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REVIEW

Strategies to improve outcome of patients with hepatocellular carcinoma receiving a liver transplantation

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Abstract

Liver transplantation is the only therapeutic option which allows to treat both, the hepatocellular carcinoma and the underlying liver disease. Indeed, liver transplantation is considered the standard of care for a subset of patients with cirrhosis and hepatocellular carcinoma. However, tumour recurrence rates are as high as 20%, and once the recurrence is established the therapeutic options are scarce and with little impact on prognosis. Strategies to minimize tumour recurrence and thus to improve outcome may be classified into 3 groups: (1) An adequate selection of candidates for liver transplantation by using the Milan criteria; (2) An optimized management within waiting list including prioritization of patients at high risk of tumour progression, and the implementation of bridging therapies, particularly when the expected length within the waiting list is longer than 6 mo; and (3) Tailored immunosuppression comprising reduced exposure to calcineurin inhibitors, particularly early after liver transplantation, and the addition of mammalian target of rapamycin inhibitors. In the present manuscript the available scientific evidence supporting these strategies is comprehensively reviewed, and future directions are provided for novel research approaches, which may contribute to the final target: to cure more patients with hepatocellular carcinoma and with an improved long term outcome.

Key words: Hepatocellular carcinoma; Recurrence; Bridging therapy; Milan criteria; Immunosuppression; Liver transplantation

Core tip: Liver transplantation is the only therapeutic option which allows to treat both, the hepatocellular carcinoma and the underlying liver disease. However, tumour recurrence rates are 15%-20% with a very poor prognosis. Strategies to minimize tumour recurrence and thus to improve outcome are focused in a careful selection of candidates for liver transplantation, an optimized management within waiting list and a tailored immunosuppression. The available scientific evidence supporting these strategies is reviewed, and future directions are provided for novel research approaches, which may contribute to the final target: to cure more

patients with hepatocellular carcinoma with an improved long term outcome.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the most frequent primary liver cancer, which accounts for 70%-80% of the hepatic malignancies[1]. It generally appears on a cirrhotic liver, and thus the common causes of cirrhosis are also involved in the oncogenesis of HCC, being particularly relevant hepatitis B virus (HBV) and HCV chronic viral infections[2-4]. It has been estimated that HBV is responsible for 50%-80% of HCC cases, whereas 10%-20% of cases are related to HCV[1].

HCC represents the fifth most common malignancy (554000 cases worldwide) and the second leading cause of cancer-related mortality, (746000 deaths annually)[5]. HCC rates are 2-4 fold increased in male population. The incidence is higher in developing countries, although its incidence in developed countries is increasing, mainly due to HCV infection[6]. Among developed countries the highest incidence rates are found in North America (9.3 cases/100000) and southern Europe (9.5 cases/100000)[5]. However this picture may change in the next decades given the exponential raising of infant obesity in United States and Europe which may trigger the number of HCCs attributable to non-alcoholic fatty liver disease[7-9].

Liver Transplantation (LT) is the only therapeutic option able to treat both the HCC and the underlying liver disease, and it is currently considered the standard of care for patients with small unresectable HCC. The proportion of patients diagnosed at early stage, who potentially would benefit from LT, is expected to increase due to the screening programs with ultrasound implemented for patients with chronic liver disease[10]. Compared to liver resection and locoregional ablative therapies, LT offers an improved long term survival (70% at 5 years). However the tumour recurrence rates after LT are 15%-20%, and the therapeutic options are very limited in this situation[11].

Current strategies to minimize HCC recurrence after LT are grouped in: (1) Adequate selection of candidates for LT; (2) Waiting list management and bridging locoregional therapies; and (3) Tailored immunosuppression. In the present manuscript the scientific evidence supporting these strategies is comprehensively reviewed, and future directions are drawn in order to improve long term outcome of LT patients with HCC.

