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SURGICAL TREATMENT PROTOCOLS FOR HEPATOCELLULAR CARCINOMA

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ABSTRACT

Hepa to cellular carcinoma (HCC) is one of the most common diseases, with an increasing incidence. With new and advanced surgical instrumentation and techniques, several curative therapies have become successful. The HCC patients are treated according to the stage of Liver tumor. For very early stage of HCC, the very first choice of therapy is liver resection but it is later being replaced by local ablative therapy which is useful as a bridging therapy toward liver transplantation and also as a replacement therapy for liver transplant when conditions are not feasible. However, liver transplantation provides better results in the HCC patients whose tumors meet the Milan criteria. The main obstacle towards the successful treatment is the HCC recurrence and at present there is no successful ways of treating and preventing HCC recurrence. For intermediate-stage HCC, the transarterial therapy is considered suitable. This surgical therapy not only provides suitable outcomes but also recovers the quality of life of HCC patients. Because of the complications of HCC, the surgical therapeutic approaches must be considered according to the tumor stage of each individual patient. The article presents an overview of treatment therapies for both early and advanced stage HCC based on the extensive review of the relevant literature.

KEYWORDS: Liver Transplant, TACE, Local Ablation, Liver Resection

INTRODUCTION

The third most common reason of cancer-associated deaths world widely is HCC (terry). The prevalence of heap to cellular carcinoma (HCC) is increasing globally and is considered to be one of the most common cancers, particularly in Asia pacific area (Bozorgzadeh *et al.,* 2007; Chuang *et al.,* 2009). This prevalance of HCC has been raised due to high risk hepatitis C virus (HCV) infection and it is believed to be doubled in the coming twenty years (Barazani et al., 2007; Duffy *et al.,* 2007) as the rate of morbidity and mortality due to HCV infection are projected to raise gradually (Rustgi, 2007). However in addition to HCV, there are multiple etiologies which are involved in the development of the disease including hepatitis B, primary sclerosing cholangitis, primary biliary cirrhosis, hemochromatosis, alcohol-related liver disease, nonalcoholic steatohepatitis and autoimmune hepatitis (Terry and Copur, 2013).

There are a large no. of therapeutic modalities which have been used for treatment therapy of hepatocellular carcinoma (HCC). Orthotropic liver transplantation (OLT) and surgical resection of liver have always been traditionally indicated for treatments of patients with HCC. However, single nodule < 3 cm ablation showed same results to resection (Mela *et al.,* 2003). Historically, despite of treatment the overall outcomes for HCC patients have been quite poor, showing only 20% to 40% of 5-year survival rate. For end-stage cirrhosis and HCC patients, survival devoid of liver transplantation is mostly less than 1 year (Duffy *et al.,* 2007).

SURGICAL THERAPIES

Liver Resection

Liver resection is the basis of treatment therapy of heap to cellular carcinoma (HCC) patients having non cirrhotic liver (40% cases in Asia and 5% in the west) (Belghiti, 2000; Lang *et al.*, 2005). These patients are vulnerable to have major hepatic resections with minor complications and high percentage of accepted outcomes i.e. 30-50% patients with 5 year survival rate.

Resection competes as the first-line treatment choice for patients with solitary and early tumors and having well-preserved liver function, which is characterized by normal hepatic venous pressure gradient i.e. less than or equal to 10 mmH, platelet count of greater than or equal to 100,000 or normal billirubin level. While patients having cirrhosis, portal hypertension and end stage liver disease showed higher risks of morbidity and mortality in comparison to non-cirrhotic ones. Due to this reason only small percentage (20-30%) of patients with portal hypertension, cirrhosis and heap to cellular carcinoma are vulnerable for liver resection. An ideal candidate for liver resection can be assorted by adequately assessing extent of tumor extension, functional reserve of liver and also keep in mind the risk factors of post operative complications and death (Galuppo *et al.,* 2013).

Cirrhotic liver resection in HCC patients is a great challenge for heap to billiary surgeons for years. It is also a life threatening therapy for liver patients. The foremost cause of mortality in hospitals is the postoperative liver failure due to many factors like massive bleeding during surgery followed by large volume of blood transfusion, scarcity of remnant liver function and risk of septic complications (Makuuchi and Sano, 2004). The new innovative standards for cirrhotic liver resection in HCC patients are characterized with survival rate of 5 year in 60% of patients, requirement of less than 10 % of blood transfusion and with only 2-3% of peri-operative mortality. However, some centers in the world have reported zero peri-operative mortality (Llovet and Bruix, 2008; Poon *et al.,* 2002; Makuuchi *et al.,* 2004; Roayaie *et al.,* 2009; Ishizawa *et al.,* 2008; Mazaffere *et al.,* 2006). The liver resections should be done aggressively if there are no safety risks. In Japan, 10 nodules were removed by liver resection from a patient with HCC in just one surgical attempt and another patient went through 5 resection operations for the removal of 10 nodules in a duration period of 8 years. Both patients after the primary resections 4 years ago and 10 years ago respectively remained perfectly well. So no considerable difference was found in the survival rate after the resections in both the patients 183. There is a major issue of recurrence of HCC after liver resection and incidence of recurrence is 50-60% at three years and at five years is 70-100% and so the HCC patients having liver resection may not remain tumor-free for long duration (Soong *et al*., 2011). The high recurrence rate of HCC following resection is due to postoperative metastases in the liver and growth of other primary lesion in remnant liver after few years of resection (kosuge *et al*., 1993)

Blood loss during resection procedure is considerably related to the patient outcome and per operative strategies used. So the blood loss is controlled by selecting adequate surgical techniques including ultrasonic dissector, pre-resection imaging planning, low central venous pressure maintenance and intermittent Pringle maneuvre. These above indications aided to reduce the blood transfusion from 80-90% to 10% in last twenty years (Makuuchi and Sano, 2004)

Ideal candidate's selection involves two main aspects. First one is the proper evaluation of the liver functional reserve and other one is tumor extension. The liver function has been determination by Child–Pugh class or more sophisticatedly by measuring in do cyanine green retention rate (ICG15) at a time of 15 min (Makuuchi *et al.,* 1993) or by evaluating hepatic venous pressure gradient (HVPG) ≤10 mmHg which is a direct way for measuring portal hypertension

(Bruix *et al.,* 1996). The prognostic factor concept of HVPG in patients going through resection procedure has been authenticated in Asia (Ishizawa *et al,* 2008). Surrogate measurement of portal hypertension involves two main factors: Splenomegaly and platelet count below 100,000/mm^3 (Simpson and Finlayson, 1995). However, in the HCC cases of resection platelet count is confirmed as independent predictor of survival (Cucchetti *et al.,* 2009).

As discussed above the second aspect of proper patient selection is tumor extention involving tumor number, tumor size, vascular invasions and microsatellite presence (Llovet *et al.,* 2005). The tumor extention is determined by CT Scan or MRI. In addition to these in traoperative ultrasonography not only aids in determinig the tumor extension by detecting nodules of 0.5-1cm but also this technique is considered as standard guide for anatomical resections (Torzilli *et al.,* 2004). Tumor recurrence set hurdles by the new tumor growth or by intrahepatic metastases (true recurrences) (Roayaie *et al.,* 2009; Ishizawa *et al.,* 2008; Poon *et al.,* 2002; Vauthay *et al*., 2002; Mazaffereo *et al.,* 2006). These two causes are differentiated by means of DNA microarray assays, integration pattern of hepatitis B virus and DNA fingerprinting by comparative genomic hybridization or loss of heterozygosity methods (Finkelstein *et al*., 2003).

