

# Liver transplantation for hepatocellular carcinoma: outcomes and treatment options for recurrence

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## Abstract

Overall survival and recurrence rates after liver transplantation (LT) for hepatocellular carcinoma (HCC) vary, however observational data support the notion that patients with HCC have an overall worse long-term prognosis after LT compared to patients transplanted without HCC. Patient selection for LT in patients with HCC fluctuated as changes in the model for end-stage liver disease score was adjusted from 2002 to 2005. In the last decade, management of HCC patients on the waiting list has varied based on center experience. Since HCC patients have better access to the donor pool compared to non-HCC patients as evidenced by their lower dropout rate from the waiting list, living donation has been implemented in certain centers. Overall patient survival, recurrence free survival, and recurrence rates have been compared between living donor LT (LDLT) and deceased donor LT, with one meta-analysis reporting a lower disease free survival in LDLT, however overall patient survival and recurrence rates showed no difference at 1, 3 and 5 years. In patients exhibiting HCC recurrence, different modalities regarding immunosuppression and therapies have been evaluated. Currently there are no consensus treatment strategies regarding post-transplant HCC recurrence in patients not suitable for locoregional therapy, hence consideration of a mammalian target of rapamycin inhibitors with the addition of sorafenib might be a feasible option with close monitoring in clinical practice despite the notable toxicities.

**Keywords** Cirrhosis, deceased-donor, liver cancer, living-donor, mTOR, sirolimus, sorafenib

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## Introduction

Hepatocellular carcinoma (HCC) is a major health concern worldwide, resulting from chronic liver injury and inflammation due to viral, non-viral and genetic etiologies. HCC has been found to be the second [1] or third [2] leading cause of cancer-related death worldwide, with the majority of cases occurring in the setting of cirrhosis [3]. As the epidemic of nonalcoholic fatty liver disease (NAFLD) and chronic hepatitis C virus continues to increase in the United States [2], HCC rates will rise accordingly. Prior to the model for end-stage liver disease (MELD) and HCC exception allocation system, patients with HCC remained on the waiting list longer than candidates without HCC, resulting in fewer than 5% of liver transplantation (LT) being performed for HCC. However, once MELD and HCC exceptions were adopted at the national

level, the number of overall transplant recipients steadily increased from nearly 5,000 patients in 2002, to 6,069 patients in 2008, while HCC patients receiving LT steadily rose (from nearly 1,000 in 2002 to 1,656 in 2008), representing over 21% of liver transplants [4] (Fig. 1).

In February 2002, patients with HCC were given transplant exception MELD scores at higher values for both T1 and T2 lesions, based on a 3-month mortality estimate in comparison to disease progression that would preclude LT [5]. Later, follow-up data indicated that these exception scores were too liberal for HCC, hence adjustments in the MELD exception prioritization scheme changed over time [6] (Table 1). In particular, half of the patients with T1 tumor criteria (one single lesion <2 cm) were discovered not to have HCC in the explanted liver [7]. As a result, HCC patients with T1 tumors do not receive MELD exception points for HCC. However, patients within T2 criteria (1 lesion  $\leq$ 5 cm or two or three lesions  $\geq$ 1 cm but  $\leq$ 3 cm in size) received 22 MELD exception points. In addition, patients receive additional MELD exception points every 90 days representing a 10% increase in mortality [6]. To receive these exception points, patients must be restaged every 90 days with cross-sectional imaging of the abdomen and chest to ensure that these criteria continue to be met.

Prior to 1996, restrictions on LT for HCC were more liberal, which resulted in 5-year overall survivals (OS) up to 50%. During that same year, Mazzaferro and colleagues introduced

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Conflict of Interest: None

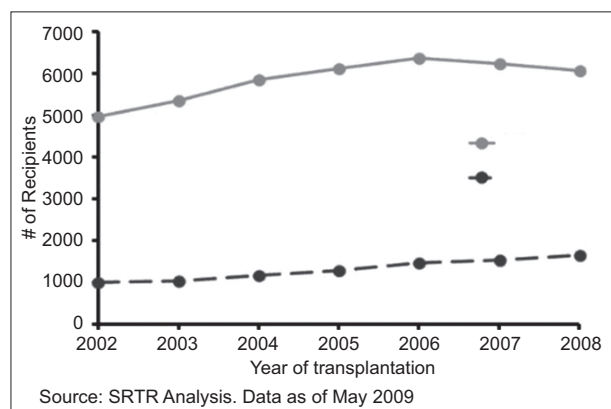
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**Table 1** Changes in the MELD prioritization exception scores for HCC over time using initial 3 month mortality risk estimates

	Original	February 2003	April 2004	March 2005
Stage I				
1 tumor <2 cm	15% risk=MELD 24	8% risk=MELD 20	0 risk=MELD calculated	0 risk=MELD calculated
Stage II				
1 tumor 2-5 cm or 2-3 tumors largest <3 cm	30% risk=MELD 29	15% risk=MELD 24	15% risk=MELD 24	15% risk=MELD 22

MELD, model for end-stage liver disease; HCC, hepatocellular carcinoma



**Figure 1** The solid line represents the total amount of liver transplant recipients from 2002-2008 (all etiologies except hepatocellular carcinoma [HCC]), in comparison to HCC liver recipients from the same era (dashed line)

the Milan criteria (any solitary HCC ≤5 cm, or up to three lesions ≤3 cm each, without vascular invasion or metastasis) which resulted in 5-year transplant survival near 70%, with recurrence seen in less than 10% [8]. The importance of these independent prognostic factors matches post-transplant survival outcomes for most other liver transplant indications. Hence, a recent international consensus conference recommended using the Milan criteria as the benchmark for selecting HCC patients for LT, and when making comparisons to other suggested expansion criteria [9].

