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REVIEW

Hepatocellular carcinoma: A comprehensive review

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Abstract

Hepatocellular carcinoma (HCC) is rapidly becoming one of the most prevalent cancers worldwide. With a rising rate, it is a prominent source of mortality. Patients with advanced fibrosis, predominantly cirrhosis and hepatitis B are predisposed to developing HCC. Individuals with chronic hepatitis B and C infections are most commonly afflicted. Different therapeutic options, including liver resection, transplantation, systemic and local therapy, must be tailored to each patient. Liver transplantation offers leading results to achieve a cure. The Milan criteria is acknowledged as the model to classify the individuals that meet requirements to undergo transplantation. Mean survival remains suboptimal because of long waiting times and limited donor organ resources. Recent debates involve expansion of these criteria to create options for patients with HCC to increase overall survival.

Key words: Liver transplantation; Hepatectomy; Milan Criteria; Sorafenib; Living donor liver transplantation; Transarterial chemoembolization; Expansion Milan Criteria; Hepatocellular carcinoma; Mammalian target of rapamycin inhibitors; University of California San Francisco Criteria; Salvage liver transplantation

Core tip: Hepatocellular carcinoma (HCC) is the prominent Primary Hepatic tumor. Survival rates average between 6 and 20 mo, making Liver transplantation is the most efficient treatment. The established Milan Criteria is now widely accepted around the world for choosing patients suffering with HCC as liver transplant candidates. Due to high mortality rates, additional variables and tumor characteristics have been researched (example, University of California, San Francisco Criteria) in order to include more patients as candidates, so as to increase overall survival. In this comprehensive review, the pathophysiology, diagnostic modalities, and treatment options are thoroughly discussed.

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INTRODUCTION

Hepatocellular carcinoma (HCC) has become the most common primary hepatic malignancy, with average survival rates between 6 and 20 mo[1]. It now ranks sixth in the world among all malignancies, contributing to the third leading cause of mortality attributed to cancer[2]. Incidence worldwide has increased, likely due to the rising incidence of chronic hepatitis B and C infections. Since 1963 when first performed by Starzl *et al*[3], liver transplantation has seen dramatic changes, though initial outcomes were suboptimal. Attempts to treat HCC with liver transplantation showed poor results. At this point, it was determined that a narrow spectrum of selection criteria was needed to increase survival during the time after transplant. In 1996, Mazzaferro *et al*[4], in his revolutionary paper, proposed stricter criteria for liver transplantation. The four-year rate of survival was 75% with an 83% survival rate without recurrence[4]. From this landmark study, the Milan Criteria (MC) was established. The MC includes three major points: an isolated malignancy $\leqslant$ 5 cm, or 2-3 tumors each < 3 cm, that does not have any evidence of invasion into the vascular system or dissemination outside the liver. The MC became accepted for assessing individuals that have HCC as candidates for transplantation[5]. Given the high mortality associated with HCC, there has been a recent discussion on expanding the current criteria to include more patients as potential transplant candidates, and, therefore, increase overall survival.

In the hopes of improving disease-free survival, there may be certain ways to help incorporate more candidates with HCC. These may include expanding the current Milan and University of California San Francisco (UCSF) criteria to include tumor markers and histology, increasing the number of living donor transplants for HCC, using sorafenib post transplant, and utilizing alternative immunosuppressive regimens.

ETIOLOGY

Worldwide, chronic hepatitis B contributes to the greatest number of HCC. Chronic hepatitis C is primarily the cause in Southern Europe and North America. Individuals that have chronic hepatitis B may develop HCC without evidence of cirrhosis[5]. However, 70%-90% of patients suffer from concurrent cirrhosis[6]. Some factors, such as elevated viral loads, and having hepatitis B envelope and surface antigens are believed to contribute to HCC incidence[7,8]. Advanced age, being male, obesity, alcohol abuse, diabetic, and family history, are variables associated with increased risks for developing HCC[6,9]. Hepatitis B and C co-infection have a cumulative effect in contributing to the formation of HCC[9,10]. Additional variables of risk for HCC are in Table 1[11,12]. The United States, as well as other developed countries, have increasingly seen non-alcoholic steatohepatitis (NASH) as a primary contributor. It is assumed that the obesity epidemic and prevalence of diabetes has played a significant role. Associated factors include: Age, male gender, hepatitis C virus (HCV)/hepatitis B virus, alcohol abuse, severity of non-alcoholic fatty liver disease/NASH, diabetes/obesity, iron overload, and genetic variants (PNPLA3, APOB, TERT)[13].

PATHOPHYSIOLOGY

The pathophysiology of HCC is an evolving topic and appears to be multifactorial. In 1981, after Beasley linked hepatitis B infection to HCC development, its cause was thought to have been identified[14]. Subsequently further research linked other etiologies of underlying cirrhosis to HCC[15]. Ongoing studies have linked metabolic syndrome as a significant cause[16]. Research has shown that repeated inflammation facilitates carcinogenesis[17]. HCC predominantly arises in a cirrhotic liver where repeated inflammation occurs along with fibrogenesis. Inflammation and fibrogenesis predispose the liver to dysplasia and subsequently malignant transformation[17]. An inflammatory microenvironment plays a prominent part in starting the advancement towards HCC[17,18].

The pathogenesis of HCC is made up of different genetic/epigenetic aberrations and alterations with many signaling pathways that lead to a known heterogeneity of the diseases biologic and clinical behavior[19]. The majority of specimens are from hepatectomies and, thus reflect a minority of patients. Cancer genetic heterogeneity of HCC is quite magnificent. Difference exist between patients including variations within stages of tumor development in a similar patient, such as in the nodules, as well as diversity within a tumor[16,20].

Recent analysis has been sought to investigate the genetic pathways that are affected during hepatocarcinogenesis[21]. p53, PIK3CA, and β-catenin appear to be frequently mutated in patients. Additional research is needed to identify the signal pathways that are disrupted, leading to uncontrolled division. Two pathways in cellular differentiation (*i.e.*, Wnt-β-catenin, Hedgehog) appear frequently altered. Up-regulated WNT signaling is believed to link preneoplastic adenomas with greater chances for malignant transformation[22,23].

Ongoing studies are looking at inactivated mutations of ARID2, a chromatin-remodeling gene, in the major subtypes of HCC[17]. Eighteen point two percent of individuals with HCV-associated HCC, primarily in Europe and the United States, had inactivation mutations of ARID2, suggesting this as a common mutation subtype in a tumor suppressor gene.

