carcinoma: Evidence from 570 Hepatectomies. *Surgery*, 151(4), 526-536.

[76] Chan, K. M., Lee, C. F., Wu, T. J., Chou, H. S., Yu, M. C., Lee, W. C., & Chen, M. F. (2012). Adverse Outcomes in Patients with Postoperative Ascites after Liver Resection for Hepatocellular Carcinoma. *World J Surg*, 36(2), 392-400.

[77] Giuliante, F., Ardito, F., Pinna, A. D., Sarno, G., Giulini, S. M., Ercolani, G., Portolani, N., Torzilli, G., Donadon, M., Aldrighetti, L., Pulitano, C., Guglielmi, A., Ruzzenente, A., Capussotti, L., Ferrero, A., Calise, F., Scuderi, V., Federico, B., & Nuzzo, G. (2012). Liver Resection for Hepatocellular Carcinoma </=3 Cm: Results of an Italian Multicenter Study on 588 Patients. *J Am Coll Surg.*

[78] Shrager, B., Jibara, G., Schwartz, M., & Roayaie, S. (2012). Resection of Hepatocellular Carcinoma without Cirrhosis. *Ann Surg*, 255(6), 1135-1143.

[79] Altekruse, S. F., McGlynn, K. A., Dickie, L. A., & Kleiner, D. E. (2012). Hepatocellular Carcinoma Confirmation, Treatment, and Survival in Surveillance, Epidemiology, and End Results Registries, 1992-2008. *Hepatology*, 55(2), 476-482.

[80] Pichlmayr, R. (1988). Is There a Place for Liver Grafting for Malignancy? *Transplant Proc*, 20(1, 1), 478-482.

[81] Bismuth, H., Chiche, L., Adam, R., Castaing, D., Diamond, T., & Dennison, A. (1993). Liver Resection Versus Transplantation for Hepatocellular Carcinoma in Cirrhotic Patients. *Ann Surg*, 218(2), 145-151.

[82] Mazzaferro, V., Regalia, E., Doci, R., Andreola, S., Pulvirenti, A., Bozzetti, F., Montalto, F., Ammatuna, M., Morabito, A., & Gennari, L. (1996). Liver Transplantation for the Treatment of Small Hepatocellular Carcinomas in Patients with Cirrhosis. *N Engl J Med*, 334(11), 693-9.

[83] Onaca, N., Davis, G. L., Goldstein, R. M., Jennings, L. W., & Klintmalm, G. B. (2007). Expanded Criteria for Liver Transplantation in Patients with Hepatocellular Carcinoma: A Report from the International Registry of Hepatic Tumors in Liver Transplantation. *Liver Transpl*, 13(3), 391-399.

[84] Takada, Y., Ito, T., Ueda, M., Sakamoto, S., Haga, H., Maetani, Y., Ogawa, K., Ogura, Y., Oike, F., Egawa, H., & Uemoto, S. (2007). Living Donor Liver Transplantation for

Patients with Hcc Exceeding the Milan Criteria: A Proposal of Expanded Criteria. *Dig Dis*, 25(4), 299-302.

[85] Toso, C., Asthana, S., Bigam, D. L., Shapiro, A. M., & Kneteman, N. M. (2009). Reassessing Selection Criteria Prior to Liver Transplantation for Hepatocellular Carcinoma Utilizing the Scientific Registry of Transplant Recipients Database. *Hepatology*, 49(3), 832-838.

[86] Yao, F. Y., Ferrell, L., Bass, N. M., Watson, J. J., Bacchetti, P., Venook, A., Ascher, N. L., & Roberts, J. P. (2001). Liver Transplantation for Hepatocellular Carcinoma: Expansion of the Tumor Size Limits Does Not Adversely Impact Survival. *Hepatology*, 33(6), 1394-1403.

[87] Sotiropoulos, G. C., Molmenti, E. P., Omar, O. S., Bockhorn, M., Brokalaki, E. I., Lang, H., Frilling, A., Broelsch, C. E., & Malago, M. (2006). Liver Transplantation for Hepatocellular Carcinoma in Patients Beyond the Milan but within the Ucsf Criteria. *Eur J Med Res*, 11(11), 467-470.