Patients that fall outside the Milan criteria have the potential to have ablative techniques to downsize large tumors in order to fall into the exception range for LT. This downstaging technique is an area of ongoing research, however, with the continued organ shortage, decisions regarding transplantation need to be considered with respect to the benefits regarding potential HCC patients, and balanced with the consequences for all potential liver recipients on the waiting list. This resulted in many attempts to expand the Milan criteria as it was considered too conservative, however, only the University of California San Francisco (UCSF) criteria (one tumor ≤6.5 cm, or three nodules with the largest ≤4.5 cm, and a total tumor diameter of ≤8 cm) have demonstrated comparable outcome data in its prospectively validated design [10,11].

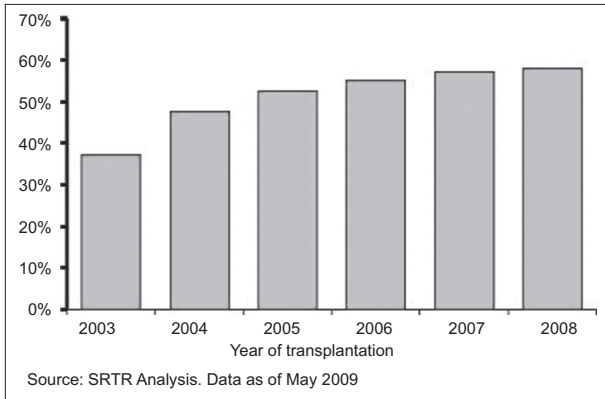
As the donor pool has stayed relatively fixed in size over the years [12], increasing the MELD exception scores for HCC patients may deprive other candidates without HCC from a potential LT depending on regional variations. Although expansion of the Milan criteria has shown good outcomes in

select individuals [10,13], it should be left up to the individual regions to come to an agreement regarding any proposal change on expanding the current Milan criteria. Caution should be taken when expanding tumor criteria as HCC recurrence post-LT is a continuum as described by the “metro-ticket” analogy [14]. The further distance you travel underground, you pay a higher ticket premium, which is analogous to the larger the HCC tumor, the higher price you pay for HCC recurrence post-LT. While the national MELD exception criteria are followed in most regions, some regions, namely region 4 and 5 have expanded their criteria slightly. Region 5 utilizes the UCSF criteria and region 4 uses locally derived staging criteria (one lesion ≤6 cm or up to three lesions [none larger than 5 cm] with a total tumor size of <9 cm) [13]. This review will discuss current concepts regarding LT in the HCC patient population.

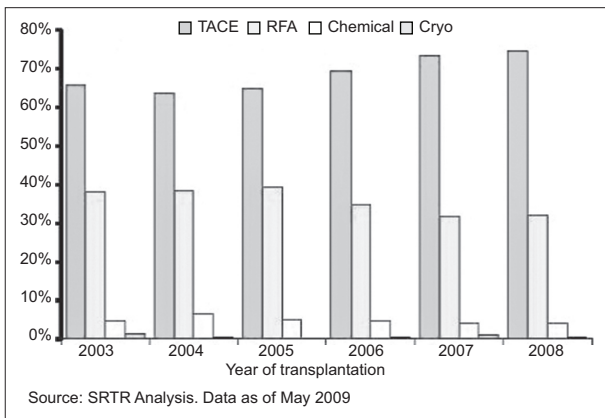
**Management and outcomes of patients with HCC on the liver transplant waiting list**

Patients with a diagnosis of HCC that are within the Milan criteria, and are expected to be on the waiting list for more than a few months, are considered for locoregional treatments [radiofrequency ablation (RFA) and transarterial chemoembolization (TACE)] [15,16]. According to the most recent national dataset, locoregional therapies are being used more frequently in patients who received a LT (Fig. 2), albeit through a regional review board, since different regions vary widely on their acceptance of such patients for transplant, while the current system does not allow patients outside Milan criteria who undergo downstaging to receive HCC exception points. As of 2008, use of TACE therapies have seen a steady rise in that nearly 75% of patients underwent this type of treatment prior to receiving a LT, as compared to a slight decline to nearly one-third of individuals having RFA therapy prior to LT (Fig. 3). Depending on the transplant centers experience, size and location of the tumor(s), patients may benefit from locoregional procedures in the hopes of preventing progression beyond the Milan criteria, thereby maintaining their priority on the liver transplant waiting list [17,18].

Although the absolute benefit in preventing waitlist dropout rates with locoregional treatment is lacking, both patient survival (79% vs. 75%, P=0.03) and graft survival (76% vs. 71%, P=0.03) at 3 years after LT has shown more benefit for HCC patients receiving ablative therapy compared to those not receiving locoregional treatment [7]. However, the authors also demonstrated the adjusted patient survival at 1 year (85% vs.