DIAGNOSIS

Patients who are high risk require surveillance. High risk groups include: Cirrhotic hepatitis B carriers, patients with hepatitis C cirrhosis, stage 4 primary biliary cirrhosis, other causes of cirrhosis, Asian males older than 50 years of age that are hepatitis B carriers, a known family member having HCC in hepatitis B carriers, and African/Northern American blacks having hepatitis B[24]. Surveillance

		Arterial phase hypo- or iso-enhancement		Arterial phase hyper-enhancement		
Diameter (mm)		< 20	⩾ 20	< 10	10-19	⩾ 20
"Washout"	None:	LR-3	LR-3	LR-3	LR-3	LR-4
"Capsule"	One:	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
Threshold growth	⩾ two:	LR-4	LR-4	LR-4	LR-5	LR-5

Figure 1 Liver Imaging Reporting and Data System. Adapted from American College of Radiology (www.acr.org).

Table 1 Etiology of hepatocellular carcinoma[12]

Risk factors for hepatocellular carcinoma
Chronic hepatitis C infection with advanced fibrosis or cirrhosis
Chronic hepatitis B infection with/without cirrhosis
Alcoholic liver disease with cirrhosis
Hereditary hemochromatosis with cirrhosis
Alpha1-antitrypsin deficiency with cirrhosis
Autoimmune hepatitis with cirrhosis
Porphyrias
Wilson's disease
Non-alcoholic fatty liver disease
Nonalcoholic steatohepatitis with cirrhosis
Primary biliary cirrhosis
Type 1 hereditary tyrosinemia
Type 1 and 2 glycogen storage disease
Hereditary ataxia-telangiectasia
Hypercitrullinemia
Aflatoxin exposure
Other carcinogens
Thorotrast
Polyvinyl choloride
Carbon chloride

includes ultrasound at 6-mo intervals[24,25]. Nodules found on ultrasound that are < 1 cm must routinely be followed by ultrasound every three to six months. If nodules are stable then routine surveillance every six months can be resumed. Nodules > 1 cm require further investigation by quadruple phase computed tomography (CT) scan or dynamic enhancement magnetic resonance imaging (MRI) with contrast[26]. Because a tumor gets its vascular source through the hepatic artery, it demonstrates a classic vascular pattern on multiphase CT scans. This pattern of enhancement during the early phase of arterial enhancement has quick washout in the delayed or portal venous phase. Diagnosis can be made purely by radiology. Saborido *et al*[27] reported a higher recurrence rate among patients who underwent tumor biopsy before liver transplantation. Currently, a pre-transplant tissue diagnosis is not required in cirrhotic patients that have the classic imaging findings for HCC[12,28]. If an imaging study does not reveal this typical vascular pattern, then another imaging study with enhancement using a different modality should be performed, or tissue diagnosis must be pursued[5]. However, the differential diagnosis between dysplastic nodules and early HCC might be cumbersome even for an experienced liver pathologist, because stromal invasion, a typical malignant feature, could be absent[23].

Liver Imaging Reporting and Data System (LI-RADS) first came about around March 2011, with widespread acceptance by many in practice. LI-RADS is a method to help standardize the assessment and ability for CT and MRI in recognizing HCC in individuals that demonstrate risk factors[29,30]. LI-RADS categorizes a liver lesion on imaging by its likelihood of being benign, HCC, or alternative diagnosis. The criteria to categorize a lesion into LI-RADS depends on the diameter as well as identifying the four primary variables useful for diagnosing HCC. These include enhancement during the arterial phase, washout following hyperenhancement, the development of a capsule, and growth compared with previous studies[29] (Figure 1). LI-RADS is in constant expansion and critique, garnering input from multiple specialists.

Another imaging study, contrast-enhanced ultrasound, is useful for identifying hepatic lesions. It can help characterize cirrhotic nodules from HCC using microbubble contrast agents[31,32]. In general, HCC does not have Kupffer cells (reticuloendothelial cells). These cells came of importance when Sonazoid, an agent used to enhance imaging about ten minutes after its administration, was introduced. Since the tumor lacks Kupffer cells, there is no enhancement in the post vascular phase, while benign lesions show continued enhancement[33].

TUMOR MARKERS AS CRITERIA FOR HCC

Historically, alpha-fetoprotein (AFP) has been used to aid in diagnosing HCC[24]. Typically, levels greater than 400 ng/mL are considered diagnostic. However, recent data has shown its sensitivity and specificity to be unreliable. AFP can be elevated in other disease manifestations such as metastatic colon cancer or intrahepatic cholangiocarcinoma[34,35]. Therefore, its use may be limited as the only tool for surveillance or diagnosis. Diagnosis should be made purely on radiological appearances and histology[26]. Interestingly, recent studies have shown that AFP may be significant in anticipating the reappearance of HCC after liver transplantation.

Other markers that aid in determining recurrence have included the size and quantity of lesions, bi-lobar disease, an involvement of macrovascular invasion

Table 2 Criteria for listing for liver transplantation and hepatocellular carcinoma: Various expansion beyond the Milan Criteria

Criteria	Ref.	No. of patients	Selection criteria	Survival rate at 5 yr	Survival rate at 5 yr using MC
MC	Mazzaferro *et al*[4]	48	Solitary HCC < 5 cm or 3 nodules < 3 cm	75% (4 yr)	-
Up to seven criteria	Mazzaferro *et al*[86]	283	Sum of the number of tumors and diameter of the largest tumor ≤ 7 cm	71.2%	73.3%
Toronto Criteria	DuBay *et al*[109]	294	Dominant lesion not poorly differentiated on biopsy, no restriction on tumor size and number	68%	72%
UCSF Criteria	Yao *et al*[81]	70	Solitary tumor ≤ 6.5 cm or 3 nodules ≤ 4.5 cm in diameter with a total tumor diameter ≤ 8 cm	75.2%	72%
Clinica universitaria de Navarra Criteria	Herrero *et al*[110]	154	Solitary tumor ≤ 6 cm or ≤ 3 nodules ≤ 5 cm in diameter	68%	66%
Kyoto Criteria	Ito *et al*[41]	125	≤ 10 nodules all ≤ 5 cm in diameter protein induced by vitamin K absence or antagonist-Ⅱ ≤ 400 mAU/mL	Overall survival 68.3%	No difference
Asan Criteria	Lee *et al*[111]	186	≤ 6 nodules with a maximum tumor diameter of ≤ 5 cm	76%	76.3%
Bologna Criteria	Del Gaudio *et al*[112]	177	Solitary HCC ≤ 6 cm or 2 nodules ≤ 5 cm or < 6 nodules ≤ 4 cm and sum diameter ≤ 12 cm	71% (3 yr)	71% (3 yr)
Metroticket Calculator	Mazzaferro *et al*[86]	> 1000	International Liver Transplant Society meeting in 2005 as a Web-based survey. Predict 5 yr survival based on tumor size	50%-70%	75%-80%
Toso Criteria	Toso *et al*[113]	288	Total tumor volume ≤ 115 cm^3	80%	82%
Silva Criteria	Boin *et al*[114]	257	≤ 3 nodules with a maximum tumor diameter of ≤ 5 cm and total tumor diameter < 10 cm	69%	62%
Hangzhou Criteria	Zheng *et al*[87]	195	Total tumor diameter < 8 cm with grate Ⅰ or Ⅱ tumor on biopsy and AFP < 400 ng/mL	72%	78%