SELECTION OF HCC PATIENTS FOR LT

The initial experiences of LT to treat HCC were disappointing since the tumour recurrence was frequent, and survival was shorter when compared with other LT aetiologies (5-year survival rates 18%-40%)[12]. Many institutions included the HCC as a formal contraindication for LT until the early 90's, when some studies showed that patients with small HCC undergoing LT had reduced tumour recurrence rates when compared to liver resection. Clinicians soon became aware of the improved outcomes when LT was restricted to patients with a limited tumour burden. Indeed in a cohort of 221 consecutive LT patients [38 patients with small HCC (< 5 cm) and 136 with cirrhosis without HCC], the survival rates were similar irrespective of whether HCC was present or not (63% *vs* 68% at 5 years respectively; $P = 0.84$). In 1996 Mazzaferro *et al*[13] prospectively analyzed a cohort of 48 patients with small unresectable HCC undergoing LT. The authors considered LT when there was a single nodule $\leqslant$ 5 cm or up to 3 nodules, $\leqslant$ 3 cm each, in the absence of macrovascular invasion or extrahepatic metastases. The 4-year survival rate was 75%, with a recurrence-free survival rate of 83%. These premises, currently known as Milan criteria, found a wide acceptance and most LT institutions implemented them as the standard of care to select HCC patients for LT[10]. However according to the Milan criteria, only 6% of patients with HCC would be eligible for LT[14], and therefore these criteria may be considered too restrictive. A significant proportion of patients above Milan criteria could still benefit from LT without increasing HCC recurrence rates[15].

There have been many attempts to expand Milan criteria, being the most frequently used summarized in Table 1. The expansion of the Milan criteria may be performed by increasing the diameter and/or the number of nodules allowed, and in some cases with additional criteria such as histological tumour differentiation, serum PIVKA-Ⅱ or α-fetoprotein.

One of the most popular criteria is the so called "up-to-seven", according to which patients without macrovascular invasion could be candidates for LT as long as the sum of the number of nodules and the diameter of the largest nodule is $\leqslant$ 7. These criteria were derived from a retrospective multicenter study with 1556 patients with HCC, from which 1070 had a HCC beyond Milan criteria. Patients outside Milan criteria but within the up-to-seven criteria had an overall 5 year-survival rate of 71.2%, similar to those found in patients within Milan criteria (73.3%). HCC recurrence rates were also similar provided that microvascular invasion was absent[16]. However this study had important limitations. The tumour was evaluated in the explanted liver rather than by using radiological techniques, and a certain grade of disagreement between both approaches is expected in clinical practice. Most importantly, the favorable outcome showed by patients within the up-to-seven criteria was only present after excluding patients

Table 1 Summary of the most relevant criteria used to select candidates with hepatocellular carcinoma for liver transplantation

Ref.	Name of criteria	No. of nodules	Diameter	Tumour different	PIVKA-Ⅱ	Prospective validation	*n*	Outcomes within Milan criteria	Outcomes within proposed criteria	*P*
Mazzaferro *et al*[13]	Milan	1 or ⩽ 3	⩽ 5 cm or ⩽ 3 cm each	-	-	+	48	4-yr survival rate 75% 4-yr recurrence free survival rate 83%	NA	
Mazzaferro *et al*[16]	Up-to-seven	TTN + DLN ⩽ 7		-	-	+[139-141]	1556	5-yr survival rate 73.3%	5-yr survival rate 71.2%	> 0.05
Yao *et al*[18]	UCSF criteria	1 or ⩽ 3	⩽ 6.5 cm or ⩽ 4.5 cm the largest one but with a TTD ⩽ 8 cm	-	-	+[21]	70	5-yr survival rate 72.4%	5-yr survival rate 75.2%	0.87
Herrero *et al*[23]	Universidad de Navarra criteria	1 or 2-3	⩽ 6 cm or ⩽ 5 cm	-	-	-	47	Not reported	5-yr survival rate 79% 3-yr recurrence free survival rate 70%	-
Lee *et al*[32]	Asan criteria	⩽ 6	⩽ 5 cm	-	-	-	221	5-yr survival rate 76% 3-yr recurrence rate 13.6%	5-yr survival rate 81.6% 3-yr recurrence rate 9.1%	0.334 0.554
DuBay *et al*[27]	Toronto criteria	No	No	+	-	-	294	5-yr overall survival rate 72% 5-yr disease free survival rate 70%	5-yr overall survival rate 70% 5-yr disease free survival 66%	0.63 0.25
Ito *et al*[24]	Kyoto criteria	⩽ 10	⩽ 5 cm	-	+	-	125	Not reported	5-yr survival 86.7% 5-yr recurrence 4.9%	-