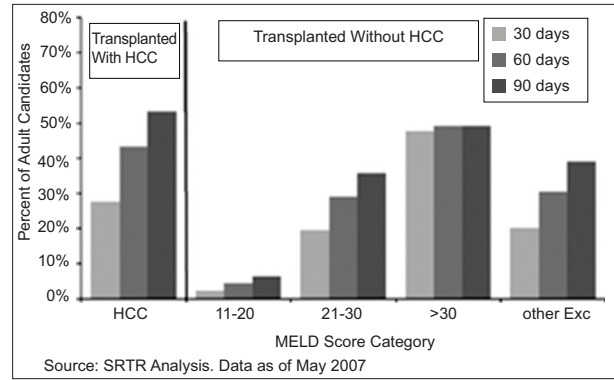


**Figure 2** The proportion of hepatocellular carcinoma liver recipients that received any pre-transplant locoregional therapy by year of transplant from 2003-2008

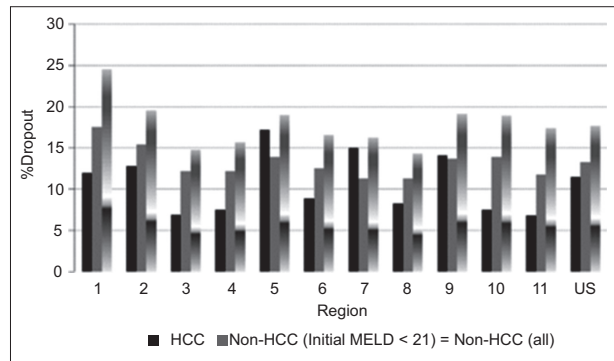


**Figure 3** The comparison of different non-surgical treatment modalities utilizing locoregional therapy from 2003-2008, prior to liver transplantation. The majority of treatment modalities remain steady over the years with the majority using transcatheter arterial chemoembolization (TACE) as a bridge to liver transplantation, followed by radiofrequency ablation (RFA) Cryo, cryotherapy

88%,  $P=0.003$ ) and 3 years (74% vs. 81%,  $P<0.001$ ) after LT were significantly worse in patients with HCC compared to those without HCC respectively. These therapies do not impact the actuarial wait time on the LT waiting list, however, it has been shown that patients with HCC tend to have shorter wait times with regards to non-HCC patients with comparison MELD scores of 21-30 points at 1, 2, and 3 month intervals (Fig. 4). In turn, those with HCC have less dropout or death rates in comparison to patients without HCC that have MELD scores of  $\leq 30$  [7]. Furthermore, a detailed analysis demonstrated that once a patient is diagnosed with HCC, lower dropout rates are seen within the first year across all UNOS regions in these patients compared to non-HCC patients (Fig. 5) [19]. As HCC patients receive locoregional therapy in most cases, the potential to arrest tumor growth without impacting their position on the waiting list is seen as a major advantage. In fact, even if the HCC tumor is successfully ablated and the patient has no residual disease, patients are still eligible for



**Figure 4** Waiting list candidates with or without hepatocellular carcinoma (HCC) who underwent liver transplantation within 1, 2 and 3 months are stratified by model for end stage liver disease (MELD) at a snapshot in time (January 1, 2006). A higher percentage of patients were transplanted with HCC within 3 months of listing compared to non-HCC patients even while exhibiting high MELD scores, or if the etiology of liver disease met other exception (EXc) criteria



**Figure 5** The percent dropout of eligible liver transplant recipients within 12 months of listing for hepatocellular carcinoma (HCC) and non-HCC patients according to region. Reprinted with permission from John Wiley and Sons MELD, model for end-stage liver disease

tumor exception point upgrades every 3 months, resulting in an increase in LT priority compared to non-HCC patients. It has been suggested that an HCC priority score be implemented to allow for similar dropout and LT rates for both HCC and non-HCC patients, with the hopes of allowing equal access to LT and similar post-transplant outcomes [19].

The long waiting time (>2 years) for HCC in some regions in the US, namely region 5, has led to an instructive “experiment of nature.” As larger cohorts of patients with HCC have been followed after locoregional therapy for longer periods of time, there is a subset of patients who seem to progress very slowly with regard to HCC. Such patients are typically characterized by slow or no increase in tumor size for years after locoregional therapy. Since most of these patients have excellent hepatic function, their urgency for transplant is not apparent. As a result, there is a movement to allow such patients to continue to receive increased MELD score increments every 90 days, but to inactivate them when their MELD score is sufficiently high to actually receive a transplant. In doing so, patients with no or

slow tumor growth would be allowed to avoid liver transplant, thereby saving them the risk of the procedure and allowing sicker patients to have access to the limited donor pool.

**Living-donor LT (LDLT) versus deceased-donor LT (DDLT)**

As the need for donor livers exceeds organ availability in most countries, LDLT has been suggested as an alternative to alleviate the organ shortage and possibly allow recipient expansion criteria in patients with HCC in comparison to DDLT [20]. The purported advantage of LDLT in HCC patients is seemingly obvious. Patients with HCC have an urgent need for transplant and the availability of a living donor would likely shorten their time to surgery, thereby preventing disease progression which might occur while waiting for a deceased donor. Previous studies have shown conflicting results with respect to recurrence rates and OS [21-25], therefore, two recent meta-analyses were completed in order to evaluate overall outcomes in LDLT versus DDLT for patients with HCC [26,27].