HCC: Hepatocellular carcinoma; MC: Milan Criteria; AFP: Alpha feto protein.

and tumor satellites, and tumor-specific biomarkers[36]. Tumor differentiation and microvascular invasion are also substantial risks, but these features are not determined until after the evaluation of the explant. Biomarkers that consist of AFP and des-gamma-carboxy prothrombin are reported to correlate with a post-transplant recurrence of HCC[37]. In a recent study, an AFP over 400 ng/mL supplemented with the total tumor volume was recommended as a predictor following transplant[38]. In another investigation by Hameed *et al*[39], an AFP level > 1000 ng/mL was highly favorable in predicting recurrence of HCC, with a comparison to vascular invasion. Individuals that have elevated preoperative AFP levels > 1000 ng/mL, were found to have 1- and 5-year rates of survival, without reappearance of HCC, of 90% and 52.7% respectively, with levels ≤ 1000 ng/mL showing 95% and 80.3% 1-5 year survival rates. Levels of > 1000 ng/mL led to excluding 4.7% of the individuals with a reduction in the recurrence rate for HCC of 20%[39].

Another recent marker for tumor growth, antagonist-Ⅱ (PIVKA-Ⅱ), might have benefit for listing criteria in HCC patients. This tumor marker is a protein brought about by the deficiency of vitamin K[40]. The Kyoto Criteria (Table 2), was created at Kyoto University by Ito *et al*[41], where they looked at 125 patients that had HCC, 70 of which were inside MC, and the rest 55 who were outside. All patients had no extrahepatic or macrovascular disease. They identified individuals who had no more than 10 tumors, of at most 5 cm with PIVKA-Ⅱ < 400 mAU/mL, demonstrating five-year rates of survival of 86.7%, similar to individuals who fell within MC[41].

Systemic inflammation has been found to have an association with worsening outcomes and recurrence of tumor in patients with HCC. The detection of inflammation has led to identifying various indicators, including the neutrophil-to-lymphocyte ratio (NLR). A Japanese study demonstrated individuals having levels of at least 5 were found to have diminished rates of survival; multivariate analysis identified NLR elevation as being the main predictor of recurrence-free survival[42].

C-reactive protein (CRP) has been another marker of inflammation frequently studied. A meta-analysis done with 1885 patients confirmed an elevation of serum CRP > 10 mg/L showed poor overall [hazard ratio (HR) = 2.15] rates of survival and diminished recurrence-free rates of survival (HR = 2.66). Levels of at least 10 mg/L were comparative to invasion of the vascular system [odds ratio (OR) = 3.05], tumor growth (OR = 2.36), increasing size (OR = 3.41) and advanced stage (OR = 3.23)[43]. Based on these various findings a score has been proposed that is a combination of elevated CRP and low albumin levels, known as the Inflammation-based index[44].

STAGING

According to the American Association for the Study of Liver Disease (AASLD), the system to categorize HCC must incorporate the stage, the individual's functional status, and the underlying function of the liver. Different systems to stage HCC have been created and validated, in various degrees. The American Joint Committee on Cancer revised the tumor, lymph nodes, and metastasis (TNM) classification of malignant tumors staging system

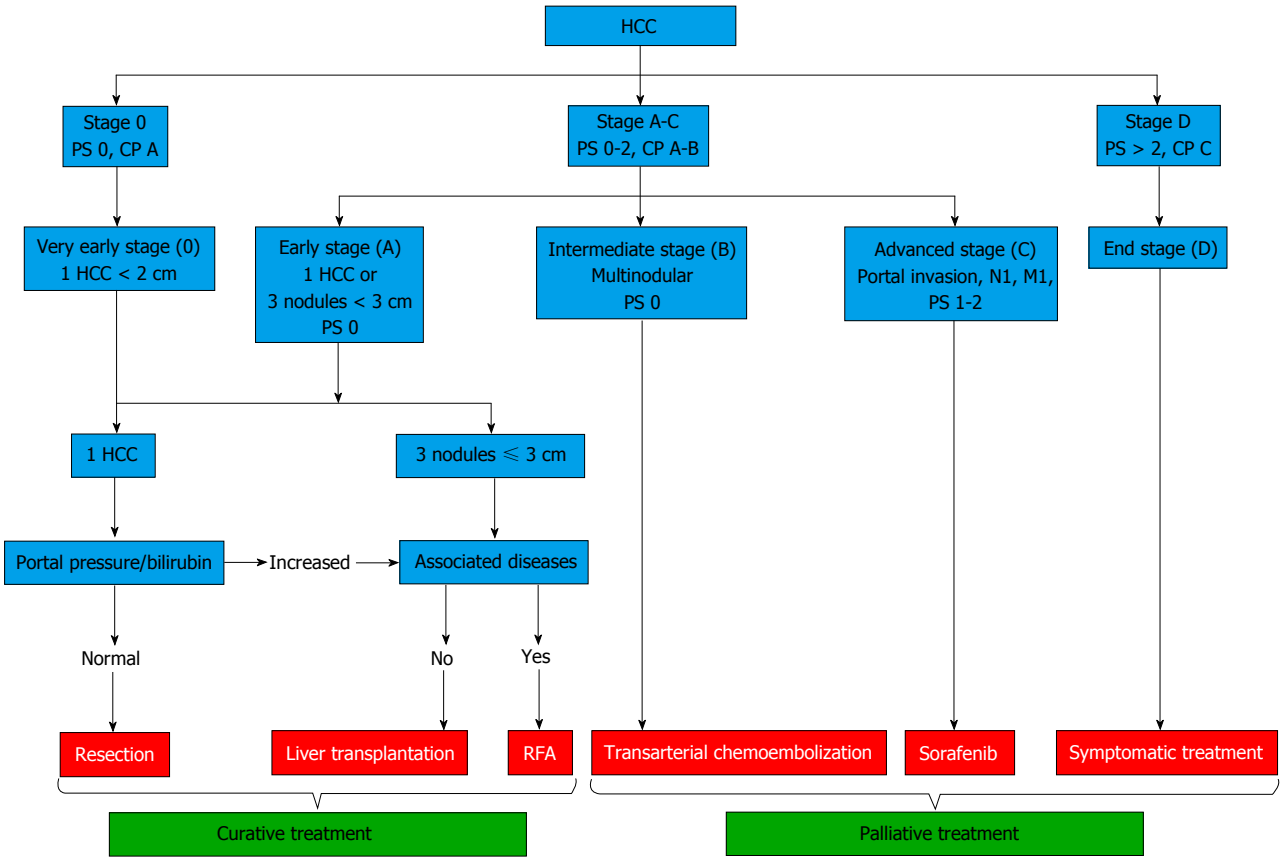

Figure 2 Barcelona-Clinic Liver Cancer Staging System[24]. HCC: Hepatocellular carcinoma; RFA: Radiofrequency ablation; CP: Child-Pugh.

in 2010[45]. Like the 2002 classification, this incorporates the number of lesions, and existence and extent of any invasion into the vasculature. However, compared to the 2002 staging system, changes surrounding the improved prognosis of multiple HCC lesions *vs* major vascular invasion was incorporated[46]. The TNM staging system has been the basis for allocating exception points for the Model for End-stage Liver Disease (MELD). The MELD score validated discriminating different stages of individuals undergoing hepatic resection.