TTN: Total tumor nodules; DLN: Diameter of the largest nodule; TTD: Total tumor diameter; NA: Not applicable.

with microvascular invasion, which cannot be assessed pre-LT[17]. Thus the up-to-seven criteria cannot be considered a safe approach to expand Milan criteria.

The UCSF criteria were described in 2001 by Yao *et al*[18], who prospectively analyzed the outcome of 70 patients with HCC undergoing LT in a single institution. Patients with a solitary tumor ⩽ 6.5 cm, or up to 3 nodules, being the largest lesion ⩽ 4.5 cm and the total tumor diameter ⩽ 8 cm, had 1-year survival rates of 90% (*vs* 50% for patients exceeding these criteria; $P = 0.0005$). Athough the tumour assessment was performed in the explanted liver, the UCSF criteria have been subsequently validated in independent retrospective studies, some of them based on pre-LT imaging techniques[19-22].

The criteria from the University of Navarra include a single tumor ⩽ 6 cm or 2-3 nodules up to 5 cm, without macrovascular invasion or extra-hepatic disease[23]. The original study included 160 LT patients from a single institution (47 patients had HCC, and 12 were above Milan criteria). There were no differences between patients within Milan criteria and above Milan criteria but within the Navarra criteria. The limitations of this proposal are the limited number of patients included, the retrospective design and the lack of external validation.

In the Kyoto criteria up to 10 nodules, less than 5 cm each, were permitted if serum PIVKA-Ⅱ was < 400 mU/mL[24]. These factors were obtained by a multivariate approach in a retrospective study with 125 LT with HCC (70 patients met the Milan criteria, and 55 patients did not). Patients above Milan criteria but within the Kyoto criteria had similar 5-year tumour recurrence rates when compared with patients within the Milan criteria (7.3% *vs* 9.7%; $P = 0.87$). When serum PIVKA-Ⅱ, which is a tumour marker related to an aggressive histological behavior of HCC, was included in the selection criteria the patients within Kyoto criteria showed reduced 5-year HCC recurrence rates (4.9%) when compared to patients above Kyoto criteria (60.5%) ($P = 0.0001$). Similarly, 5-year survival rates significantly differed between these groups (86.7% *vs* 34.4%, respectively; $P = 0.0001$). Similar results were described in independent cohorts[25,26].

In the Toronto criteria there were no limits in terms of diameter of the main nodule or the number of nodules, provided that extrahepatic metastasis, macrovascular invasion and poor histological differentiation were ruled out, and there was a preserved performance status[27]. There were similar 5-year survival rates and 5-year disease-free survival rates between the patients within the Milan criteria and patients beyond Milan criteria but within Toronto criteria. Interestingly, a histological parameter was implemented in the Toronto criteria, as it is histological differentiation according to the Edmonson scale[28]. Far from being a limitation, the addition of histological differentiation may add relevant information[29,30] and it can be assessed, although with some limitations, in a regular liver biopsy performed before the LT. However most of the patients with HCC are diagnosed by imaging techniques and the liver biopsy would not be performed otherwise. The risk of needle track seeding

after the liver biopsy[31] casts doubts on recommending this procedure to all patients with HCC before LT. Unfortunately the Toronto criteria have not been validated in independent cohorts.

In the Asan criteria ⩽ 6 tumors with a maximum tumor diameter of ⩽ 5 cm, and without macrovascular invasion or extra-hepatic involvement were considered[32]. The original study analyzed the outcome of 221 patients with HCC undergoing LT in a single institution. The 5-year survival rates within Milan criteria were 76%, similar to those found in patients above Milan criteria and within Asan criteria (76.3%) (P = 0.334).