In one meta-analysis [27], a total of 7 studies with 1310 subjects were used to compare patient survival, recurrence free survival (RFS) and recurrence rates in patients with HCC receiving a LDLT or a DDLT. In 5 studies comparing 792 patients, 1-year survival rates (OR 1.03, 95%CI 0.62-1.73, P=0.9) were similar in LDLT vs. DDLT recipients. Three-year patient survival was reported in 7 studies with 1283 patients (OR 1.07, 95%CI 0.77-1.48, P=0.69), while 4 studies with 740 patients reported 5-year survival (OR 0.64, 95%CI 0.33-1.24, P=0.18), all of which showed no differences in overall patient survival for LDLT and DDLT recipients. In terms of RFS, the 1-year (3 studies with 796 patients; OR 0.86, 95% CI 0.54-1.38, P=0.54), 3-year (4 studies with 755 patients; OR 1.04, 95% CI 0.69-1.58, P=0.84) and 5-year (3 studies with 663 patients; OR 1.11, 95%CI 0.7-1.77, P=0.65) showed similar outcomes for LDLT and DDLT recipients. With regard to tumor recurrence rates, the 1- and 3-year recurrence rates were reported in 4 studies with 638 patients (1-year, OR 1.55, 95%CI 0.36-6.58, P=0.55; 3-year, OR 2.57, 95%CI 0.53-12.41, P=0.24), while 5-year recurrence rates were represented by 3 trials with 546 patients (OR 1.21, 95%CI 0.44-3.32, P=0.71). There were no significant differences in recurrence rates between LDLT and DDLT recipients.

In another meta-analysis [26], a total of 16 studies were used for comparison. The mean time from transplant to HCC recurrence ranged from 4.6 to 38 months, with the median time from recurrence to death ranging from 6 to 30.6 months. The disease free survival (DFS) was significantly shorter in patients receiving LDLT in 3 of 10 studies analyzed, with 3-year DFS ranging from 42-95.5% compared to 41-100% after DDLT. The overall hazard ratio (HR) was not significantly different when comparing cohort studies from eastern and western countries for DFS after LDLT vs. DDLT, however, the overall HR for DFS was 1.59 (95%CI 1.02-2.49, P=0.041) after LDLT when 8 cohort studies were combined. The HR for OS after LDLT compared with DDLT was 0.97 (95%CI 0.73-1.27, P=0.81). Therefore,

this meta-analysis suggests that DFS is worse after LDLT compared to DDLT for HCC, however reports of underlying tumor biology are limited in those undergoing a shorter wait list time observed with LDLT (Table 2). Hence, more research is needed to determine if these observed differences are truly due to underlying tumor biology or study bias. The finding that there is no apparent benefit in survival for HCC patients undergoing LDLT is somewhat surprising. The reasons for this are not entirely clear. However, one contributing factor may be that HCC patients selected for LDLT may have tumor characteristics associated with worse tumor biology than DDLT. The evidence supporting this claim is based on clinical experience as well as findings in the National Institutes of Health sponsored trial, the adult-to-adult living donor liver transplant study (A2ALL) [28]. In the report from this group, there was a trend toward LDLT recipients having worse tumor characteristics. The selection of such patients for LDLT could lead to worse outcomes. In addition, a study from the same group showed that recipients with HCC were more than two-fold likely to have their donors approved for the operation. This might suggest that the transplant team may be more likely to approve donors for HCC patients based on the pressure to perform the surgery in desperate patients.

**Risk factors for HCC recurrence: mammalian targets of rapamycin (mTORs) after LT**

HCC recurrence rates after LT are estimated to occur in up to 20% [9], and occur more frequently within the first 2 years [29,30], have limited treatment options, and result in an overall poor prognosis, with a median survival of less than 1 year [31]. These recurrence rates have been shown in post-LT patients predominantly to arise based on tumor biology including poorly differentiated tumors and macro/microvascular invasion [14,32]. Some studies have suggested that immunosuppression (IS) with an mTOR inhibitor may reduce the risk of HCC recurrence post-LT [33,34]. The use of mTOR inhibitors is one such strategy used for both IS and

**Table 2** Summary of 1-, 3-, and 5-year outcomes based on meta-analysis in patients with HCC receiving LDLT or DDLT and sirolimus-based immunosuppression

	LDLT	DDLT	SRL-IS	SRL-free IS
Patient (overall) survival	No difference	No difference	Increased	Decreased
Recurrence/disease free survival	3-year significantly decreased to no difference	No difference	Increased	Decreased
Tumor recurrence rates	No difference	No difference	Decreased	Increased

*LDLT, living-donor liver transplantation; DDLT, deceased-donor liver transplantation; SRL, sirolimus; IS, immunosuppression; HCC, hepatocellular carcinoma*

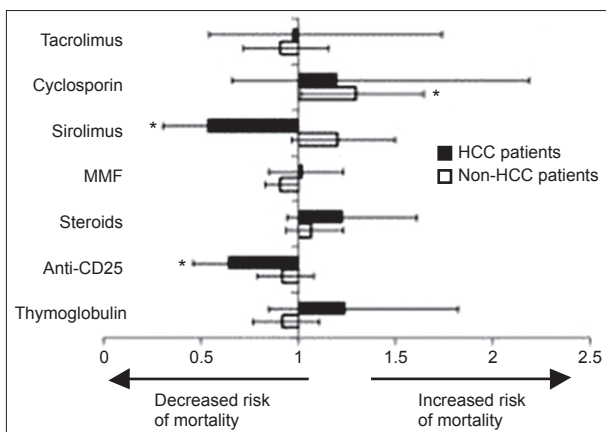
anti-proliferative/anti-angiogenic properties that inhibits cell growth and survival [35-37]. The reluctance to use mTOR in the early post-transplant setting could be due to poor wound healing and/or hepatic artery thrombosis [38]. In fact, sirolimus (SRL), the most widely prescribed mTOR inhibitor in LT has received two “black-box” warnings against its use in liver transplant recipients based on an increased risk of hepatic artery thrombosis and death. Despite these warnings, up to 10% of liver recipients are administered this drug by one year after transplant. However, these mTOR medications like SRL have been shown in multiple studies to reduce HCC recurrence rates when used as the main IS agent in patients receiving LT for HCC, even though higher rejection rates have been reported [39-41].