The Okuda staging system, developed in 1985, by Okuda *et al*[47], includes the length of the tumor and three markers identifying the degree of cirrhosis. This includes the total bilirubin, albumin, and quantity of ascites. In one study, the noted survival was 8.3, 2.0, and 0.7 mo for patients that were untreated with stages Ⅰ, Ⅱ, and Ⅲ, in the Okuda System respectively[48]. The Okuda system appears to be purely clinical, and patients staged in this system are not candidates for resection. This staging system does not stratify patients by extrahepatic or macrovascular involvement. The Cancer of the Liver Italian Program score (CLIP), proposed in 1998, combines features of the tumor (macroscopic tumor morphology, serum AFP levels, and any evidence or lack of portal vein thrombosis) with a cirrhosis index of severity to reach a prognostic score between 0 and 6[46,49]. The CLIP staging system was found to have some limitations, especially in determining rates of survival in patients planning for surgical resection with HCC[47].

The Barcelona-Clınic Liver Cancer (BCLC) staging system (Figure 2) came about from data obtained in multiple studies done by the Barcelona-Clinic Liver Cancer Group[50]. The BCLC became a standardized measure of identifying prognosis for patients with HCC[11]. The primary benefit of the BCLC system has been its ability to identify patients having early HCC that may be helped by curative therapies. It differentiates itself from other individuals having a progressive disease that may demonstrate assistance with other life-sustaining therapies. This compares to Child-Pugh (CP), which evaluates only how severe the underlying hepatic dysfunction is in cirrhotic patients. BCLC takes into account the individuals performance capability, tumor burden, the involvement of the vasculature, metastatic disease, CP stage, and evidence of portal hypertension[1].

TUMOR HISTOLOGY

Well-differentiated, clear cell and fibrolamellar tumors, and the presence of tumor encapsulation are associated with a better prognosis[51]. Some suggest the utility of using tumor grade to select patients for treatment (*e.g.*, liver transplantation), although this has not yet been accepted into practice[51]. Also, this creates another invasive procedure in the pre-transplant workup, and biopsy has the potential risk of seeding the tumor through the needle tract. There have been reports of tracking and seeding within the soft tissue, peritoneum,

and intermittent involvement of the proximal ribs many months and years after the biopsy[52].

CURRENT MANAGEMENT OF HCC

With the establishment of the MELD system, five-year survival without HCC therapy, with local tumor ablation, surgical resection and liver transplantation was 15.2%, 37.6%, 55.5% and 77.2% respectively[53]. Current management of HCC includes surgical resection/hepatectomy, liver transplantation (deceased and living), thermal or chemical ablation, chemoembolization, and medical treatment.

LOCAL REGIONAL THERAPY FOR HCC

Because of the scarcity of donor grafts, some patients with HCC may experience long waiting times, which varies based on geographical location, during which their disease may progress or recur. Local treatment has been a mainstay to slow or arrest the advancement of the disease while patients are waiting for transplantation[54]. Transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) have become prominent clinical tools of therapy[55]. TACE can be used to manage unresectable and multifocal HCC and to downstage lesions prior to liver transplantation, but not as a primary curative procedure[24]. During the progression of HCC, it exhibits extreme neo-angiogenic activity[55]. TACE uses an infusion of a cytotoxic agent deployed inside the artery followed by the embolization of blood vessels that supply the tumor. This results in a cytotoxic and ischemic effect[26]. TACE combines the delivery of chemotherapy, *via* a catheter, mixed with various agents followed by stagnation of the vasculature achieved with embolic agents. It is relatively safe. However, complications like post-embolization syndrome can affect up to 50% of patients that may induce acute liver failure, with an associated risk of post-procedure mortality[56]. Absolute contraindications to TACE include no hepatopetal flow (thrombus in the portal vein), hepatic encephalopathy, and evidence of obstruction in the biliary system. Some relative contraindications include bilirubin > 2 mg/dL, lactate dehydrogenase > 425 unit/L, aspartate aminotransferase > 100 unit/L, tumor load involving > 50% of the liver, cardiac or renal insufficiency, ascites, recent variceal bleed, or significantly low platelets[57]. RFA is the most common local ablation therapy[58]. It has been one of the best alternative therapies for patients having early HCC that cannot undergo surgical removal or transplantation. Percutaneous ethanol injection (PEI), like RFA, can be utilized as alternative therapy in small HCC for patients deemed poor surgical candidates for resection, given limited hepatic reserve. Injecting 95% ethanol into the tumor *via* a needle produces local coagulation necrosis and fibrosis, with thrombosis of tumor microvasculature and tissue ischemia[58]. Ideal applicants to undergo PEI should have a tumor with a size encompassing less than 30% of the encompassing liver. PEI shouldn't be used for individuals that demonstrate spread outside the liver, with evidence of a thrombus in the portal vein, CP class C with a prothrombin time > 40% of standardized level, thrombocytopenia of > 40000/micro/L[59]. The introduction of ethanol and RFA were found to be as efficient in lesions < 2 cm in size[60]. However, RFA has more predictable necrotic effects for all tumor sizes, with superior efficacy as compared to alcohol injection for bigger tumors[24]. Most programs use the MC as the endpoint of down-staging, and this must be maintained for at least 3-6 mo[16,61,62].

RESECTION

Hepatic resection is a possible curative therapy, considered ideal for individuals with maintained hepatic reserve[25]. Patients with single lesions and without any evidence of invasion of the vasculature can be offered resection. Individuals without any proof of cirrhosis or having preserved synthetic function with cirrhosis, standardized levels of bilirubin and the pressure gradient of < 10 mmHg in the hepatic vein (Grade Ⅱ recommendation) are potential candidates[24,63]. In addition, EASL guidelines (Table 3) also recommend platelet counts being over 100000[26,64]. Rates of continued survival without recurrence averaged 40% or better, with a five-year survival of 60%, but results up to 90% are reported for certain individuals. Perioperative mortality is low, reported as 2%-3% with less than 10% requirements for blood transfusions[26]. Current guidelines, notably AASLD and EASL, recommend RFA if patients are not suitable for surgical resection. Recent debates have argued that RFA may be a decent alternative to surgical resection with similar outcomes and side effect profiles. A total of 19 studies comparing resection to RFA were reviewed, of which three were randomized controlled trials with the rest being retrospective observational studies. The conclusion was that for small HCC (< 2 cm) RFA was a reasonable option, until further studies become available. Small HCC presents an easy access, without any significant technical limitations, with complete necrosis, including the desired safety margin, being most likely achieved. This is compared to nodules greater than 2 cm, especially if greater than 3 cm, and/or in locations where tumor ablation may not be effective or safe, surgical removal is preferred. This often correlates to subcapsular locations, making atypical resections possible[65].