Hitherto these attempts to expand Milan criteria had a little impact in clinical practice because of inherent methodological limitations. Further studies are needed to identify the best approach to expand Milan criteria safely. Although there is a general agreement to exclude HCC patients with macrovascular invasion or extrahepatic spreading, the intrahepatic tumour burden allowed is a matter of debate, as they are the additional parameters to be included. The ideal criteria to select candidates with HCC for LT should be based on solid data, and future studies addressing this issue should fulfill the following premises: (1) Enough sample size and statistical power; (2) Criteria based on objective parameters with prognostic capability, easily measured before LT; (3) Cut-off points derived from robust statistical methods; (4) Similar overall and disease free survival rates as Milan criteria; and (5) External validation in a prospective multicentric cohort.

On the other hand the expansion of the Milan criteria should be tempered. A liberal policy would not only impair outcomes, but would also limit the access to LT of patients with other liver diseases, particularly in areas with increased incidence rates of HCC. Thus any attempt to expand Milan criteria need to provide similar long term outcome when compared to other aetiologies for LT, and specific studies will be needed in each area considering the HCC prevalence, the number of donors available, and the impact of this strategy on the waiting list.

The idea of expanding Milan criteria by using only the size of the tumour and the number of nodules is too simplistic. Each series may show a different threshold for the maximum tumour diameter or for the number of nodules permitted, but the results may not be reproducible in other countries, or even in a different institution within the same country. The reason may be that the biological tumour behavior is widely variable between patients with similar HCC burden. There are many surrogate markers related to an aggressive tumour behavior in HCC, which can be categorized into histological and serum markers.

Microvascular invasion (mVI) occurs when the tumour phenotype is sufficiently evolved to degrade extracellular matrix which surround vascular structures, and invades the vascular lumen. HCC cells are then free to metastasize either in a different location of the liver (multinodular disease), or in other organs (extrahepatic spreading). Thus mVI is a critical hallmark in HCC progression, and the strongest prognostic factor as demonstrated in a metaanalysis of observational studies (RR = 3.41 for tumour recurrence and RR = 2.41 for mortality at 3 years)[17]. However the diagnosis of mVI has proven to be difficult even for experienced pathologists with the whole HCC specimen[33]. The mVI assessment in a regular liver biopsy has not been validated, but implementing this information to the selection of HCC patients for LT would allow to expand safely the Milan criteria[10,34]. Hitherto there have been many attempts to identify surrogate biomarkers of mVI, including serum markers [*i.e.,* alpha-fetoprotein (AFP), PIVKA-Ⅱ, neutrophil to lymphocyte ratio][35-38], histological markers (*i.e.,* poor differentiation and extranodular growth)[39-41], and imaging techniques (*i.e.,* presence of capsule in an magnetic resonance imaging, smooth margin in computed tomography scan or positive positron emission tomography)[42-44], but none of them are reliable enough to impact on the decision-making process. Further studies are needed either to identify new not invasive biomarkers of mVI, or to validate its diagnosis in a regular liver biopsy. There are other histological features related to poor prognosis in HCC patients such as capsular invasion, lymphatic permeation, presence of satellite nodules and tumour differentiation, being the later the only one able to be detected in a liver biopsy before LT. Many studies have shown that patients with poorly differentiated tumours have increased risk of recurrence and reduced survival rates[39-41].

Among serum markers, AFP is the most widely used. Monitoring AFP levels was used in the past as an screening to detect early HCC in patients with chronic liver disease, but in the most recent guidelines the only recognized screening technique was liver ultrasound[10]. AFP was abandoned because of its suboptimal sensitivity. In patients with HCC candidates to LT there is controversy about what is the best threshold to exclude a patient from the waiting list[45,46]. In addition AFP serum levels may be modified within waiting list by the use of locoregional therapies such as transarterial chemoembolization (TACE)[47]. Serum PIVKA-Ⅱ, also known as Des-gamma-carboxyprothrombin, is preferred to AFP in some LT institutions, particularly in eastern countries, because of an increased accuracy reported in some studies[48]. However AFP appears more sensitive than PIVKA-Ⅱ for early HCC[49]. Increased serum PIVKA-Ⅱ concentrations are found in patients with more advanced HCC, and in patients with mVI[50-52]. The combination of PIVKA-Ⅱ and AFP provided increased accuracy than any of them alone[53]. Other biomarkers related to systemic inflammation such as neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and inflammation-based index have been associated with poor survival in HCC[54,55], but their role in predicting HCC recurrence after LT is controversial[29,56,57], probably because these parameters are highly influenced by

many environmental factors different from tumour progression.