In 2011, a meta-analysis was conducted to determine if using SRL based regimens as IS after LT improves survival and recurrence of HCC in patients that had a diagnosis of HCC pre-transplant [33,34,39,40,42]. A total of 5 controlled studies from different countries (3 retrospective, 1 matched-cohort and a case-control study) included 2950 participants and found that SRL-based regimens improved overall 1-, 3-, and 5-year survival (OR 4.53, 95%CI 2.31-8.89; OR 1.97, 95% CI 1.29-3.00; OR 2.47, 95%CI 1.72-3.55), respectively, compared to SRL-free regimens. One study compared the different mortality risks after LT using various IS protocols (Fig. 6) [33] and showed a significant difference in survival in patients using SRL-based IS. Furthermore, SRL-based regimens showed an overall decrease in tumor recurrence (OR 0.42, 95%CI 0.21-0.83) compared to SRL-free regimens without any significant post-transplant complications observed between the two groups.

An updated meta-analysis described outcomes in patients using SRL as the main IS agent who underwent LT for HCC [43]. Of these 5 studies [34,39,40,44,45], 474 total patients were

included in the final analysis, of which 77% were male, with an average age around 56 years old, having a median follow up ranging from 18 to 49 months. The overall results suggest that the recurrence rate of HCC after LT was lower in the SRL group (5-13%) compared with patients using calcineurin inhibitors (CNIs) (17-39%) with an overall advantage in all categories for the SRL group: lower recurrence rate (OR 0.3, 95% CI 0.16-0.55,  $P<0.001$ ), lower recurrence related mortality (OR 0.29, 95% CI 0.12-0.70,  $P=0.005$ ), and lower overall mortality (OR=0.35, 95% CI 0.2-0.61,  $P<0.001$ ) respectively. The overall 1-, 3-, and 5-year RFS was superior in the SRL group which ranged from 93-96%, 82-86% and 79-80%, while patients taking CNIs had worse overall RFS ranging from 70-78%, 64-65% and 54-60% during the same time frame respectively. The overall 1-, 3-, and 5-year OS was also much better in the SRL group (94-95%, 85%, and 80%) in comparison with the CNI group (79-83%, 66%, and 59-62%) respectively (Table 2). Similarly, overall mortality on pooled analysis was significantly lower in SRL-treated patients vs. the CNI group (OR=0.35, 95%CI 0.2-0.61,  $P<0.001$ ). Although limitations exist in meta-analysis which include: non-randomized data, lack of subgroup analysis regarding patients exceeding the Milan criteria, and possible publication bias based on the different weighted studies, overall SRL seems to be safe, effective and potentially promising regarding the OS benefits for LT recipients having a pre-transplant diagnosis of HCC. However, more prospective studies are needed to determine if improvements in survival are due to SRL alone, or from reduction in CNIs.

More recently, a systematic review compared everolimus (another mTOR inhibitor) and SRL with CNI use on post-LT recurrence of HCC [46]. Of the 42 studies that included 3,666 HCC LT recipients analyzed, CNI use was associated with higher rates of HCC recurrence (448/3227 or 13.8%) compared to mTORs (35/439 or 8%,  $P<0.001$ ), although patients treated with CNIs had lower rates of microvascular invasion and higher proportion of HCC within Milan criteria. The rates of HCC recurrence did not differ if transplanted outside of Milan criteria when comparing CNI or mTOR use, while locoregional therapy data was limited when analyzing the results. A subgroup analysis demonstrated that although patients taking everolimus had shorter follow-up data, overall HCC recurrence post-LT was less frequently observed compared to SRL use (8/196 or 4.1% vs. 23/218 or 10.5%,  $P=0.02$ ). Furthermore, no data was available with respect to dosage and IS levels when mTORs were used. Of note, one major difference between everolimus and SRL is that data using everolimus has led to FDA approval in LT recipients after 30 days without a black box warning [47]. Although the present analysis of multiple studies favors the use of mTOR (everolimus >SRL) for LT in HCC patients compared to CNI use, these findings need longer patient follow up and comparable cohorts in order to make similar comparisons between everolimus and SRL use before final conclusions can be drawn. Furthermore, when comparing overall mTOR and CNI use, the results were not significantly different when RCT studies were included, hence mTOR superiority over CNI use for prevention of HCC recurrence post-LT remains controversial at this time.



**Figure 6** The overall hazard ratios ( $\pm 95\%$  confidence interval) are represented on the x-axis of this horizontal box plot and compare the risk of mortality after liver transplantation using various immunosuppression regimens. Results were corrected for model for end-stage liver disease (MELD), year of transplant, primary liver disease (non-hepatocellular carcinoma [HCC]), age at transplant, and, when applicable, total tissue volume,  $\alpha$ -fetoprotein, and pre-transplant HCC treatment.