Despite curative resection, recurrence remains common[66]. Recurrence develops either from the microscopic residual disease that remains after resection or from *de novo* cancer that comes about in hepatitis or cirrhosis[67]. Most often, recurrence occurs in the liver. Controversy does exist over whether resection or transplantation offer better options for individuals with a low MELD and fall within MC. This also depends on the wait time of a particular country or United Network for Organ Sharing region. In a recent study by Squires *et*

Table 3 Clinical practice guidelines for liver transplantation in hepatocellular carcinoma - European Association for the Study of the Liver and European Organization for Research and Treatment of Cancer

Guideline	Level of evidence	Strength of recommendation
Liver transplantation is considered to be the first-line treatment option for patients with single tumors less than 5 cm or ⩽ 3 nodules ⩽ 3 cm (Milan criteria) not suitable for resection Perioperative mortality and one-year mortality are expected to be approximately 3% and ⩽ 10%, respectively	2A	1A
Extension of tumor limit criteria for liver transplantation for HCC has not been established. Modest expansion of Milan Criteria applying the "up-to-seven" in patients without microvascular invasion achieves competitive outcomes, and thus this indication requires prospective validation	2B	2B
Neoadjuvant treatment can be considered for loco-regional therapies if the waiting list exceeds six months due to good cost-effectiveness data and tumor response rates, even though impact on long-term outcome is uncertain	2D	2B
Down-staging policies for HCCs exceeding conventional criteria cannot be recommended and should be explored in the context of prospective studies aimed at survival and disease progression end-points Assessment of downstaging should follow modified RECIST criteria	2D	2C
Living donor liver transplantation is an alternative option in patients with a waiting list exceeding six to seven months, and offers a suitable setting to explore extended indications within research programs	2A	2B

Adapted from the EASL-EORTC clinical practice guidelines: Management of hepatocellular carcinoma. *J Hepatol* 2012; 56: 908. The level of evidence and strength of recommendation are based on the National Cancer Institute classification and GRADE system, respectively. HCC: Hepatocellular carcinoma; RECIST: Response Evaluation Criteria In Solid Tumors.

al[68], they looked at 257 patients, of which 131 individuals had transplant compared to 126 that underwent resection. MC was met in all transplant patients, and only in 45 (36%) patients who had a resection. Follow up median was 30 mo, and the average time waiting for transplantation was 55 d, without having any individuals being dropped from the list while waiting.

Individuals within MC demonstrated greater five-year comprehensive survival (65.7% *vs* 43.8%; $P = 0.005$) and RFA (85.3% *vs* 22.7%; $P < 0.001$) compared to resection. Individuals having hepatitis C, with transplant, ($n = 87$) showed significant improvement in 5-year results as correlated with individuals within Milan have undergone resection ($n = 21$; OS: 63.5% *vs* 23.3%; $P = 0.001$; RFS: 83.5% *vs* 23.7%; $P < 0.001$)[68]. In this study, they showed that transplant not only increased longevity from recurrence but improved five-year survival, illustrated as well for subjects having preserved synthetic function or low MELD.

Salvage liver transplantation is postulated as a possible option in the reappearance of HCC after surgical resection. It is promising in that it could relieve the burden of increasing waiting times for listed patients as well as limited organ resources, but it still has not been thoroughly evaluated. Recently, in a study by Hu *et al*[69], they retrospectively monitored outcomes and factors that influenced the survival of 53 individuals that underwent salvage liver transplantation from 2004-2012 in a single center Zhejiang University in China. Patients that had salvage liver transplantation were found inside MC, Hangzhou criteria (Table 2) or outside both Milan and Hangzhou criteria. Results showed that individuals not within Milan but inside Hangzhou criteria showed one and three-year rates of survival of 70.1% and 70.1%, comparable to patients inside MC. Tumor-free survival was also similar[69].

LIVER TRANSPLANTATION FOR HCC

Current reports that came out of the Organ Procurement and Transplantation Networks (OPTN) and European Liver Transplant Registry revealed HCC being the cause of 17.2% of liver transplantation for the United States[70]. HCC was initially a primary reason for transplantation. It was believed that this would get rid of the tumor and provide a cure for the primary liver disease[71]. However, it came to fruition that the amount of tumor load correlated with the success of transplantation; patients who had diffuse disease did not have favorable outcomes, whereas individuals that had minimal tumor quantity may have the opportunity for a cure. Selection of patients was a source of constant debate, given a worldwide organ shortage, controlling the amount of tumor present during the time till transplant, exploring live donors, and different immunosuppressive or supplementary therapy[71]. During this period, it was found that patients who had incidental lesions found in their explants postoperatively had similar outcomes to patients who had a nonmalignant disease. Individuals identified with minimal tumor load from HCC during surgery that was not seen through imaging because of the small size had excellent results similar to patients without malignant disease[72]. The size of less than 5 cm was the cutoff. As stated earlier, Mazzaferro's study established the MC, creating guidelines for selecting patients to undergo transplantation for HCC[4]. An agreement among guidelines is that transplantation has become the best option to treat cirrhotic's in Child's class B that may or may not having portal hypertension, being within Milan. Surgical resection still is an accepted initial therapy in early HCC with maintained hepatic reserve[26]. Individuals require a detailed review to evaluate the size and amount of tumors and to exclude any involvement outside

Table 4 Organ Procurement and Transplantation Networks classification system for nodules seen on images of cirrhotic livers

OPTN class 0	
Incomplete or technically inadequate study	Repeat study required for adequate assessment; automatic priority MELD points cannot be assigned on basis of an imaging study categorized as OPTN class 0
OPTN class 5	
Meets radiologic criteria for HCC	May qualify for automatic exception, depending on stage
Class 5A: ⩾ 1 cm and < 2 cm measured on late arterial or portal venous phase images	Increased contrast enhancement in late hepatic arterial phase AND washout during later phases of contrast enhancement AND peripheral rim enhancement (capsule or pseudocapsule)
Class 5A-g: Same size as OPTN class 5A HCC	Increased contrast enhancement in late hepatic arterial phase AND growth by 50% or more documented on serial CT or MR images obtained ⩽ 6 mo apart
Class 5B: Maximum diameter ⩾ 2 cm and ⩽ 5 cm	Increased contrast enhancement in late hepatic arterial phase AND either washout during later contrast phases OR peripheral rim enhancement (capsule or pseudocapsule) OR growth by 50% or more documented on serial CT or MR images obtained ⩽ 6 mo apart (OPTN class 5B-g)
Class 5T: Prior regional treatment for HCC	Describes any residual lesion or perfusion defect at site of prior UNOS class 5 lesion
Class 5X: Maximum diameter ⩾ 5 cm	Increased contrast enhancement in late hepatic arterial phase AND either washout during later contrast phases OR peripheral rim enhancement (capsule or pseudocapsule)