The combination of demographic features, the underlying liver disease, tumour burden, histological characteristics and serum biomarkers by using novel multivariate approaches allowing to manage an increased amount of information such as machine learning classifiers or artificial neural networks, which have already proven their utility in other LT scenarios[58], might be the key for a safe expansion of the Milan criteria.

WAITING LIST MANAGEMENT AND BRIDGING THERAPY

The shortage of donors is universal and causes an imbalance between candidates for LT and number of organs available. The patients included in the waiting list should face a risk of drop-out, either because of death or due to a significant worsening of the underlying liver disease. In patients with HCC the drop-out is usually related to tumour progression. The waiting list management should be programmed carefully, and adapted to each clinical scenario in order to guarantee an equal access to LT for patients with different aetiologies of liver disease.

From 2002 the Model for end stage liver disease (MELD) was widely accepted as the standard of care to predict short term survival within waiting list, and has been adopted to prioritize the sickest patients for LT. However the MELD score does not reflect the risk of HCC progression. The proposal to palliate this problem consisted in adding extra-MELD points on an empirical basis according to the time within the waiting list. First experiences resulted in an increased benefit to patients with HCC, with more patients transplanted, decreased waiting list mortality and drop-out rates[59,60]. Indeed this was a very positive picture for HCC patients but it was linked to an imbalance in the access to LT between HCC patients and patients with other liver diseases[59-63].

A moderate delay within the waiting list would allow for a better selection of HCC candidates for LT according to some authors. The patients with the most aggressive tumours would experience an early tumour progression and they would not be transplanted. Indeed a recent analysis of a nationwide American database showed that a longer waiting time for LT resulted in improved survival rates after LT for HCC patients, while the disparities in the access to LT among different aetiologies were reduced[64]. The optimal balance between the length within waiting list and the outcome after LT for HCC patients has not been established yet. The current allocation policy for patients with HCC is to add extra-MELD points only when there is a significant risk of drop-out (*i.e.,* T2 HCC stage). This may palliate the problem but it is far from solving it. A recent study used Monte-Carlo simulations and multiple logistic regression to calculate a corrected MELD score for HCC patients. The so called HCC-MELD formula included also AFP and provided the same priority for HCC patients as the equivalent of conventional MELD score did for other LT aetiologies[65]. The main limitations were the lack of consideration of tumour volume at listing and tumour progression within the waiting list. In addition changes in AFP after bridging therapies may decrease the HCC-MELD score in patients with positive response to therapy, and these patients have shown particularly reduced tumour recurrence rates.

Neoadjuvant locoregional therapies are recommended when the expected time to LT is longer than 6 mo in order to prevent drop-out and increase long term survival, while minimizing the risk of tumour recurrence after LT[23,66-72]. However many LT institutions treat most of the patients within the waiting list, since the actual time to LT may be unpredictable, and this strategy has demonstrated a favourable cost-effect balance[73]. The radiological response to bridging therapy may also help to assess the HCC biological behavior[74-76], and to prioritize HCC patients for LT[77-81]. Patients with tumour growth beyond Milan criteria after locoregional therapies should not undergo LT.

There are different modalities of locoregional therapies to be used as bridging for LT. The most frequently applied are liver resection (LR), TACE and radiofrequency ablation (RFA). None of these therapies have shown to be superior to the others and the selection should be tailored according to the BCLC schema[72]. LR can be used as a first line-bridging therapy procedure to LT in experienced units, with a morbidity of 39%, and an early mortality rate of 3%[82]. The main advantage of LR is that the whole HCC specimen will be available for histological examination. The information coming from the histology is very valuable as noted above, and may serve to identify predictors of poor outcome. In the presence of these factors the tumour recurrence is almost universal and many LT teams include high-risk patients within waiting list for LT immediately after LR. Other authors would consider LT only in patients with tumour recurrence after LR (salvage LT), but this strategy may result in worse survival rates and increased recurrence rates, unless a careful selection of cases is carried out[83-87].