LIVER TRAN SPLANT

Liver transplant is recommended as standard care for HCC patients in early stage and as a main driving force of alternative treatment strategies for HCC patients with intermediate stage Mazaffereo et al., 1996. When HCC is diagnosed in a patient with diminished liver function reserve, liver transplantation becomes a consideration (Myron Shwartz). Most cases of HCC (greater than 70%) occur because of cirrhosis background. The resection of cirrhotic liver is linked with high morbidity and mortality rate so transplantation of liver is considered as the prime treatment option as it can provide considerable oncological resection and also treatment for the underlying hepatic disease (Vakili *et al*., 2009).

In a prospective study an authentic selection criteria was established for selecting transplant patients and then, this selection criteria became universal and termed as the Milan criteria (MC) according to the origin. In clinical practice, MC have been used to aid the physicians and surgeons to consider early-stage HCC for better curative treatments like liver transplant. MC instantly became the standard of care for early stage HCC patients as convincing outcomes of post transplantation were observed. According to MC, a patient is eligible for transplantation only if he is having a lesion $\leq$ 5cm or up to 3 lesions $\leq$ 3cm, no extra hepatic manifestation and no vascular invasion (Duffy *et al.,* 2007)

Following MC, the rates of patient's 5 year survival and tumor recurrence after transplantation are 75% and 10% respectively (1-3). As the Milan criteria have successfully implicated in a large number of studies so they are also integrated in BCLC staging system (Llovet *et al.,* 1999; Llovet *et al.,* 2008) and also in the UNOS pre-transplant staging system for organ allocation (Freeman *et al*., 2002). In a systematic review 90 studies were included, comprising of 17,780 patients. In these studies Milan criteria were found to be independent prognostic factor for outcome of post transplantation (Mazzaferro *et al.,* 2011).

Both the number and size of tumors are important features in determining the post transplant recurrence rate of HCC, so the biology and expansion extant of tumor should be considered whenever the selection of patient beyond MC. This has been definitely explained and well demonstrated by Metro ticket concept (the greater the expansion of HCC staging criteria for selecting patients for liver transplant, the greater the recurrence rate and poorer the survival) (Mazzaferro *et al.,* 2009)

After approximately 10 years of establishment of MC, other proposals were given and MC were challenged by

researchers so that those patients might also be considered for transplantation which were not meeting MC and could have same post transplant survival span by expanding the required accepted value of tumor expansion for liver transplant. Albeit up till now, many expanded criteria including University of California San Francisco criteria (UCSF) ; (single tumor of size 6.5 cm, maximally 3 total tumors with no tumor having size of 4.5 cm and cumulative tumor size of 8 cm), but none of the expanded criteria has been selected as reference standard for the selection of liver transplant candidates (Mazzaferro *et al.,* 1996)

May be concluded that MC is the benchmark for the liver transplantion stratagies of patients with HCC and also remain the cornerstone for making decision for patients of any stage of HCC (Clavien et al, 2012) When liver ransplantation was compared to resection, it was found that transplantation involves a higher rate of perioperative mortalities and acts as an adjunct to the side-effects and high risks of long-term immunosuppression. However alternatively, it eradicates not only the cirrhosis along with its complications but also eliminates the potential of the cirrhotic liver to show carcinogenesis. However, after some while of liver transplant the reappearance of HCC is a foremost problem. HCC was found in 17.5% of adults and 35% of patients over the age of 50 years, who were undergoing liver transplant with cirrhosis (Mela *et al.,* 2003). Various large cohort studies in the United States and Japan presented that most of the patients who were in the waiting list, falling within the Millan criterion with early stage HCC, donot show remarkable carcinogenic rate for at least a duration of one year (Bruix and Sherman, 2009).

The main drawback of liver transplantation is the shortage of the liver donors. Almost 20% of liver transplant candidates drop out of the lists before going through procedure due to the increase in the waiting time, so it will jeopardize the treatment outcomes (Yao *et al.,* 2001). The scarcity of organs, along with the increasing incidence of HCC, largely caused by hepatitis C epidemic, make it more critical than ever to to have an optimized criteria for selecting candidates and their priority for transplantation. Different strategies have been taken up by the liver transplant community, including no priority for HCC (implicated in the Euro transplant system), or a center-oriented system according to which the local team selects the best candidate who could get maximum benefit from the organ of donor (implicated in many other European centers) or on the basis of continuous scoring system of Model for End-Stage Liver Disease (MELD) developed by united network of organ sharing (UNOS) implicated in the United States since february 2002. (Freeman *et al*., 2002; Wiesner *et al.,* 2004; Adler *et al,* 2008) MELD was basically developed to forecast the survival rate of end stage liver disease patients, in 3 month duration (Kamath *et al.,* 2001)

This priority scoring system for HCC has only been applied to those patients who are in the set limits of Milan criteria. The UNOS staging further divided the Milan criteria into two stages, one is T1 i.e. one lesion < 2cm and second one is T2 stage i.e. one lesion of 2-5 cm or 2-3 lesions each of ≤ 3cm. The major problem for conducting priority policies is to figure out those patients who are at risk of drop-out. In some studies these high risk patients are recognized as those having multinodular tumors, steady increase of >15 ng/ml per month [140], serum AFP levels > 200 ng/ml or neoadjuvant treatment failure (Pomfret et al., 2010) or those undergoing the procedure of resection with subsequent high risk of recurrence (Sala et al., 2004) The waiting time for transplant differ widely in different areas of the world, therefore it is suggested to adapt the priority policies by keeping in mind these variables. Four models have been considered by the panel in the situation of transplantation for HCC patients: (1) neoadjuvant treatment therapies for patients in the waiting list (2) priority and delisting policies for patients (3) down staging and extension of criteria for liver transplantation (4) living donor liver transplantation.

Neo-Adjuvant Treatment Therapies for Patients in the Waiting List

HCC patients who are on liver transplant waiting list, the tumor growth may increase beyond the accepted criteria and this may result in drop out of these patients from the waiting list. In order to prevent drop out neo adjuvant therapy is used in the form of bridging therapy during waiting time. Neo-adjuvant therapy is also used as down-staging method to enable patients with intermediate HCC to qualify for liver transplant procedure. The treatment of HCC patients before including them in waiting list or while they are already waiting has been demonstrated as standard of care in most of the transplant centers.(Cescon *et al.,* 2013; Millonig et al., 2007; Mazzaferro et al., 2004; Lencioni et al., 2005; Del Gaudio et al., 2008; Fujiki et al., 2014). Radio frequency ablation and transcatheter chemoembolization are the most frequent used strategies as loco regional therapy and both have been improved to have positive effect on the control of tumor growth (Golfieri *et al.,* 2011). Whereas the new modalities like radioembolization with Y90, drug eluting beads, sorafenib and stereotatic radiation therapy are considered as tools for downstaging advanced HCC patients to be included in waiting list. The neo-adjuvant therapy is used with two goals in the aspect of liver transplant. The first one is to help prevent the HCC patients of dropping out from the waiting list. The second goal is to treat and follow up the patients who lie outside the accepted criteria for liver transplant until they reach the UNOS T2 stage of HCC, meeting Millan criteria or UCSF (Yao et al., 2001) or other criteria for liver transplant. In this case the locoregional strategies used are considered as downstaging methods. Irrespective of the type of treatment selected, the impact of neo-adjuvant treatment therapy is always determined by modified response evaluation criteria in solid tumors (mRECIST) (Lencioni et al., 2010; Llovet et al., 2008). The RECIST evaluation criteria was modulated in 2008 as mRECIST, which is based on the idea that the induction of in tratumoral necrotic areas should be taken into account, and not only decrease in overall size of tumor during estimation of reduction in tumor load (Bruix et al., 2005). Patients may be pursued with either contrast-enhanced dynamic magnetic resonance imaging or contrast-enhanced spiral computed tomography. it is recommended to intravenously administer contrast for MRI and CT, if contrast is not medically contraindicated (Cescon et al., 2013). The effect of these locoregional treatments on the rates of recurrence, drop-out and survival rates are determined by only non-randomized studies. It has been reported from initial studies that the risk of drop-out of HCC patients from waiting list is found to be 15-30% per year. (Galuppo *et al.,* 2013, Yao *et al,* 2001) Various cohort studies and case series reported and suggested that locoregional treatments have almost 0%-25% of positive impact to reduce the drop-out rate (Galuppo *et al.,* 2013, Pomfret *et al.,* 2010; Mazzeferro *et al.,* 2004). Various case control studies (Decaens et al., 2004; Porrett et al., 2006) and a seminal study inferred that the locoregional treated cases have same survival rates as untreated cases (Manjo *et al.,* 1996). However on the contrary, Markov-based-cost-effectiveness analysis, pointed to be beneficial for neo-adjuvant therapy when the duration of waiting time go beyond six months (Llovet *et al.,* 2002). On the basis of cost-effectiveness studies and small pilot studies published so far, it is not recommended to administer sorafenib to the UNOS-T2 stage HCC patients who are in the waiting list (Vitale *et al.*, 2010; Tuesdale *et al.*, 2011).