\*Significant variables. Reprinted with permission from John Wiley and Sons MMF, mycophenolate mofetil

To answer and address the issues above, a multicenter international randomized controlled trial is underway and is estimated to be completed in 2018. This study will analyze 5 year follow-up data to determine if the mTOR inhibitor SRL can improve HCC RFS in LT recipients with a pre-transplant diagnosis of HCC compared to SRL-free regimens [48]. All eligible LT patients (deceased donor, split-liver, or living donors) with a histological diagnosis of HCC in the explanted liver, will be given 4-6 weeks of a CNI medication (mTOR inhibitor-free), then randomized and separated into two groups: 1) mTOR inhibitor-free IS; and 2) SRL containing IS±CNI 4-6 weeks later at a loading dose of 5 mg/day and 2 mg/day thereafter. Steroid reduction is encouraged by 3 months in both groups post-LT with a desired trough level for SRL of 4-10 ng/mL on routine lab analysis. Patients simultaneously using mycophenolic acid prodrugs and CNIs are expected to have these medications reduced by 50% with the ideal long-term goal of SRL monotherapy in arm two. Groups will be stratified into high (extending beyond Milan criteria, undergoing salvage transplantation or HCC in non-cirrhotic liver) or low risk (within Milan criteria). An estimated 255 patients per arm is expected, with the hypothesis of 5-year RFS of 60% in arm 1 and 72% in arm 2, which corresponds to a clinically relevant hazard ratio of 0.643. If the hypothesis holds true, that mTOR inhibition with SRL can improve RFS while providing adequate IS, then the standard of care regarding IS might change in the near future in patients with HCC post-LT.

### **Sorafenib in combination with mTORs for recurrent HCC after LT**

As sorafenib is a multikinase inhibitor of Raf, vascular endothelial- and platelet-derived growth factor receptors, it mediates cell proliferation and angiogenesis, resulting in an increase in OS and improvement in radiologic progression in patients with HCC [49]. However, there is limited data regarding the concomitant use of sorafenib and mTOR inhibitors in patients post-LT with recurrent HCC [50-52]. It has been hypothesized that combination therapy could have synergistic effects [53,54]. A recent multicenter retrospective study evaluated patients with recurrent HCC after LT who were treated with mTOR inhibitors and sorafenib during tumor relapse as patients were not candidates for locoregional therapy [55]. Two groups were assigned, with the first termed the safety population (n=31), who received sorafenib and an mTOR inhibitor for either palliative or adjuvant treatment. This group consisted of 48% of the population diagnosed with chronic hepatitis C cirrhosis with HCC, while 52% had alcoholic cirrhosis of which only 7% were found to have incidental HCC. Most underwent DDLT (93%) and were within the Milan criteria. The second population was termed the efficacy group (n=26), who received the same two drug regimen, instead for systemic treatment for tumor relapse. There were no differences in clinical parameters between the two groups. Once recurrence of HCC was confirmed, IS was switched

in each patient to an mTOR inhibitor (23 patients received everolimus, 8 received SRL). Then, after stable graft function, sorafenib was added at median times of 1.1 month after everolimus initiation and 1.4 months after SRL initiation. The starting dose was 400 mg/day in the majority of patients, as the toxicity or immunologic consequences were unknown with this combination. Sorafenib was later increased to a maximum tolerated dose of 800 mg/day, and maintained until toxicity, tumor progression, hepatic decompensation or death ensued. Radiologic follow up for treatment response was conducted every 12 weeks with assessments of tumor size as well as new lesions according to the Response Evaluation Criteria in Solid Tumors [56].

The overall results for dual administration of sorafenib and an mTOR inhibitor in this study were described as follows. The median time from LT to recurrence was 22.6 months (range 2.2-103.1 months), with nearly two-thirds (20/31) representing extrahepatic recurrence without liver involvement, about 19% having extrahepatic with hepatic recurrence, and nearly 16% having hepatic recurrence only. The antitumor efficacy had an overall clinical benefit rate of 53.8% (14/26 patients), with 3.8% (1/26) showing a partial response and the remaining 50% demonstrating disease stabilization. Patients with disease progression were seen in 38.5% (10/26), while 7.7% (2/26) could not be evaluated as sorafenib was given for <4 weeks and no imaging studies for tumor reassessment were obtained. The median OS after HCC relapse was about 40 months (95%CI 10.1-70.1 months), while the median OS since the start of the treatment with sorafenib was 19.3 months (95%CI=13.4-25.1 months). After initiating sorafenib treatment, the median time to disease progression was 6.77 months (95%CI 2.3-11.1 months). The most common toxicities experienced in this cohort of patients were: diarrhea (77.4%), asthenia (58.1%), and hand-foot syndrome (54.8%); while serious adverse events leading to death was seen in 2 patients overall: the first patient experiencing uncontrolled gastric hemorrhage not related to portal hypertension or ulcer disease, and the other having a central nervous system hemorrhage 18 days after initiating therapy, in which treatment was stopped, however 4 weeks later the patient expired. The possible explanation resulting in the latter cause of bleeding was suspicion of, but unconfirmed leptomenigeal metastases. There were no recorded or suspected episodes of acute or chronic graft rejection related to mTOR inhibitors and sorafenib.

### **Concluding remarks**

Management of patients with HCC on the waiting list vary by different institutions, however, centers that have LDLT options should consider this as an alternative for patients with HCC as the donor pool is limited and the OS and tumor recurrence rates of HCC have similar outcomes compared to DDLT. Although DFS might be worse after LDLT, discussions should be undertaken with potential donors and recipients. Changes in IS with mTORs have been

studied in recurrent HCC, and the addition of sorafenib to these regimens have shown promise in improving OS and delaying disease progression. Currently, a multicenter international randomized control trial is underway to address the issue of mTOR IS ± sorafenib and recurrent HCC.