TACE is the most frequently used locoregional bridging therapy for LT. It has been hypothesized an increased risk of arterial and biliary complications after LT in patients with a previous TACE due to an endothelial damage, but this was not confirmed in a recent study with 456 HCC transplanted patients[88]. The use of TACE with drug eluting beads has improved the performance of the technique with complete tumour necrosis rates as high as 76.2%, and with a better safety profile[67,89]. In spite of this, RFA is preferred for single tumours less than 5 cm[80]. The available studies comparing RFA *vs* TACE suggested that complete response is more frequent with RFA, while drop-out rates are diminished[80,90]. In addition, RFA is a safer procedure with reduced rates of adverse events (4.6%)[91,92]. However the new protocols of TACE with drug eluting

beads have not been tested against RFA in a randomized fashion. The heterogeneity in reporting outcome and in the inclusion criteria among the available studies make impossible to perform pooled data analysis, and no recommendation can be made of which is the optimal bridging protocol in HCC patients candidates for LT. Other locoregional therapies have been evaluated with promising results (*i.e.,* percutaneous ethanol injection, percutaneous laser ablation, microwave ablation, and radioembolization)[72,91,93], but further studies are needed to confirm their utility, and to describe which patients may benefit the most of these novel approaches.

Sorafenib is an oral multi-tyrosine kinase inhibitor with antiangiogenic properties which has shown to prolong survival in patients with advanced HCC[94]. The role of sorafenib in the LT setting has been nicely reviewed by Castelli *et al*[95]. Theoretically, sorafenib would be used as an adjuvant therapy to locoregional ablation to reduce tumour recurrence after LT, and this approach is thought to be cost-effective for T2 HCC patients[96]. However the antiangiogenic effects of sorafenib could be deleterious in the perioperative period, and important safety concerns were arisen in the available series including biliary complications and hepatic artery thrombosis[97]. The combination of radioembolization and sorafenib as bridging for LT was poorly tolerated in a pilot prospective study with 23 patients, and the risk of biliary complications after LT was enhanced[98,99]. The combination of sorafenib with locoregional therapies as bridging for LT should not be recommended.

STRATEGIES TO IMPROVE OUTCOME AFTER LIVER TRANSPLANTATION

Despite a careful selection of candidates for LT by the Milan criteria, and an optimization of bridging locoregional therapies within the waiting list, HCC recurrence rates are 15%-20%[100]. In addition pre-LT imaging techniques may lead to misdiagnosis either by not detecting HCC nodules (incidental HCC), or by inducing a wrong staging, which usually means patients transplanted above Milan criteria and increased tumour recurrence rates[16]. Even in some patients fulfilling Milan criteria the histological evaluation shows features of poor prognosis such as mVI, poor differentiation or capsular invasion. In these situations the implementation of post-LT strategies to minimize HCC recurrence may be the only option to improve outcome[101].

The whole concept of tumour recurrence requires that a remnant of circulating HCC cells should be left behind after the LT, and remained unnoticed by the immune system. The use of immunosuppressive drugs after LT is needed to prevent the consequences of acute cellular rejection, including chronic rejection and graft loss[102]. In normal conditions the immune system is able to detect tumour cells and to destroy them[103]. However the use of high doses of immunosuppressants may abolish the immune surveillance in the early post-LT period[104-108], as happens in other immunosuppressive conditions such as HIV chronic infection[109].