2.2. Living Donor Liver Transplantation

The healthy living donor's right liver lobe is utilized for transplantation of liver and is emerged as a substituent strategy to deceased liver transplantation (Trotter *et al.,* 2002; Clavien *et al.,* 2007).

Researchers and doctors showed great enthusiasm for living donor liver transplant (LDLT) in year 2000, and it was guesstimated that a considerable proportion of the patients with diagnosis of HCC would be transplanted with living donor liver (Bruix and Llovet, 2002). But unfortunately the life threatening complications and the allied risks of death to

the healthy donor have reduced the attention of liver transplant community (Siegler *et al.,* 2006; ghoblier *et al.,* 2008). LDLT cases are less than 5% of total adult liver transplants which is remarkably less than living donor kidney tranplant cases comprising of 40% of all kidney transplants(Browns *et al.,* 2008).

LDLT is also performed in the countries having well established protocols for the donation of organs from non-heart-beating or brain dead donors. This is done due to shortage of donor, growth of tumors beyond acceptable criteria, deaths affiliated with long waiting times on the waiting list. The major problem in LDLT is safety of donor, as LDLT may lead to complication risks and death (Clavien *et al.,* 2012). The benefits and risks of LDLT should be kept in mind for both donor and recipient. This concept of allocation of benefits and risk factors in transplantation is termed as double equipoise (Clavien *et al.,* 2012; Cronin and Mullis, 2008; Sarasin *et al.,* 2001). The term double equipoise was proposed to explain the steadiness between the survival benefits of recipient with the use of LDLT and the risk or death of healthy donor (Cronin and Millis, 2008). The benefits and risks need to be understood and openly discussed by all patients having such cases, and meeting the equipoise test.

LDLT must only be performed in centers with high expertise in hepatic surgery and liver transplantation. The studies outcomes of comparison of LDLT with deceased LT remained controversial. Albeit a few studies recommended that higher risk of recurrence is associated with LDLT (Lo *et al.,* 2007; Fisher *et al.,* 2007). It was suggested by cost-effectiveness studies that in HCC patients LDLT may be performed, if their waiting time for liver transplant exceeds beyond 7 months (Sarasin *et al.,* 2001).

Some researchers proposed that prior to transplantation, a 3-month observation period should be considered to prevent the transplantation of potentially aggressive tumors (Kulik *et al.,* 2004; Fisher *et al.,* 2007). LDLT is recommended as supreme setting to investigate the HCC indications in extended form (Majno and Mazzaferro, 2006), so the panel of board does not proposed this strategy for any broadened indication, except in the milieu of research analysis.

Patient Survival Rates following Liver Transplantation for Hepa to cellular Carcinoma:

Table 1

Author (Year)	N	Survival Rate	
		1 Year	5 Years
Jonas (2001)	120	90%	71%
Alan (2000)	112	78%	57%
Regalia (2001)	122		80%
Fegueras (2001)	307		63%
Jain (2000)	4000	79%	67%
Yao (2003)	70	91.30%	72.40%
Shimoda (2004)	HCC+HCV 67	75%	55%
	HCV only 396	84%	75%
Zavaglia (2005)	155	84%	72%
Bozorgzadeh (2007)	37 HCV+HCC	89.10%	49.30%
	34 HCC only	94.10%	76.40%

HCC Due to Viral Hepatitis and Transplantation

The majority of patients who are diagnosed with HCC have infection of hepatitis virus. A major issue after liver transplantation is the recurrence of hepatitis that considerably influence overall prognosis. The problem associated with HBV has now been resolved with the regular utilization of passive immunoprophylaxis with hepatitis B immune globulin and only about 10% of patients have the risk of recurrence of infection, antiviral drugs including adefovir and lamivudine

have been used in ameliorating its course should recurrent HBV develop (Schwartz, 2004). However, hepatitis C infection recurrence is a serious issue. Almost 100% of HCV infected patients prior to transplant remain so afterwards (Feurer *et al.*, 2002) as at 1 year almost 50% will suffer from chronic hepatitis (Schwartz, 2004) and at 5 years almost 20% will have cirrhosis (Berenguer *et al.*, 2000). Five-year survival is reduced by 5–10% in transplanted HCV patients as compared to transplanted patients for any liver disease that does not involve recurrence.

Recent treatment therapy for HCV, involving ribavirin and interferon, is not easy to administer in post transplant setting and reported sustained clearing of HCV is only ranging from 20 to 25%. Hepatitis C has been a salient factor that must be kept onto account in considering the on the whole risk of liver transplantation in HCV associated HCC patients.

Post-Transplant Immunosuppressant and HCC

According to UNOS data, hepatitis C and hepatocellular carcinoma are the most common reasons for liver transplantation. A large number of patients with HCC also have HCV infection. The best approach to avoid HCV recurrence is to eliminate HCV infection before liver transplant. This concept is because the studies showed that it is not easy to start antiviral treatment therapy involving IFN during the postransplant period as it has a poor usefulness and efficacy with significant side effects such as hematological toxicity, bacterial infections and organ rejections, which lead to dose reduction or discontinuation of antiviral treatment or dose reduction. So, the HCV treatment is not suggested prior to the development of damage to the graft in the early phase, it should only be started during rapid and severe progression of fibrosis with an increased risk of graft loss, particularly in the case of cholestatic hepatitis. Current course of antiviral therapy comprises of PEG-IFN/RBV, and different studies have shown that a sustained virological response is achieved in 8–45%. Several reviews of post transplant usage of PEG-IFN/RBV demonstrated that the rate of sustained virological response is about 30% (Berenguar, 2008; Wang *et al.*, 2006; Xrouchakis *et al.*, 2008). Due to the new drug developments for HCV infection, most researchers deem that the post-transplant HCV recurrence treatments will also improve in the future.