[88] Yao, F. Y., Ferrell, L., Bass, N. M., Bacchetti, P., Ascher, N. L., & Roberts, J. P. (2002). Liver Transplantation for Hepatocellular Carcinoma: Comparison of the Proposed Ucsf Criteria with the Milan Criteria and the Pittsburgh Modified Tnm Criteria. *Liver Transpl*, 8(9), 765-774.

[89] Mazzaferro, V., Llovet, J. M., Miceli, R., Bhoori, S., Schiavo, M., Mariani, L., Camerini, T., Roayaie, S., Schwartz, M. E., Grazi, G. L., Adam, R., Neuhaus, P., Salizzoni, M., Bruix, J., Forner, A., De Carlis, L., Cillo, U., Burroughs, A. K., Troisi, R., Rossi, M., Gerunda, G. E., Lerut, J., Belghiti, J., Boin, I., Gugenheim, J., Rochling, F., Van Hoek, B., & Majno, P. (2009). Predicting Survival after Liver Transplantation in Patients with Hepatocellular Carcinoma Beyond the Milan Criteria: A Retrospective, Exploratory Analysis. *Lancet Oncol*, 10(1), 35-43.

[90] Klintmalm, G. B. (1998). Liver Transplantation for Hepatocellular Carcinoma: A Registry Report of the Impact of Tumor Characteristics on Outcome. *Ann Surg*, 228(4), 479-490.

[91] Pawlik, T. M., Delman, K. A., Vauthey, J. N., Nagorney, D. M., Ng, I. O., Ikai, I., Yamaoka, Y., Belghiti, J., Lauwers, G. Y., Poon, R. T., & Abdalla, E. K. (2005). Tumor Size Predicts Vascular Invasion and Histologic Grade: Implications for Selection of Surgical Treatment for Hepatocellular Carcinoma. *Liver Transpl*, 11(9), 1086-1092.

[92] Roayaie, S., Haim, M. B., Emre, S., Fishbein, T. M., Sheiner, P. A., Miller, C. M., & Schwartz, M. E. (2000). Comparison of Surgical Outcomes for Hepatocellular Carcinoma in Patients with Hepatitis B Versus Hepatitis C: A Western Experience. *Ann Surg Oncol*, 7(10), 764-770.

[93] Kneteman, N. M., Oberholzer, J., Al Saghier, M., Meeberg, G. A., Blitz, M., Ma, M. M., Wong, W. W., Gutfreund, K., Mason, A. L., Jewell, L. D., Shapiro, A. M., Bain, V. G., & Bigam, D. L. (2004). Sirolimus-Based Immunosuppression for Liver Transplan-

tation in the Presence of Extended Criteria for Hepatocellular Carcinoma. *Liver Transpl*, 10(10), 1301-1311.

[94] Toso, C., Meeberg, G. A., Bigam, D. L., Oberholzer, J., Shapiro, A. M., Gutfreund, K., Mason, A. L., Wong, W. W., Bain, V. G., & Kneteman, N. M. (2007). De Novo Sirolimus-Based Immunosuppression after Liver Transplantation for Hepatocellular Carcinoma: Long-Term Outcomes and Side Effects. *Transplantation*, 83(9), 1162-1168.

[95] Zimmerman, M. A., Trotter, J. F., Wachs, M., Bak, T., Campsen, J., Skibba, A., & Kam, I. (2008). Sirolimus-Based Immunosuppression Following Liver Transplantation for Hepatocellular Carcinoma. *Liver Transpl*, 14(5), 633-638.

[96] Yao, F. Y., Bass, N. M., Nikolai, B., Davern, T. J., Kerlan, R., Wu, V., Ascher, N. L., & Roberts, J. P. (2002). Liver Transplantation for Hepatocellular Carcinoma: Analysis of Survival According to the Intention-to-Treat Principle and Dropout from the Waiting List. *Liver Transpl*, 8(10), 873-883.