Adpated from Wald *et al*[30]. HCC: Hepatocellular carcinoma; OPTN: Organ Procurement and Transplantation Networks; MELD: Model for End stage Liver Disease; CT: Computed tomography; MR: Magnetic resonance; UNOS: United Network for Organ Sharing.

the liver with or without vascular spread (*i.e.*, Tumor thrombus in the hepatic or portal system). If a nodule is found with CT or MRI in a patient with cirrhosis, based on OPTN, it should have an organization of LI-RADS nodules[70].

Individuals with HCC have minimal use from the MELD criteria, as minimal liver dysfunction was often concurrently present and did not progress until later in their disease course. This was in comparison to individuals with hepatic dysfunction from other etiologies, presenting with worsening hepatic dysfunction at the time of diagnosis. HCC individuals are often on the waiting list for some time, having a range of 104 to 387 d, with a wide overall fluctuating timeline[73]. These individuals may also be dropped from the list for numerous reasons including: Tumor progression beyond MC, metastatic disease, vascular invasion, progression of their liver disease or complications (infection, renal failure), or non-tumor related contraindications (*i.e.*, alcohol relapse). Therefore in 2002, the idea of the MELD exception points was created. Now, individuals that have ALTSG stage T2 HCC (which is a primary HCC lesion within 2 and 5 cm, with at most three lesions all no greater than 3 cm) will be assigned a higher priority MELD score[74]. They are awarded 22 MELD points because their 3-mo mortality approximates patients with liver failure and a score of 22. Patients receive an increase by 10% every three months, only if their disease remains within MC. Patients having T1 HCC (an isolated lesion < 2 cm) had been formerly allocated additional MELD points, but this practice was abandoned after a further study showed excellent 3-mo survival with such small lesions[75]. With the allocation points for HCC, the individuals receiving MELD exception was escalated from 10.5% in 2002 to 15.5% in 2008. The guidelines to help classify HCC in the UNOS/OPTN system (Table 4)[30] was developed to help continue MELD exception point allocation for individuals having HCC that was capable of being diagnosed without doubt, through imaging. The OPTN class 5 nodules correlate with definite imaging interpretation for HCC. Class 5B and 5T nodules can also account for continuous allocation for a greater MELD score of 22.

Class 5B and 5T nodules can also account for continuous allocation for a greater MELD score of 22.

A Mayo Clinic trial compared a new approach for allocating organs and looked at pre and post-MELD time span. There was statistical significance favoring improved principles including: The time span until liver transplant (LT) - 2.28 years *vs* 0.69 years ($P < 0.001$), individuals transplanted 0.439 transplant/person-years *vs* 1.454 transplant/person-years ($P < 0.001$), waiting list survival after five months of 90.3% *vs* 95.7% ($P < 0.001$) with the rate of falling off the list in five months, of 16.5% *vs* 8.5% ($P < 0.001$)[75]. These findings illustrated that this novel incorporation criterion improved in increasing rates of the incidence of Deceased Donor Liver Transplant (DDLT) for HCC individuals. Also, five-month rates to fall off the list greatly diminished, with increased survival rates in this time span, while noted to be waiting during the post-MELD period[76]. These findings indicated these novel MELD allocation criterion showed definite benefit to candidates with HCC for transplantation.

RECURRENCE POST TRANSPLANTATION

The recurrence of HCC, post-transplant, remains a clinically relevant problem. Based on the literature in the post-transplant period, HCC recurrence uniformly occurs with an incidence of 10%-20%[18]. Recurrence post-transplant typically occurs within the first two years. Repeated transplantation has not been encouraged due to diminished rates of survival and lack of organs, with the average survival rate lower than one year[77]. In a study where 60 LT recipients were evaluated, the overall median survival measured post reappearance was roughly ten and a half months (ranging from one-136), with primarily delayed recurrence as well as being eligible to undergo resection were felt to correlate in a positive

manner with overall survival[19]. Another meta-analysis, by Chen *et al*[9] studied 1198 patients and showed that the presence of involvement into the vasculature, tumor diameter > 5 cm, tumor status beyond Milan, and poor differentiation were felt as prominent variables for the risk for recurrence of HCC[31]. The gross features of HCC, including the size and total amount of the lesion, both variables part of Milan, are identified as the greatest predictors of results. The entire tumor size, defined as the total of all tumor diameters, was found to correlate with a fourfold increase in tumor recurrence if greater than 10 cm[30]. Despite this, there is currently no precise formula to predict recurrence accurately. In the post-transplant period, roughly 10% to 15% of individuals with HCC inside Milan, undergo recurrence[78]. Further evidence suggests that independent variables beyond the size of the tumor and total number of tumors may be linked to a more aggressive tumor biology, resulting in an increased chance of HCC recurrence post-transplant[39,79].

The diagnostic accuracy of MRI and CT has shown to be in the range of 45%-60% and for cases with lesions under stage, noted for 21%-43%[36]. This is likely because the relationship comparing imaging criterion and histopathology for cirrhotic hepatic explants needs further investigation. Also, the sensitivity of different multidetector-row CT for HCC less than 1 cm is not as sensitive[22].

Recent studies have tried to find characteristics to predict better tumor recurrence including tumor markers, inflammatory markers, tumor histology, explant pathology. Because of the risk of recurrence, some have been intimidated to expand the current criteria used in guidelines to list patients with HCC. Nevertheless, it is an avenue that needs to be investigated.

EXPANSION OF CRITERIA FOR LIVER TRANSPLANTATION FOR HCC

Although undergoing transplantation provides positive outcomes, when it comes to HCC, the limited number of viable organs restricts the number of patients getting transplanted. Allocation guidelines will have to incorporate that individuals with HCC may come off the waitlist as their tumor progresses while also taking into account the patients that have inherent liver disease waiting for transplantation[80]. Irrespective of the reason for transplantation, the purpose is to provide individuals with the utmost benefit despite the limitations of resources from deceased and living donors, in an impartial, ethical, and fiscal manner. The initial studies of the MC determined that the earlier stages of HCC yielded significant benefit from transplantation. The latter stages, in whom transplantation could potentially offer some benefit, are not included, and this has created open forums about the potential necessity to expand the criteria, to incorporate more patients[26].