The role of triple therapy of PEG-IFN/RBV with protease inhibitors is ambiguous. However, Verna EC et al. represented a multicenter study considering triple therapy plus Telaprevir in treatment of post-transplant HCV recurrence. It was reported that there was increased sustained viral response rates than those with standard treatment including PEG-IFN/RBV alone (Verna *et al.*, 2013). These results are balanced with increased rates of adverse events including kidney dysfunction, increased risk of readmissions, and death of the patient. Other regimen protocols are under investigation in patients with cirrhosis, especially non interferon regimens. The impact of these treatment combinations in the liver transplant setting is

Still to be investigated (Galuppo *et al.*, 2013)

LOCAL ABLATION

Local ablation is the first line choice for patients with early stages of HCC who are not appropriate for surgical procedures. Since the last two decades, many methods for thermal or chemical demolition of tumor have been developed and tested clinically (Lencioni, 2010). The thermal ablative treatment therapies are considered as either cryoablation by causing the tissue to freeze at -20°C and -60 °C or hyperthermic treatments by heating the tissue at 60–100 °C including radiofrequency ablation (RFA), laser ablation and microwave ablation. Mostly procedure is done via percutaneous approach; however in some cases ablation via laparoscopy is suggested. Due to the long duration of waiting period to have

a cadaveric donor liver, it is essential that transplant candidates should be treated in the waiting period in order to avoid the progression of tumor. The most common modalities which have been used include chemoembolization (CE), radiofrequency ablation (RFA) and percutaneous ethanol injection (PEI). The PEI has been recommended as efficient technique in destroying small sized HCC tumors (2cm). For tumors (2– 4 cm), the efficiency of PEI decreases and those exceeding 4 cm, it is not useful. Due to its usefulness and simplicity, it is the favored type of treatment technique at various centers to treat small and solitary tumor lesions. It is however limited by the ease of access of the tumor lesions which are allocated high at liver domeand are not easy to approach. Such tumors are easily visualized by saline instillation into the abdominal cavity before the administration of injection.

For HCC patients, Chemoembolization is considered as a well-established treatment technique. Studies showed that chemoembolization considerably lengthen the life span in dependant of liver transplant. The effectiveness of this treatment technique is based on the fact that the entire circulation of HCC tumors is derived from hepatic artery. The risk factors associated with CE increase with the decrease in liver function and patients with child Pugh C cirrhosis have contraindication for this procedure. CE is particularly used when many lesions are present in an anatomic area of liver or the tumor size is 4 cm. RFA might be done laparoscopic ally, percutaneously or open, using ultrasound guidelines. In a study we found that complete ablation is attainable more favorably by RFA as compared to PEI, as evaluated by imaging studies.

Percutaneous Ethanol Injeaction, PEI

It is a technique used to chemically destruct the tumor. It is a good strategy to the cure nodular-type HCC that attains complete necrosis in 90% of tumors bearing size <2 cm, 70% in tumors of size 2–3 cm and 50% in those having size between 3 and 5 cm (Sala et al., 2004; Lencioni, 2010; Livraghi et al., 1995). This technique has a limitation that the diffusion of ethanol is It has been considered that ethanol diffusion is obstructed either by the tumor capsule or by intratumoral fibrotic septa. It results in reduction in curative capacity of PEI technique, especially for the tumors which have size larger than 2 cm. To overcome this issue, a particular device with single-session PEI is introduced, as a result 80–90% of sustained complete response rate is observed in tumors having size smaller than 4 cm (Kuang et al., 2009). About 47-53% of patients with HCC of early stage and Child–Pugh A cirrhosis have a 5 year survival rate with PEI (Livraghi *et al.,* 1995; Lencioni *et al.,* 1995). With the use of PEI technique the major drawback is that the local tumor recurrence rate is high and this recurrence rate may increase up to 43% in lesions > 3 cm (Khan et al., 2000). Another chemical ablation technique is Percutaneous acetic acid injection (PAI) but it is not not offering significant advantages to PEI (Huo *et al.,* 2003). RFA is the most frequent alternative strategy to PEI for the purpose of local ablation of HCC patients. In RF ablation the energy is generated to induce coagulative necrosis of the tumor forming a safety ring in peritumoral tissues, which might eradicate small-undetected satellites. Various previous studies explained that RF involves only a few treatment sessions to attain comparable anti-tumoral outcomes. RFA technique was compared to PEI for the treatment of early stage HCC, in five controlled randomized trials. These studies constantly explained that RFA has more benefits and is far better for antitumor effect than PEI, resulting in improved local control of the ailment as 2 year local recurrence rate after RFA and PEI are 2–18% and 11–45% respectively (Lin et al 2005; Shina et al., 2005; Lin et al., 2004). The evaluation of effect of RFA on survival is more controversial.

Survival benefits supporting RFA as compared to PEI were determined.

A Japanese study comprising of 232 patients (Shina et al., 2005), assessed that the survival benefits of patients

favored RFA Vs PEI. However, the two European randomized controlled trials reported the absence of difference in RFA and PEI in the context of survival rate (Lencioni et al., 2003; Brunello *et al.,* 2008) From the same group two further RCT involving subgroup assessment of tumors with size larger than were investigated and reported the advantage of survival in the tumor subgroup analysis of size larger than 2 cm favoring RF as compared to either PAI or PEI (Lin et al., 2005). The three independent meta-analyses have verified RFA offers a survival benefit in the tumors of size > 2 cm as compared to that of PEI (Cho et al., 2009; Germani et al., 2010). The major disadvantage of RFA is that it has high major complications rate (4%) verses PEI (2.7%) (Imamura et al., 2008; Bouza et al., 2009)

TACE

TACE has been the most commonly utilized form of neoadjuvant treatment therapy, either alone or in combined form with resection/ablation, in HCC patients who are listed for transplantation or taken in a protocol of down staging the patients (Galuppo *et al.,* 2013).

It is the combination of two therapeutic strategies. First strategy is to administer chemotherapeutic agents mixed with lipiodol in the form of a vehicle into the feeding vessels of the tumor. Lipiodol is an oily contrast applied for lymph graphic studies and is specifically retained within the tumor; hence the exposure of cancerous cells to chemotherapy is raised. Second strategy, the feeding artery is obstructed with the help of micro particles causing ischemia and exposure to chemotherapeutic agents is prolonged. Hepatic artery occlusion is generally attained with the use of Gel foam particles, however starch microspheres, polyvinyl alchohol (PVA), autologous blood clots and metallic coils have not been used for occlusion purpose (Marelli et al., 2007). The advanced HCC patients who are incompatible for radical therapy, experienced improved survival treated with TACE as compared to the best supportive care (Llovet and Bruix, 2003). Side effects of TACE range from the postembolization syndrome to hepatic insufficiency. The major intention of utilizing TACE is to have a bridge therapy to transplantation to control local tumor growth until a donor organ is available for transplant (Peterson et al., 2013). TACE is the favored single-treatment technique in down staging strategy, particularly for multifocal tumors but combination of modalities of resection, RFA, TACE and PEI help to downstage HCC patients more efficiently than TACE alone (Peng et al., 2013).