[97] Lo, C. M., & Fan, S. T. (2004). Liver Transplantation for Hepatocellular Carcinoma. *Br J Surg*, 91(2), 131-3.

[98] Dahm, F., Georgiev, P., & Clavien, P. A. (2005). Small-for-Size Syndrome after Partial Liver Transplantation: Definition, Mechanisms of Disease and Clinical Implications. *Am J Transplant*, 5(11), 2605-2610.

[99] Emond, J. C., Renz, J. F., Ferrell, L. D., Rosenthal, P., Lim, R. C., Roberts, J. P., Lake, J. R., & Ascher, N. L. (1996). Functional Analysis of Grafts from Living Donors. Implications for the Treatment of Older Recipients. *Ann Surg*, 224(4), 544-552, discussion 52-4.

[100] Yao, F. Y., Kerlan, R. K., Jr, Hirose, R., Davern, T. J., 3rd, Bass, N. M., Feng, S., Peters, M., Terrault, N., Freise, C. E., Ascher, N. L., & Roberts, J. P. (2008). Excellent Outcome Following Down-Staging of Hepatocellular Carcinoma Prior to Liver Transplantation: An Intention-to-Treat Analysis. *Hepatology*, 48(3), 819-827.

[101] Chan, K. M., Yu, M. C., Chou, H. S., Wu, T. J., Lee, C. F., & Lee, W. C. (2011). Significance of Tumor Necrosis for Outcome of Patients with Hepatocellular Carcinoma Receiving Locoregional Therapy Prior to Liver Transplantation. *Ann Surg Oncol*, 18(9), 2638-2646.

[102] Rahbari, N. N., Mehrabi, A., Mollberg, N. M., Muller, S. A., Koch, M., Buchler, M. W., & Weitz, J. (2011). Hepatocellular Carcinoma: Current Management and Perspectives for the Future. *Ann Surg*, 253(3), 453-469.

[103] Fisher, R. A., Kulik, L. M., Freise, C. E., Lok, A. S., Shearon, T. H., Brown, R. S., Jr., Ghobrial, R. M., Fair, J. H., Olthoff, K. M., Kam, I., & Berg, C. L. (2007). Hepatocellular Carcinoma Recurrence and Death Following Living and Deceased Donor Liver Transplantation. *Am J Transplant*, 7(6), 1601-1608.

[104] Poon, R. T., Fan, S. T., Lo, C. M., Liu, C. L., & Wong, J. (2007). Difference in Tumor Invasiveness in Cirrhotic Patients with Hepatocellular Carcinoma Fulfilling the Mi-

lan Criteria Treated by Resection and Transplantation: Impact on Long-Term Survival. *Ann Surg*, 245(1), 51-58.

[105] Jonas, S., Bechstein, W. O., Steinmuller, T., Herrmann, M., Radke, C., Berg, T., Settmacher, U., & Neuhaus, P. (2001). Vascular Invasion and Histopathologic Grading Determine Outcome after Liver Transplantation for Hepatocellular Carcinoma in Cirrhosis. *Hepatology*, 33(5), 1080-1086.

[106] Yang, Z. F., Poon, R. T., Luo, Y., Cheung, C. K., Ho, D. W., Lo, C. M., & Fan, S. T. (2004). Up-Regulation of Vascular Endothelial Growth Factor (Vegf) in Small-for-Size Liver Grafts Enhances Macrophage Activities through Vegf Receptor 2-Dependent Pathway. *J Immunol*, 173(4), 2507-2515.

[107] Koniaris, L. G., Levi, D. M., Pedroso, F. E., Franceschi, D., Tzakis, A. G., Santamaria-Barria, J. A., Tang, J., Anderson, M., Misra, S., Solomon, N. L., Jin, X., Di Pasco, P. J., Byrne, M. M., & Zimmers, T. A. (2011). Is Surgical Resection Superior to Transplantation in the Treatment of Hepatocellular Carcinoma? *Ann Surg*, 254(3), 527-537, discussion 37-8.