In LT patients with HCC the relationship between immunosuppression and tumour recurrence is poorly understood, but it is attracting more attention in the recent years. However the variability in the immunosuppression protocols among different institutions make it difficult to design studies addressing this issue with reduced risk of bias[106]. The current evidence is mainly based in observational studies, most of them retrospective and with a limited sample size, and thus their results should be taken with caution. Among immunosuppressive drugs used in LT patients, only calcineurin inhibitors and mammalian target of rapamycin (mTOR) inhibitors have shown to influence HCC recurrence, increasing and decreasing the risk respectively. Azathioprine is preferred in some centres for patients transplanted with HCV claiming for amelioration of viral recurrence and prevention of graft loss[110]. Long term use of azathioprine increases the risk of non-melanoma skin cancer[111] and lymphoma, the later when high doses are used especially in elderly patients[112], but there is no proved role on HCC. On the other hand mycophenolate seems to be protective against malignancy in the transplant population[113,114] but again there is no evidence supporting any significant effect on HCC. With regard to induction agents, the anti-interleukin-2 receptor basiliximab does not increase the risk of cancer, but anti-thymocyte globulins have been associated with an increased risk of lymphoma[115].

The use of calcineurin inhibitors, which are the mainstay of immunosuppression protocols after LT, is able to activate proto-oncogenes and pathways of cancer in a dose-dependent fashion such as transforming growth factor beta, thus promoting tumour proliferation, resistance to apoptosis and metastasis[116,117]. In a retrospective study with 70 LT patients receiving cyclosporine, the drug exposure calculated with the trapezoidal rule was increased in patients with HCC recurrence (trough concentrations 278.3 ng/mL *vs* 169.9 ng/mL; $P < 0.001$)[118]. However there were only 7 patients with HCC recurrence in this cohort, and it was not possible to control for confounding factors. In another study from the same group, 139 LT patients with HCC were analyzed, being 60 patients under tacrolimus and 79 patients under cyclosporine[119]. The rates of HCC recurrence were increased in patients with higher exposure to calcineurin inhibitors defined as tacrolimus > 10 ng/mL or cyclosporine > 220 ng/mL (RR = 4.01; $P = 0.014$). However the wide interval of recruitment with patients transplanted before and after the implementation of the Milan criteria, the heterogeneous length of drug exposure considered for each patient, and the lack of control for concomitant immunosuppression weakened the

conclusions. Another study with 219 LT patients from two European institutions evaluated the exposure to calcineurin inhibitors within the first month after LT with respect to HCC recurrence[120]. After controlling for possible confounding factors such as tumour features and concomitant immunosuppression, the increased exposure to calcineurin inhibitors within the first month after LT (tacrolimus > 10 ng/mL or cyclosporine > 300 ng/mL) was an independent predictor of HCC recurrence (RR = 2.82; P = 0.005), either if the patient was within or above Milan criteria. The exposure to calcineurin inhibitors after the first month post-LT was similar in patients with and without tumour recurrence, highlighting the early post-LT period as one in which the minimization of calcineurin inhibitors should be encouraged.