Chemoembolization remarkably slows down macro vascular invasion and tumor progression. The survival advantage of TAE or chemoembolization has been considered as the objective of seven randomized controlled trials, which showeed contradictory outcomes. The survival advantage of chemoembolization or TAE were observed in two studies (Lo et al., 2002; Llovet et al., 2002), one study demonstrated treatment therapy as an independent forecaster of survival (Llovet *et al.,* 2002). Meta-analysis of all these studies, comprising 516 patients, showed a survival benefit of chemoembolization/embolization as compared to the control group (Llovet and Bruix, 2003). All these studies after systemic analysis recommended a remarkable survival benefit of chemoembolization with doxorubicin or cisplatin in four studies, but in three studies with embolization alone no benefit was observed (Llovet and Bruix, 2003). In general, the median survival for intermediate HCC patients is assumed to be almost 16 months, however following chemoembolization the median survival is found to be about 20 months. As a result of these analyses, TACE has been recommended as standard of care for intermediate HCC patients who follow the criteria of the intermediate-stage of the BCLC staging system, i.e. those having HCC with multiple nodules, absence of evidence of micro vascular invasion and no cancer-related symptoms. In a meta-analysis conducted by Cochrane investigators the TACE efficacy was challenged (Oliveri *et al.,* 2011)

Chemoembolization with Drug-Eluting Beads (TACE-DEB)

The novel system of Drug-eluting beads (DEB) involves PVA beads of size 500–700 μm. These beads are particularly proposed to release chemotherapeutic agents at a slow rate (Galuppo et al., 2013). It is a strategy launched to have better and improved anti-tumoral activity and clinical advantages. The perfect scheme for TACE should show sustained and maximum in tratumoral concentration of the agents of chemotherapy with least systemic coverage, along with standardized obstruction of tumor vessel. Embolic microspheres have the capability to seize chemotherapeutic agents and release these agents in a controlled mode over a duration of 1-week. This form of therapy raise the local drug concentration with insignificant systemic toxicity (Varela *et al.,* 2007). TACE and TACE-DEB were compared in a phase II randomized trial and it was reported that TACE-DEB showed less intense drug-related adverse effects and liver toxicity(Lammer *et al.,* 2010).

Radioembolization and External Radiation

Radioembolization is a technique which involves the infusion of radioactive material like microspheres coated with Yttrium-90 (90Y) (Hilgard et al., 2010; Salem *et al.,* 2010) or Iodine-131 (^{131}I)-labeled lipiodol (Raoul et al., 1997) or same radioactive agents into hepatic artery. The intra-arterial-injection of microspheres will preferentially deliver the radioactive substance to the area bearing tumor and selectively produce low-penetrating and high energy radiation to the tumor.

The most accepted radioembolization technique utilizes microspheres containing 90Y, which is a ß-emitting isotope. This treatment involves the need of a specialized center of third level with trained interventional radiologists and sophisticated equipment. Severe intestinal radiation and lung shunting should be avoided before the procedure (Kulik et al., 2008).

Different Cohort studies reported the long-term impact and estimated a median survival period of 17.2 months for intermediate HCC patients (Salem et al., 2010) and 12 months for advance staged HCC patients having portal vein invasion (Kulik et al., 2008; Hilgard et al., 2010; Sangro et al., 2009). Around 35-50% of Objective response rate has been reported (Salem et al., 2010). Liver associated toxicity has been shown by 20% of patients and 3% of patients showed treatment linked death (Salem et al., 2010).

CONCLUSIONS

HCC management depends on the tumor stage, patient performance status and liver function reserve and involves a multidisciplinary approach for optimal management. hepatic resection and liver transplantation are the only potential curative treatment strategies in early stage of tumor. There have been major advances in trans-arterial and local ablative therapies. RFA is comparable to surgical resection when applied in the early stage HCC in well-selected HCC patients. The safety and efficacy of conventional TACE and Radioembolization has been improved via drug-eluting beads and glass or resin sphere.

REFERENCES

1. Terry K and M S Copur, Molecular Targeted Therapy of Hepatocellular Carcinoma, Journal of Cancer Therapy, 2013, 4, 426-439.
2. Bozorgzadeh A, M Orloff, P Abt, G Tsoulfas, D Younan, R Kashyap, A Jain, P Mantry, B Maliakkal, A Khorana,

and S Schwartz. Survival Outcomes in Liver Transplantation for Hepatocellular Carcinoma, Comparing Impact of Hepatitis C Versus Other Etiology of Cirrhosis. Liver transplantation, 2007, 13: 807-813.

3. Chuang SC, La Vecchia C, Boffetta P: Liver cancer: descriptive epidemiology and risk factors other than HBV and HCV infection. Cancer letters 2009, 286:9-14
4. Barazani Y, Hiatt JR, Tong MJ, et al. Chronic viral hepatitis and hepatocellular carcinoma. World J Surg. 2007; 31:1245–1250.
5. Duffy JP, MD, Andrew Vardanian,, Elizabeth Benjamin, Melissa Watson, Douglas G. Farmer, Rafik M. Ghobrial, Gerald Lipshutz, Hasan Yersiz, David S K. Lu, Charles Lass man, Myron J Tong, Jonathan R. Hiatt and Ronald W. Busuttil, Liver Transplantation Criteria For Hepa to cellular Carcinoma Should Be Expanded A 22-Year Experience With 467 Patients at UCLA. Annals of Surgery • Volume 246, Number 3, September 2007
6. Rustgi VK. The epidemiology of hepatitis C infection in the United States J Gastroenterol 2007; 42: 513–21.
7. Mela M, A. Mancuso & A. K Burroughs Liver Transplantation and Hepatobiliary Medicine, Review article: hepatocellular carcinoma: indications for liver transplantation. Aliment Pharmacol Ther 2003; 17: 130–137.
8. Belghiti J, Hiramatsu K, Benoist S, Massault P, Sauvanet A, Farges O. Seven hundred forty-seven hepatectomies in the 1990s: an update to evaluate the actual risk of liver resection. J Am Coll Surg 2000; 191:38–46.
9. Lang H, Sotiropoulos GC, Dömland M, Frühauf NR, Paul A and Hüsing J. Liver resection for heap to cellular carcinoma in non-cirrhotic liver without underlying viral hepatitis Br J Surg 2005; 92:198–202.
10. Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996; 111:1018–1022
11. Cucchetti A, Piscaglia F, Caturelli E, Benvegnù L, Vivarelli M, Ercolani G, et al. Comparison of recurrence of hepatocellular carcinoma after resection in patients with cirrhosis to its occurrence in a surveilled cirrhotic population. Ann Surg Oncol 2009; 16:413–422.
12. The Surgical Approach to HCC: Our Progress and Results in Japan Masatoshi Makuuchi and Keiji Sano Liver Transplantation, Vol 10, No 2, Suppl 1 (February), 2004: pp S46–S52
13. Llovet JM, Bruix J. Novel advancements in the management of heap to cellular carcinoma in 2008. J Hepatol 2008; 48:S20–S37.
14. Roayaie S, Blume IN, Thung SN, Guido M, Fiel MI, Hiotis S, et al. A system of classifying microvascular invasion to predict outcome after resection in patients with heap to cellular carcinoma Gastroenterology 2009; 137:850–855.
15. Poon RT, Fan ST, Lo CM, Liu CL, Lam CM, Yuen WK, et al. Extended hepatic resection for heap to cellular carcinoma in patients with cirrhosis: is it justified? Ann Surg 2002; 236:602–611.
16. Mazzaferro V, Romito R, Schiavo M, Mariani L, Camerini T, Bhoori S, et al. Prevention of heap to cellular carcinoma recurrence with alpha-interferon after liver resection in HCV cirrhosis. Hepa to logy 2006; 44: 1543–1554.

17. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for heap to cellular carcinoma. Gastroenterology 2008; 134:1908–1916.

18. Makuuchi M, Sano K. The surgical approach to HCC: our progress and results in Japan. Liver Transpl 2004; 10:S46–S52.

19. Ruey-Shyang Soong, Ming-Chin Yu, Kun-Ming Chan, Hong-Shiue Chou, Ting-Jung Wu, Chen-Fang Lee, Tsung-Han Wu, Wei-Chen Lee Analysis of the recurrence risk factors for the patients with heap to cellular carcinoma meeting University of California San Francisco criteria after curative hepatectomy. World Journal of Surgical Oncology 2011, 9:9

20. Makuuchi M, Kosuge T, Takayama T, Yamazaki S, Kakazu T, Miyagawa S, et al. Surgery for small liver cancers. Semin Surg Oncol 1993; 9: 298–304

21. Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC. Surgical resection of heap to cellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology 1996; 111:1018–1022

22. Simpson KJ, Finlayson ND. Clinical evaluation of liver disease Baillieres Clin Gastroenterol 1995; 9:639–659

23. Cucchetti A, Piscaglia F, Caturelli E, Benvegnù L, Vivarelli M, Ercolani G. Comparison of recurrence of heap to cellular carcinoma after resection in patients with cirrhosis to its occurrence in a surveilled cirrhotic population. Ann Surg Oncol 2009; 16:413–422.