## References

- Organization. WH. Mortality Database. WHO Statistical Information System 2008.
- El-Serag HB, Rudolph KL. Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* 2007;**132**:2557-2576.
- Colombo M, de Franchis R, Del Ninno E, et al. Hepatocellular carcinoma in Italian patients with cirrhosis. *N Engl J Med* 1991;**325**:675-680.
- Ioannou GN, Perkins JD, Carithers RL, Jr. Liver transplantation for hepatocellular carcinoma: impact of the MELD allocation system and predictors of survival. *Gastroenterology* 2008;**134**:1342-1351.
- Freeman RB, Jr, Wiesner RH, Harper A, et al. The new liver allocation system: moving toward evidence-based transplantation policy. *Liver Transplant* 2002;**8**:851-858.
- Washburn K. Model for end stage liver disease and hepatocellular carcinoma: a moving target. *Transplant Rev (Orlando)* 2010;**24**:11-17.
- Freeman RB, Jr, Steffick DE, Guidinger MK, et al. Liver and intestine transplantation in the United States, 1997-2006. *Am J Transplant* 2008;**8**:958-976.
- Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996;**334**:693-699.
- Clavien PA, Lesurtel M, Bossuyt PM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012;**13**:e11-e22.
- Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001;**33**:1394-1403.
- Yao FY, Xiao L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. *Am J Transplant* 2007;**7**:2587-2596.
- Berg CL, Steffick DE, Edwards EB, et al. Liver and intestine transplantation in the United States 1998-2007. *Am J Transplant* 2009;**9**:907-931.
- Onaca N, Davis GL, Goldstein RM, et al. Expanded criteria for liver transplantation in patients with hepatocellular carcinoma: a report from the International Registry of Hepatic Tumors in Liver Transplantation. *Liver Transplant* 2007;**13**:391-399.
- 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.
- Millonig G, Graziadei IW, Freund MC, et al. Response to preoperative chemoembolization correlates with outcome after liver transplantation in patients with hepatocellular carcinoma. *Liver Transplant* 2007;**13**:272-279.
- Mazzaferro V, Battiston C, Perrone S, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. *Ann Surg* 2004;**240**:900-909.
- Maddala YK, Stadheim L, Andrews JC, et al. Drop-out rates of patients with hepatocellular cancer listed for liver transplantation: outcome with chemoembolization. *Liver Transplant* 2004;**10**:449-455.
- Yao FY, Bass NM, Nikolai B, et al. A follow-up analysis of the pattern and predictors of dropout from the waiting list for liver transplantation in patients with hepatocellular carcinoma: implications for the current organ allocation policy. *Liver Transplant* 2003;**9**:684-692.
- Washburn K, Edwards E, Harper A, et al. Hepatocellular carcinoma patients are advantaged in the current liver transplant allocation system. *Am J Transplant* 2010;**10**:1643-1648.
- Bhangui P, Vibert E, Majno P, et al. Intention-to-treat analysis of liver transplantation for hepatocellular carcinoma: living versus deceased donor transplantation. *Hepatology* 2011;**53**:1570-1579.
- Hwang S, Lee SG, Joh JW, et al. Liver transplantation for adult patients with hepatocellular carcinoma in Korea: comparison between cadaveric donor and living donor liver transplantations. *Liver Transplant* 2005;**11**:1265-1272.
- Fisher RA, Kulik LM, Freise CE, et al. Hepatocellular carcinoma recurrence and death following living and deceased donor liver transplantation. *Am J Transplant* 2007;**7**:1601-1608.
- Lo CM, Fan ST, Liu CL, et al. Living donor versus deceased donor liver transplantation for early irresectable hepatocellular carcinoma. *Brit J Surg* 2007;**94**:78-86.
- Vakili K, Pomposelli JJ, Cheah YL, et al. Living donor liver transplantation for hepatocellular carcinoma: Increased recurrence but improved survival. *Liver Transplant* 2009;**15**:1861-1866.
- Di Sandro S, Slim AO, Giacomoni A, et al. Living donor liver transplantation for hepatocellular carcinoma: long-term results compared with deceased donor liver transplantation. *Transplant Proc* 2009;**41**:1283-1285.
- Grant RC, Sandhu L, Dixon PR, et al. Living vs. deceased donor liver transplantation for hepatocellular carcinoma: a systematic review and meta-analysis. *Clin Transplant* 2013;**27**:140-147.
- Liang W, Wu L, Ling X, et al. Living donor liver transplantation versus deceased donor liver transplantation for hepatocellular carcinoma: a meta-analysis. *Liver Transplant* 2012;**18**:1226-1236.
- Kulik LM, Fisher RA, Rodrigo DR, et al. Outcomes of living and deceased donor liver transplant recipients with hepatocellular carcinoma: results of the A2ALL cohort. *Am J Transplant* 2012;**12**:2997-3007.
- Cescon M, Ravaioli M, Grazi GL, et al. Prognostic factors for tumor recurrence after a 12-year, single-center experience of liver transplantations in patients with hepatocellular carcinoma. *J Transplant* 2010;2010.
- Kornberg A, Kupper B, Tannapfel A, et al. Long-term survival after recurrent hepatocellular carcinoma in liver transplant patients: clinical patterns and outcome variables. *Eur J Surg Oncol* 2010;**36**:275-280.
- Hollebecque A, Decaens T, Boleslawski E, et al. Natural history and therapeutic management of recurrent hepatocellular carcinoma after liver transplantation. *Gastroenterol Clin Biol* 2009;**33**:361-369.
- Herrero JJ, Sangro B, Quiroga J, et al. Influence of tumor characteristics on the outcome of liver transplantation among patients with liver cirrhosis and hepatocellular carcinoma. *Liver Transplant* 2001;**7**:631-636.
- Toso C, Merani S, Bigam DL, et al. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. *Hepatology* 2010;**51**:1237-1243.
- Zimmerman MA, Trotter JF, Wachs M, et al. Sirolimus-based immunosuppression following liver transplantation for hepatocellular carcinoma. *Liver Transplant* 2008;**14**:633-638.
- Bjornsti MA, Houghton PJ. The TOR pathway: a target for cancer therapy. *Nat Rev Cancer* 2004;**4**:335-348.
- Price DJ, Grove JR, Calvo V, et al. Rapamycin-induced inhibition of the 70-kilodalton S6 protein kinase. *Science* 1992;**257**:973-977.