In 2001, Yao *et al*[81] studied 70 subjects that had expanded guidelines for HCC and liver transplantation. Their results showed that when having these certain observed criteria [isolated tumor size, 1 lesion < 6.5 cm, or < 3 nodules with the biggest lesion diameter < 4.5 cm and the entire tumor burden diameter < 8 cm] survival rate were 90% and 75.2%, at 1 and 5 years, respectively, after orthotopic liver transplantation (OLT) *vs* 50% 1-year survival when individuals were outside these guidelines ($P = 0.0005$)[81]. This widely used UCSF criteria showed that modest expansion showed similar results to MC and, therefore, allowed a greater number of patients with HCC the opportunity for transplantation.

In 2006 Decaens *et al*[82] suggested expanding the criteria to incorporate the characteristics of the lesion within the explanted liver. This study was a large independent series testing the utility of the suggested criteria for pre-transplant evaluation. Four hundred and seventy nine patients were listed, between 1985 and 1998, and 467 underwent LT for HCC. Individuals were categorized into both the Milan and UCSF categories, according to pre or post-transplantation tumor characteristics, with imaging at the time listed and the time of liver transplant, respectively. The survival rates for five years were measured utilizing Kaplan-Meiers method in comparison to the log-rank test. Pre-transplant UCSF guidelines were measured by the principle for the intention-to-treat. With these criteria, 279 subjects were categorized within Milan, 44 outside Milan while within UCSF (this being the subgroup that could benefit from expanding criteria), and 145 subjects were outside both Milan and UCSF.

Given the minimal time frame of four months, the 5-year survival was 60.1%, 45.6%, and 34.7%, respectively ($P = 0.001$). Survival rates were mathematically decreased for the group within UCSF but outside Milan, in comparison with patients within Milan. However, it was noted that the results were not significant ($P = 0.10$). Five-year survival was 70.4%, 63.6%, and 34.1%, for subjects within Milan ($n = 184$), within UCSF but outside Milan ($n = 39$), as well as individuals both outside UCSF and Milan ($n = 238$), correspondingly ($P = 0.001$). Results for five-year survival showed no difference when comparing individuals inside Milan and those inside UCSF but not within Milan ($P = 0.33$). This data was extrapolated for pre-transplant assessment and demonstrated that the UCSF guidelines correlate to a 5-year survival below 50%[72,82].

CHALLENGING THE MC

To some, the MC seem too constrained, and various clinical studies have challenged their limits with suggestions of new parameters to select patients[76].

Even with these findings, the AASLD guidelines do not suggest expanding the current transplant criteria past the MC[24]. The EASL guidelines state that the HCC limit extension guidelines are currently not identified. The broadening of MC, utilizing "up-to-seven" in individuals with no evidence of microvascular invasion, has noted favorable outcomes and requires further prospective

confirmation[26]. Individuals that will be transplanted while in Milan have 5-year survival rates of 70% or greater, as compared to other congregations that demonstrated 5-year survival rates being approximately 50% when undergoing transplantation in expanded criteria[41,72]. The survival rate is arguably the lowest that is accepted, but given the minimal amount of available organs, extending criteria is still an ongoing debate[83]. Therefore, many patients who have a possibility of doing well post-transplant are not viable candidates at most transplant centers. Because of this, different expansion criteria have been proposed with varying degree of success (Table 3).

The Metroticket project was introduced at the International Liver Transplant Society meeting in 2005 as a Web-based survey in an attempt to gather an appropriate amount of subjects to aid with robust statistical analysis[84,85]. The project collected data from more than 1000 individuals outside of MC that underwent transplantation. The result of the project is the Metroticket calculator, which can be used to predict 5-year survival based on a patient's tumor characteristics (size of the total nodules, length of the largest nodules, and involvement into the vasculature if available)[76,86]. The Metroticket predicts survival beyond the MC, the upper limit of liver transplantation being the "rule of 7" where the length of the biggest nodule and the total amount of nodules cannot exceed 7[72]. In a study by Lei *et al*[84], they found that he was able to calculate the rates of survival in 230 situations, by utilizing the Metroticket model. The three- and five-year survivals are 64.7% and 56.2% respectively, and what had been seen was 71.3% and 57.8%, respectively. However, the predicted five-year rate of survival was 43.5%, with observations being only 8.7%, implying that validity for HCC with macro-invasion may need to be revised[84].

LIVING DONOR LIVER TRANSPLANT FOR HCC

With current listing guidelines of HCC, only a limited number of patients can qualify to be placed on LT lists. The demand for donor livers has continued to grow over the last two decades, and this has placed greater weight on the need for efficient and effective means of increasing the supply. Over the last few years, while having the ability to perform living donor liver transplantation (LDLT), various institutions thought to broaden their guidelines[87]. At this time, the use of LDLT makes up roughly fewer than 5% of adult LTs, disproportionately lower when compared to renal transplantation, which has similar donors comprising 40% of the population[26]. In Asian countries, the majority of liver transplantations for HCC patients are LDLT, and these account for 96% of liver transplantation for HCC[88-90].

The current benefits of LDLT are an intensive donor evaluation, time available for optimization before transplantation, as well as a nominal time for cold ischemia[91-93]. There is also a reduction in the mortality for recipients in comparison with deceased donors[91]. Some ethical issues have arisen with LDLT with respect to overall well-being of the donor as well as possible monetary exchange for organs[93]. People who oppose LDLT state it is not acceptable to bring healthy donors into such long-term risk for disability or even mortality. Currently it is estimated that right hepatic lobe transplantation mortality is approximately 0.5%[91]. Another important issue regarding a variable that influences the recurrence of HCC following LDLT is the procedure itself. This may represent more risk when measured with DDLT. A large multicenter cohort trial from Japan and Korea demonstrated that when applying MC and UCSF guidelines for LDLT there were equivalent long-term outcomes when compared to DDLT, but some authors recently illustrated a greater incidence of recurrence of HCC in LDLT in comparison to DDLT[89]. Six studies compared DDLT and LDLT for HCC, and there was no any conclusive data demonstrating a difference in outcome between the grafts. There was a greater risk of HCC recurring in patients that were fast-tracked, as LDLT may lengthen the time from the diagnosis until the transplant. This would not allow the necessary time for the tumor to behave biologically and materialize[71]. In 2010, the consensus conference recommended that individuals that had HCC, who opted to have LDLT, may benefit from the consideration of a 3 month observation period prior to transplant because of this finding[71]. LDLT remains another promising, yet controversial option for patients with HCC, who face increased mortality waiting for transplantation.

MEDICAL TREATMENT

The pathophysiologic complexity of HCC has made medical treatment of HCC challenging. It has been difficult to provide adequate tumor therapy but at the same time maintaining liver function.