24. Llovet JM, Schwartz M, Mazzaferro V. Resection and liver transplantation for hepatocellular carcinoma. Semin Liver Dis 2005; 25:181–200

25. Torzilli G, Olivari N, Moroni E, Del Fabbro D, Gambetti A, Leoni P. Contrast-enhanced intraoperative ultrasonography in surgery for heap to cellular carcinoma in cirrhosis. Liver Transpl 2004; 10:S34–S38

26. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early heap to cellular carcinoma: resection versus transplantation. Hepatology 1999; 30:1434–1440

27. Roayaie S, Blume IN, Thung SN, Guido M, Fiel MI, Hiotis S, et al. A system of classifying microvascular invasion to predict outcome after resection in patients with heap to cellular carcinoma Gastroenterology 2009; 137:850–855.

28. Vauthey JN, Lauwers GY, Esnaola NF, Do KA, Belghiti J, Mirza N. Simplified staging for heap to cellular carcinoma J Clin Oncol 2002;20:1527–1536.

29. Belghiti J, Panis Y, Farges O, Benhamou JP, Fekete F. Intrahepatic recurrence after resection of heap to cellular carcinoma complicating cirrhosis. Ann Surg 1991; 214:114–117

30. Finkelstein SD, Marsh W, Demetris AJ, Swalsky PA, Sasatomi E, Bonham A. Micro dissection-based allelotyping discriminates de novo tumor from intrahepatic spread in heap to cellular carcinoma. Hepatology 2003; 37:871–879.

31. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F. Liver transplantation for the treatment of

small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334:693–699.

32. Schwartz M, I Dvorchik, S Roayaie, MI Fiel, S Finkelstein, JW Marsh, JA Martignetti and JM Llovet, liver transplantation for hepatocellularcarcinoma: extension of indications based on molecular markers J Hepatol. 2008 October; 49(4): 581–588. doi:10.1016/j.jhep.2008.03.032.
33. Vakili K, James J. Pomposelli, Yee Lee Cheah, Mohamed Akoad, W. David Lewis, Urmila Khettry, Fredric Gordon, Khalid Khwaja, Roger Jenkins and Elizabeth A. Living Donor Liver Transplantation for Hepa to cellular Carcinoma: Increased Recurrence but Improved Survival. Liver transplantation 15:1861-1866, 2009
34. Ravaioli M, Ercolani G, Cescon M et al. Liver transplantation for heap to cellular carcinoma: Further considerations on selection criteria. Liver Transpl 2004; 10: 1195–1202.
35. Mazzaferro V, Regalia E, Doci R et al. Liver transplantation for the treatment of small heap to cellular carcinomas in patients with cirrhosis N Engl J Med 1996; 334: 693–699.
36. Llovet JM, Schwartz M, Fuster J, Bruix J. Expanded criteria for heap to cellular carcinoma through down-staging prior to liver transplantation: Not yet there. Semin Liver Dis 2006; 26: 248–253
37. Llovet JM, Brú C, Bruix J. Prognosis of heap to cellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999; 19:329–338
38. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX. Design and endpoints of clinical trials in hepatocellular carcinoma J Natl Cancer Inst 2008; 100:698–711
39. Freeman Jr RB, Wiesner RH, Harper A, McD iarmid SV, Lake J, Edwards E. UNOS/OPTN Liver Disease Severity Score, UNOS/OPTN Liver and Intestine, and UNOS/OPTN Pediatric Transplantation Committees. The new liver allocation system: moving toward evidence-based transplantation policy. Liver Transpl 2002; 8:851–858.
40. Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R. Milan criteria in liver transplantation for HCC: an evidence-based analysis on 15 years of experience. Liver Transpl 2011; 17:S44–S57.
41. Mazzaferro V, Llovet JM, Miceli R, et al. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. Lancet Oncol. 2009; 10:35–43
42. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334:693–699.
43. Clavien PA, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol 2012; 13:e11–e22.
44. Llovet JM, Fuster J, Bruix J. Intention-to-treat analysis of surgical treatment for early hepatocellular carcinoma: resection versus transplantation. Hepatology 1999; 30:1434–1440
45. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001; 33:1394–

1403.

46. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology 2001; 33:1394–1403.

47. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, et al. A model to predict survival in patients with end-stage liver disease Hepatology 2001; 33:464–470.

48. Vibert E, Azuolay D, Hoti E, Iacopinelli S, Samuel D, Salloum C, et al. Progression of alphafetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical factor. Am J Transplant 2010; 10:127–137.

49. Pomfret EA, Washburn K, Wald C, Nalesnik MA, Douglas D, Russo M, et al. Report of a national conference on liver allocation in patients with heap to cellular carcinoma in the United States. Liver Transpl 2010; 16:262–278.

50. Sala M, Fuster J, Llovet JM, Navasa M, Solé M, Varela M, et al. High pathological risk of recurrence after surgical resection for hepatocellular carcinoma: an indication for salvage liver transplantation. Liver Transpl 2004; 10:1294–1300.

51. Cescon M, Alessandro Cucchetti, Matteo Ravaioli, Antonio Daniele Pinna Hepa to cellular carcinoma loco regional therapies for patients in the waiting list Impact on transplant ability and recurrence rate Journal of Hepatology 2013 vol. 58 j 609–618

52. Millonig G, Graziadei IW, Freund MC, Jaschke W, Stadlmann S, Ladurner R. Response to preoperative chemoembolization correlates with outcome after liver transplantation in patients with hepatocellular carcinoma. Liver Transpl 2007; 13:272–279.

53. Mazzaferro V, Battiston C, Perrone S, Pulvirenti A, Regalia E, Romito R. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. Ann Surg 2004; 240:900–909.

54. Lencioni R, Cioni D, Crocetti L, Franchini C, Pina CD, Lera J. Early-stage heap to cellular carcinoma in patients with cirrhosis: long-term results of percutaneous image-guided radiofrequency ablation. Radiology 2005; 234:961–967.

55. Del Gaudio M, Ercolani G, Ravaioli M, Cescon M, Lauro A, Vivarelli M, et al. Liver transplantation for recurrent heap to cellular carcinoma on cirrhosis after liver resection: University of Bologna experience. Am J Transplant 2008; 8:1177–1185.

56. Golfieri R, Cappelli A, Cucchetti A, Piscaglia F, Carpenzano M, Peri E. Efficacy of selective transarterial chemoembolization in inducing tumor necrosis in small (<5 cm) heap to cellular carcinomas. Hepatology 2011; 53:1580–1589.

57. Fujiki M, F Aucejo, M Choi, R Kim. Neo-adjuvant therapy for hepatocellular carcinoma before liver transplantation: Where do we stand? World J Gastroenterol 2014 May 14; 20(18): 5308-5319

58. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular

carcinoma: expansion of the tumour size limits does not adversely impact survival. Hepatology 2001; 33:1394–1403.