37. Villanueva A, Chiang DY, Newell P, et al. Pivotal role of mTOR signaling in hepatocellular carcinoma. *Gastroenterology* 2008;**135**:1972-83, 1983 e1-e11.
38. Panaro F, Piardi T, Gheza F, et al. Causes of sirolimus discontinuation in 97 liver transplant recipients. *Transplant Proc* 2011;**43**:1128-1131.
39. Vivarelli M, Dazzi A, Zanello M, et al. Effect of different immunosuppressive schedules on recurrence-free survival after liver transplantation for hepatocellular carcinoma. *Transplantation* 2010;**89**:227-231.
40. Chinnakotla S, Davis GL, Vasani S, et al. Impact of sirolimus on the recurrence of hepatocellular carcinoma after liver transplantation. *Liver Transplant* 2009;**15**:1834-1842.
41. Zimmerman MA, Trotter JF, Wachs M, et al. Predictors of long-term outcome following liver transplantation for hepatocellular carcinoma: a single-center experience. *Transplant Int* 2007;**20**:747-753.
42. Zhou J, Wang Z, Wu ZQ, et al. Sirolimus-based immunosuppression therapy in liver transplantation for patients with hepatocellular carcinoma exceeding the Milan criteria. *Transplant Proc* 2008;**40**:3548-3553.
43. Menon KV, Hakeem AR, Heaton ND. Meta-analysis: recurrence and survival following the use of sirolimus in liver transplantation for hepatocellular carcinoma. *Aliment Pharmacol Ther* 2013;**37**:411-419.
44. Nocera A, Andorno E, Tagliamacco A, et al. Sirolimus therapy in liver transplant patients: an initial experience at a single center. *Transplant Proc* 2008;**40**:1950-1952.
45. Toso C, Meeberg GA, Bigam DL, et al. De novo sirolimus-based immunosuppression after liver transplantation for hepatocellular carcinoma: long-term outcomes and side effects. *Transplantation* 2007;**83**:1162-1168.
46. Cholongitas E, Mamou C, Rodriguez-Castro KI, et al. Mammalian target of rapamycin inhibitors are associated with lower rates of hepatocellular carcinoma recurrence after liver transplantation: a systematic review. *Transplant Int* 2014;**27**:1039-1049.
47. Saliba F, De Simone P, Nevens F, et al. Renal function at two years in liver transplant patients receiving everolimus: results of a randomized, multicenter study. *Am J Transplant* 2013;**13**:1734-1745.
48. Schnitzbauer AA, Zuelke C, Graeb C, et al. A prospective randomised, open-labeled, trial comparing sirolimus-containing versus mTOR-inhibitor-free immunosuppression in patients undergoing liver transplantation for hepatocellular carcinoma. *BMC Cancer* 2010;**10**:190.
49. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;**359**:378-390.
50. Bhoori S, Toffanin S, Sposito C, et al. Personalized molecular targeted therapy in advanced, recurrent hepatocellular carcinoma after liver transplantation: a proof of principle. *J Hepatol* 2010;**52**:771-775.
51. Kim R, El-Gazzaz G, Tan A, et al. Safety and feasibility of using sorafenib in recurrent hepatocellular carcinoma after orthotopic liver transplantation. *Oncology* 2010;**79**:62-66.
52. Waidmann O, Hofmann WP, Zeuzem S, et al. mTOR inhibitors and sorafenib for recurrent hepatocellular carcinoma after orthotopic liver transplantation. *J Hepatol* 2011;**54**:396-398.
53. Newell P, Toffanin S, Villanueva A, et al. Ras pathway activation in hepatocellular carcinoma and anti-tumoral effect of combined sorafenib and rapamycin *in vivo*. *J Hepatol* 2009;**51**:725-733.
54. Wang Z, Zhou J, Fan J, et al. Effect of rapamycin alone and in combination with sorafenib in an orthotopic model of human hepatocellular carcinoma. *Clin Cancer Res* 2008;**14**:5124-5130.
55. Gomez-Martin C, Bustamante J, Castroagudin JF, et al. Efficacy and safety of sorafenib in combination with mammalian target of rapamycin inhibitors for recurrent hepatocellular carcinoma after liver transplantation. *Liver Transplant* 2012;**18**:45-52.
56. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;**92**:205-216.