Sorafenib, which is an oral tyrosine kinase inhibitor, was the original therapy that demonstrated any improvement in mortality for progressive HCC[94-96]. It is recommended as initial treatment for individuals with the maintained hepatic reserve but cannot attain advantages from surgical removal, transplantation, ablation or TACE (grade- Ⅰ recommendation)[24]. Sorafenib is still shown to be the exclusive treatment that has shown any mortality benefit in this category. Tamoxifen, anti-androgens, octreotide or herbal drugs are not recommended.

The sorafenib HCC Assessment Randomized Protocol trial illustrated safety and mortality benefit in individuals that have progressive HCC. This randomized study of 602 patients, with maintained hepatic reserve (> 95% CP A) were on a continuous regimen of Sorafenib 400mg twice-daily, or a placebo[96]. If patients did not respond or had deleterious effects to Sorafenib, there was no second line agent available[26].

More recently, there have been further studies using sorafenib as neoadjuvant therapy or as bridging therapy prior to LT[96]. Some preclude that sorafenib may also have a role in preventing tumor relapse[97]. The studies in

the last three years have been small ranging from 1-39 patients but do provide some optimism that sorafenib may have a role in decreasing tumor recurrence post transplantation[98].

In the recent sorafenib as Adjuvant Treatment in the Prevention of Recurrence of Hepatocellular Carcinoma trial, effectiveness and safety with supplementary sorafenib was tested. Eligibility criteria included individuals that underwent local ablative therapy or resection surgically, with the intention of a cure but developed a significant risk of recurrence[99]. The main criteria for inclusion included: CP score between five and seven, ECOG PS 0, with the lack of any redevelopment measured by CT or MRI. The study's criteria of exclusion was made up of ascites, the redevelopment of HCC, any spread outside the liver or involvement of major vasculature, and any prior major systemic HCC therapy. Individuals were separated by curative treatment, geographical location, risk of recurring, and their CP score. They were arbitrarily assigned in an equal distribution, consisting of two therapeutic arms: Sorafenib 400 mg twice daily or placebo therapy, for a length of at most four years. The main endpoint included survival without recurrence of HCC documented by an independent reviewer. Secondary goals were the timeframe until HCC recurred and the overall survival[100].

In this randomized study, 1114 patients were included (556 received Sorafenib and 558 were randomized to placebo). There was no noted variation in survival free recurrence, time to recurrence and overall survival benefit. There was a shorter median therapy time for sorafenib (12.5 mo *vs* 22.2 mo) and smaller average daily doses (578 mg *vs* 778 mg). The rates for cutting short sorafenib treatment were much higher due to adverse effects (24% *vs* 7%) and withdrawal of consent (17% *vs* 6%). Unfortunately, their primary endpoint was not met. Initial smaller studies do suggest that further extensive studies need to investigate the possibility of supplementary treatment with sorafenib for HCC.

IMMUNOSUPPRESSION POST TRANSPLANT: MTOR INHIBITORS

Mammalian target of rapamycin (mTOR) inhibitors have significant roles with monitoring cell growth, propagation, and continuation through cytoplasmic serine/threonine kinase. These inhibitors might play a part in targeting cancer cells. Overexpression using mTOR has been identified within 15% to 41% of HCC, and their inhibitors have demonstrated properties on cancer cells of HCC as well as animal models[101].

Sirolimus has also been proposed as a better option in individuals with HCC because of its antiproliferative activity[102]. In many transplant centers, sirolimus has been used as monotherapy or in adjunct, for patients who have had adverse effects of calcineurin inhibitors[103]. Also, for patients who have developed non-hepatic malignancies post transplant, some LT centers have switched patients to sirolimus, again, because of its anti-angiogenic properties[102,104].

The ongoing phase 3 SILVER study (Immunosuppression in Patients Undergoing Liver Transplantation for Hepatocellular Carcinoma) could demonstrate the effect immunosuppression with sirolimus will have with HCC reappearance after undergoing transplantation for this primary hepatic malignancy (Clinical Trials government identifier NCT00355862). The data obtained should provide greater certainty when inquiring about situations with mTOR inhibitor/SFN combinations[83]. There is an obvious risk of cancer recurrence with immunosuppression post transplantation, including the recurrence of HCC. It is postulated that HCC patients would benefit from personalized regimens after transplantation[105]. Even after identifying the potential benefits of mTOR inhibitors on HCC, the studies done are not prospective and are uncontrolled. A large prospective, case-controlled data analysis demonstrated a significant improvement in survival with sirolimus than tacrolimus. In a retrospective, systematic review study by Cholongitas *et al*[101], they looked at 3666 HCC liver transplanted patients in around 42 clinical studies from January 2007 to October 2013. Their results showed patients on calcineurin inhibitors (CNIs) had higher rates of redeveloping HCC, as compared to individuals undergoing therapy with mTORi (448/3227 or 13.8% *vs* 35/439 or 8%, $P < 0.001$). CNI therapy had greater recurrence for HCC in Milan (74% *vs* 69%) with fewer episodes through involvement micro vascularly, in comparison with mTORi therapy treatment (22% *vs* 44%) ($P < 0.05$). It was noted that everolimus treatment demonstrated quite an improvement for HCC recurrence, when compared to sirolimus and CNIs (4.1% *vs* 10.5% *vs* 13.8%, correspondingly, $P < 0.05$)[101].

Few initial studies have shown induction of partial remission or stability with sirolimus in advanced HCC[101]. Further studies are needed to evaluate the promising role of mTOR inhibitors and HCC, with a recent ongoing trial looking at this very data post transplant[106].

Post-transplant, side effects of sirolimus include thrombosis of the hepatic artery, delayed wound healing, incisional hernias, hyperlipidemia, bone marrow suppression, mouth ulcers, skin rashes, albuminuria, and pneumonitis, among others[102,107]. These risks are difficult to quantify because the incidence (and even the presence) of side effects varies widely by reporting. Because of the side effect profile of sirolimus and everolimus, specifically hepatic artery thrombosis, it is recommended that mTOR inhibitors not be used in the initial three months after transplantation[103,108].

CONCLUSION

HCC has become a significant burden globally, contributing to major morbidity and mortality. Since the 1980's, the number of cases domestically has been increasing. Undergoing transplantation offers excellent

results, and the MC provides guidelines for patients who should undergo transplant evaluation[24]. Many patients who may have potentially positive outcomes after transplant are often excluded, leaving them with dismal treatment options. Recent discussions have involved expansion to the guidelines to include greater tumor size, tumor quantity, and incorporating tumor markers and histology in the listing criteria. Also, with the addition of chemotherapy, changes in immunosuppression regimens, increasing the use of living donors and salvage transplantation post resection, the data looks promising, with comparable survival rates. These findings may support future studies investigating these possibilities, with goals of improving mortality for individuals with HCC.

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