59. Lencioni R, Llovet JM. Modified RECIST (mRECIST) assessment for hepatocellular carcinoma. Sem Liv Dis 2010; 30:52–60.
60. Llovet JM, Di Bisceglie AM, Bruix J, Kramer BS, Lencioni R, Zhu AX, et al. Panel of experts in HCC-design clinical trials. Design and endpoints of clinical trials in hepatocellular carcinoma. J Natl Cancer Inst 2008; 100:698–711.
61. Bruix J, Sherman M. Practice Guidelines Committee, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma. Hepatology 2005; 42:1208–1236.
62. Decaens T, Roudot-Thoraval F, Bresson-Hadni S, Meyer C, Gugenheim J, Durand F, et al. Impact of pretransplantation transarterial chemoembolization on survival and recurrence after liver transplantation for hepatocellular carcinoma. Liver Transpl 2005;11:767–775.
63. Porrett PM, Peterman H, Rosen M, Sonnad S, Soulen M, Markmann JF. Lack of benefit of pre-transplant locoregional hepatic therapy for hepatocellular cancer in the current MELD era. Liver Transpl 2006; 12:665–673.
64. Llovet JM, Mas X, Aponte JJ, Fuster J, Navasa M, Christensen E, et al. Cost effectiveness of adjuvant therapy for hepatocellular carcinoma during the waiting list for liver transplantation. Gut 2002; 50:123–128.
65. Vitale A, Volk ML, Pastorelli D, Lonardi S, Farinati F, Burra P, et al. Use of sorafenib in patients with hepatocellular carcinoma before liver transplantation:a cost–benefit analysis while awaiting data on sorafenib safety. Hepatology 2010; 51:165–173.
66. Truesdale AE, Caldwell SH, Shah NL, Argo CK, Al-Osaimi AM, Schmitt TM, et al. Sorafenib therapy for hepatocellular carcinoma prior to liver transplant is associated with increased complications after transplant. Transpl Int 2011; 24:991–998.
67. Trotter JF, Wachs M, Everson GT, Kam I. Adult-to-adult transplantation of the right hepatic lobe from a living donor. N Engl J Med 2002; 346:1074–1082.
68. Clavien PA, Petrowsky H, DeOliveira ML, Graf R. Strategies for safer liver surgery and partial liver transplantation. N Engl J Med 2007; 356:1545–1559.
69. Bruix J, Llovet JM. Prognostic prediction and treatment strategy in heap to cellular carcinoma. Hepatology 2002; 35:519–524.
70. Siegler M, Simmerling MC, Siegler JH, Cronin 2nd DC. Recipient deaths during donor surgery: a new ethical problem in living donor liver transplantation (LDLT). Liver Transpl 2006;12:358–360.
71. Ghobrial RM, Freise CE, Trotter JF, Tong L, Ojo AO, Fair JH, et al. A2ALL Study Group. Donor morbidity after living donation for liver transplantation. Gastroenterology 2008; 135:468–476.
72. Browns Jr RS. Live donors in liver transplantation. Gastroenterology 2008; 134:1802–1813.
73. Cronin 2nd DC, Millis JM. Living donor liver transplantation: the ethics and the practice. Hepatology

2008;47:11–13.

74. Sarasin FP, Majno PE, Llovet JM, Bruix J, Mentha G, Hadengue A. Living donor liver transplantation for early hepatocellular carcinoma: a lifeexpectancy and cost–effectiveness perspective. Hepatology 2001; 33:1073–1079.
75. Lo CM, Fan ST, Liu CL, Chan SC, Ng IO, Wong J. Living donor versus deceased donor liver transplantation for early irresectable hepatocellular carcinoma. Br J Surg 2007; 94:78–86.
76. Fisher RA, Kulik LM, Freise CE, Lok AS, Shearon TH, Brown Jr RS, et al. A2ALL Study Group. Hepatocellular carcinoma recurrence and death following living and deceased donor liver transplantation. Am J Transplant 2007; 7:1601–1608.
77. Kulik L, Abecassis M. Living donor liver transplantation for hepatocellular carcinoma. Gastroenterology 2004; 127:S277–S282.
78. Majno P, Mazzaferro V. Living donor liver transplantation for hepatocellular carcinoma exceeding conventional criteria: questions, answers an demands for a common language. Liver Transpl 2006; 12:896–898.
79. Lencioni R. Loco-regional treatment of hepatocellular carcinoma. Hepatology 2010; 52:762–773.
80. Livraghi T, Bolondi L, Lazzaroni S, Marin G, Morabito A, Rapaccini GL, et al. Percutaneous ethanol injection in the treatment of hepatocellular carcinoma in cirrhosis. A study on 207 patients. Cancer 1992; 15:925–929.
81. Kuang M, Lu MD, Xie XY, Xu HX, Xu ZF, Liu GJ, et al. Percutaneous ethanol ablation of early-stage hepatocellular carcinoma by using a multi-pronged needle with single treatment session and high-dose ethanol injection. Radiology 2009; 253:552–561.
82. Lencioni R, Bartolozzi C, Caramella D, Paolicchi A, Carrai M, Maltinti G. Treatment of small hepatocellular carcinoma with percutaneous ethanol injection. Analysis of prognostic factors in 105 Western patients. Cancer 1995; 76:1737–1746.
83. Majno PE, R Adam,H Bismuth, D Castaing, A Ariche, J Krissat, H Perrin and Daniel Azoulay, Hepatobiliary Surgery and Liver Transplant Research Center, Influence of Preoperative Transarterial Lipiodol Chemoembolization on Resection and Transplantation for Hepatocellular Carcinoma in Patients With Cirrhosis. ANNALS OF SURGERY. Vol. 226, No. 6, 688-703
84. Livraghi T, Giorgio A, Marin G, Salmi A, De Sio I, Bolondi L, et al. Hepatocellular carcinoma and cirrhosis in 746 patients: long-term results of percutaneous ethanol injection. Radiology 1995; 197:101–108.
85. Khan KN, Yatsuhashi H, Yamasaki K, Yamasaki M, Inoue O, Koga M, et al. Prospective analysis of risk factors for early intrahepatic recurrence of hepatocellular carcinoma following ethanol injection. J Hepatol 2000; 32:269–278.
86. Huo TI, Huang YH, Wu JC, Lee PC, Chang FY, Lee SD, et al. Comparison of percutaneous acetic acid injection and percutaneous ethanol injection for hepatocellular carcinoma in cirrhotic patients: a prospective study. Scand J Gastroenterol 2003; 38:770–778.
87. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Randomised controlled trial comparing percutaneous radiofrequency

thermal ablation, percutaneous ethanol injection, and percutaneous acetic acid injection to treat hepatocellular carcinoma of 3 cm or less Gut 2005; 54:1151–1156.

88. Shiina S, Teratani T, Obi S, Sato S, Tateishi R, Fujishima T, et al. A randomized controlled trial of radiofrequency ablation versus ethanol injection for small hepatocellular carcinoma. Gastroenterology 2005; 129:122–130.
89. Lin SM, Lin CJ, Lin CC, Hsu CW, Chen YC. Radiofrequency ablation improves prognosis compared with ethanol injection for hepatocellular carcinoma < or =4 cm. Gastroenterology 2004; 127:1714–1723.
90. Lencioni R, Allgaier HP, Cioni D, Olschewski M, Deibert P, Crocetti L, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection Radiology 2003;228:235–240.
91. Brunello F, Veltri A, Carucci P, Pagano E, Ciccone G, Moretto P, et al. Radiofrequency ablation versus ethanol injection for early hepatocellular carcinoma: a randomized controlled trial. Scand J Gastroenterol 2008; 43:727–735.
92. Cho YK, Kim JK, Kim MY, Rhim H, Han JK. Systematic review of randomized trials for hepatocellular carcinoma treated with percutaneous ablation therapies. Hepatology 2009; 49:453–459.
93. Germani G, Pleguezuelo M, Gurusamy K, Meyer T, Isgro G, Burroughs AK. Clinical outcomes of radiofrequency ablation, percutaneous alcohol and acetic acid injection for hepatocellular carcinoma: a meta-analysis. J Hepatol 2010; 52:380–388.
94. Bouza C, López-Cuadrado T, Alcázar R, Saz-Parkinson Z, Amate JM. Metaanalysis of percutaneous radiofrequency ablation versus ethanol injection in hepatocellular carcinoma. BMC Gastroenterology 2009; 9:31.
95. Imamura J, Tateishi R, Shiina S, Goto E, Sato T, Ohki T, et al. Neoplastic seeding after radiofrequency ablation for hepatocellular carcinoma. Am J Gastroenterology 2008; 103:3057–3062.
96. Schwartz M, Liver Transplantation in Patients With Hepatocellular Carcinoma Liver Transplantation, Vol 10, No 2, Suppl 1 (February), 2004: pp S81–S85
97. Feurer ID, Wright JK, Payne JL, Kain AC, Wise PE, Hale P, et al. Effects of hepatitis C virus infection and its recurrence after liver transplantation on functional performance and health-related quality of life. J Gastrointestinal Surg 2002; 6:108 –115.
98. Sheiner PA, Boros P, Klion FM, Thung SN, Schluger LK, Lau JY, et al. The efficacy of prophylactic interferon alfa-2b in preventing recurrent hepatitis C after liver transplantation. Hepatology 1998; 28:831– 838.
99. Berenguer M, Prieto M, Rayon JM, Mora J, Pastor M, Ortiz V, et al. Natural history of clinically compensated hepatitis C virusrelated graft cirrhosis after liver transplantation. Hepatology 2000; 32:852– 858.
100. Yokoyama I, Carr B, Saitsu H, Iwatsuki S, Starzl TE. Accelerated growth rates of recurrent hepatocellular carcinoma after liver transplantation. Cancer 1991; 68:2095–2100.
101. Galuppo R, A McCall, and R Gedaly. The Role of Bridging Therapy in Hepatocellular Carcinoma. International Journal of Hepatology. International Journal of Hepatology.2013, Article ID 419302, 8 pages

http://dx.doi.org/10.1155/2013/419302

102. M. Berenguer, "Systematic review of the treatment of established recurrent hepatitis C with pegylated interferon in combination with ribavirin," *Journal of Hepatology*, vol. 49, no. 2, pp. 274–287, 2008.

103. C. S. Wang, H. H. Ko, E. M. Yoshida, C. A. Marra, and K. Richardson, "Interferon-based combination anti-viral therapy for hepatitis C virus after liver transplantation: a review and quantitative analysis," *American Journal of Transplantation*, vol. 6, no. 7, pp. 1586–1599, 2006.

104. E. Xirouchakis, C. Triantos, P. Manousou et al., "Pegylatedinterferon and ribavirin in liver transplant candidates and recipients with HCV cirrhosis: systematic review and metaanalysis of prospective controlled studies," *Journal of Viral Hepatitis*, vol. 15, no. 10, pp. 699–709, 2008.

105. E. C. Verna, J. R. Burton, J. G. O'Leary et al., "Multicenter study of protease inhibitor-triple therapy in HCV-infected liver transplant recipients: report from the crush-C group," *Journal of Hepatology*, vol. 58, supplement 1, pp. S10–S11, 2013

106. galluppo 2013

107. L. Marelli, R. Stigliano, C. Triantos et al., "Transarterial therapy for hepatocellular carcinoma: which technique is more effective? a systematic review of cohort and randomized studies," *CardioVascular and Interventional Radiology*, vol. 30, no. 1, pp. 6–25, 2007.

108. J. M. Llovet and J. Bruix, "Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival," *Hepatology*, vol. 37, no. 2, pp.429–442, 2003.

109. J. Petersen, B. Henninger, B. Glodny, andW. Jaschke, "Transarterial chemoembolisation in hepatocellular carcinoma,"*Wiener MedizinischeWochenschrift*, vol. 163, no. 5–6, pp. 123–127, 2013

110. Z. W. Peng, Y. J. Zhang, M. S. Chen et al., "Radiofrequency ablation with or without transcatheter arterial chemoembolization in the treatment of hepatocellular carcinoma: a prospective randomized trial," *Journal of Clinical Oncology*, vol. 31, no. 4, pp. 426–432, 2013.

111. Lin DY, Liaw YF, Lee TY, Lai CM. Hepatic arterial embolization in patients with unresectable hepatocellular carcinoma – a randomized controlled trial Gastroenterology 1988; 94:453–456

112. Pelletier G, Roche A, Ink O, Anciaux ML, Derhy S, Rougier P, et al. A randomized trial of hepatic arterial chemoembolization in patients with unresectable hepatocellular carcinoma. J Hepatol 1990; 11:181–184

113. Group d'Etude et de Traitment du Carcinome Hépatocellulaire. A comparison of lipiodol chemoembolization and conservative treatment for unresectable hepatocellular carcinoma. N Engl J Med 1995; 332: 1256–1261.

114. Bruix J, Llovet JM, Castells A, Montana X, Bru C, Ayuso MC, et al. Transarterial embolization versus symptomatic treatment in patients with advanced hepatocellular carcinoma: results of a randomized, controlled trial in a single institution. Hepatology 1998; 27:1578–1583

115. Pelletier G, Ducreux M, Gay F, Luboinski M, Hagege H, Dao T, et al. Treatment of unresectable hepatocellular carcinoma with lipiodol chemoembolization: a multicenter randomized trial. J Hepatol 1998; 29:129–134

116. Lo CM, Ngan H, Tso WK, Liu CL, Lam CM, Poon RT, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology 2002; 35:1164–1171.

117. Llovet JM, Real MI, Montana X, Planas R, Coll S, Aponte J, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet 2002; 359:1734–1739.

118. Llovet JM, Bruix J. Systematic review of randomized trials for unresectable hepatocellular carcinoma: chemoembolization improves survival. Hepatology 2003; 37:429–442.

119. Oliveri RS, Wetterslev J, Gluud C. Transarterial (chemo)embolisation for unresectable hepatocellular carcinoma. Cochrane Database Syst Rev 2011; 3:CD004787. doi:10.1002/14651858.CD004787.pub.

120. Varela M, Real MI, Burrel M, Forner A, Sala M, Brunet M, et al. Chemoembolization of hepatocellular carcinoma with drug eluting beads: efficacy and doxorubicin pharmacokinetics. J Hepatol 2007; 46:474–481.

121. Lammer J, Malagari K, Vogl T, Pilleul F, Denys A, Watkinson A, et al. Prospective randomised study of doxorubicin-eluting-bead embolization in the treatment of hepatocellular carcinoma: results of the PRECISION V study. Cardiovasc Intervent Radiol 2010; 33: 41–52.

122. Raoul JL, Guyader D, Bretagne JF, Heautot JF, Duvauferrier R, Bourguet P, et al. Prospective randomized trial of chemoembolization versus intra-arterial injection of 131I-labeled-iodized oil in the treatment of hepatocellular carcinoma. Hepatology 1997; 26:1156–1161

123. Salem R, Lewandowski RJ, Mulcahy MF, Riaz A, Ryu RK, Ibrahim S, et al. Radioembolization for hepatocellular carcinoma using Yttrium-90 microspheres: a comprehensive report of long-term outcomes. Gastroenterology 2010; 138:52–64.