The mTOR is a serine/threonine kinase involved in cellular growth, proliferation, metabolism and angiogenesis. The mTOR pathway is up-regulated in approximately half of patients with HCC[121]. The mTOR inhibitors sirolimus and everolimus have shown anti-cancer properties in animal models including HCC[121-123]. The mTOR inhibitors are able to prevent acute cellular rejection after LT, and allow for reducing the exposure to calcineurin inhibitors, and thus acting as renal sparing agents[124]. Regarding prevention of HCC recurrence there are five retrospective studies with sirolimus[125-129], whose results have been recently summarized in two meta-analyses[130,131] with the same conclusion: sirolimus may protect against HCC recurrence after LT, and patients treated with sirolimus showed improved overall survival rates. However the level of evidence is poor. These studies are heterogeneous, retrospective, and with an increased risk of reporting bias. There are no randomized controlled trials evaluating the role of mTOR inhibitors in preventing HCC recurrence. The SILVER study is a multicentre randomized controlled trial which preliminary results are expected to be available in 2016, and may shed some light in the actual role of sirolimus in LT patients with HCC[132]. The major concern with sirolimus relies in its safety profile. A large phase Ⅱ randomized trial (n = 222) evaluated de novo sirolimus and reduced tacrolimus after liver transplantation compared with a control arm composed by conventional tacrolimus[133]. The study had to be prematurely stopped due to an imbalance of adverse outcomes between groups. Patients under sirolimus experienced increased rates of graft failure (26.4% *vs* 12.5%) and mortality (20% *vs* 8% at 24 mo; P = 0.010), and a trend towards more hepatic artery thrombosis (8.3% *vs* 2.7%; P = 0.065). In addition the analysis of the Scientific Registry of Transplant Recipients (SRTR) database (n = 26414) showed an increased risk of all-cause mortality in patients with hepatitis C treated with sirolimus (HR = 1.29; 95%CI: 1.08-1.55)[134]. Everolimus has a selective effect on mTOR complex 1, and it has been proposed to be more potent than sirolimus[135], and with an improved metabolic profile[136]. Unfortunately the evidence linking everolimus and HCC recurrence after LT is lacking. In the current scenario the systematic use of mTOR inhibitors after LT to prevent HCC recurrence may not be justified, but selected patients either with features of poor prognosis in the explanted liver (*i.e.,* above Milan criteria, poor tumour differentiation and/or microvascular invasion), or with up-regulated mTOR pathway may benefit of combining early tacrolimus minimization and *de novo* everolimus. Future randomized controlled trials should evaluate the convenience, efficacy and safety of this approach.

Sorafenib have shown to delay HCC recurrence and metastasis after LT in a rat model[137]. In a prospective not randomized pilot study, 7 patients with HCC above Milan criteria were treated with sorafenib after LT, and compared with 12 matched historical controls in whom sorafenib had not been used[138]. Sorafenib was well tolerated with no severe adverse effects and there was a trend to less HCC recurrence in the group treated with sorafenib (29% *vs* 75%; P = 0.07). The combination of sorafenib and mTOR inhibitors should be avoided because of increased risk of severe adverse events[95]. At any rate these are very early experiences and no further recommendations should be derived until larger randomized controlled trials are performed.

CONCLUSION

The efforts to improve outcome of patients with HCC undergoing LT should be driven to prevent tumour recurrence by combining the following approaches: (1) Adequate selection of candidates for LT by using Milan criteria. A moderate expansion of the Milan criteria may be possible without a significant increase in HCC recurrence rates, but this expansion should be based in objective criteria strongly associated with the biological tumour behavior; (2) Optimization in waiting-list management. Bridging locoregional therapies should be used whenever possible to prevent drop-out and to minimize HCC recurrence after LT, particularly when the expected time to LT is longer than 6 mo. The best protocol to be used remains as a matter of debate; and (3) Tailored immunosuppression protocols: Currently, early minimization of calcineurin inhibitors combined with an mTOR inhibitor may be the most rationale schema, but specific randomized controlled trials are needed for a general recommendation.

Taken as a whole the scientific evidence regarding strategies to prevent HCC recurrence after LT needs to be strengthened. Research projects addressing this issue face important caveats such as the increased sample size needed, prolonged length of recruitment and follow up of patients, and increased costs. Further studies are needed to identify non-invasive biomarkers of HCC with prognostic capability, to establish the optimal management within waiting list, and to develop new immunosuppressive drugs with antiproliferative properties, able to prevent tumour recurrence in high-

risk patients.

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REFERENCES

1 **Rosenthal GE**, Mettler G, Pare S, Riegger M, Ward M, Landefeld CS. A new diagnostic index for predicting cervical infection with either Chlamydia trachomatis or Neisseria gonorrhoeae. *J Gen Intern Med* 2010; **5**: 319-326 [PMID: 2115576 DOI: 10.1634/theoncologist.2010-S4-05]

2 **Raimondi S**, Bruno S, Mondelli MU, Maisonneuve P. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. *J Hepatol* 2009; **50**: 1142-1154 [PMID: 19395111 DOI: 10.1016/j.jhep.2009.01.019]

3 **Fattovich G**, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. *J Hepatol* 2008; **48**: 335-352 [PMID: 18096267 DOI: 10.1016/j.jhep.2007.11.011]

4 **El-Serag HB**. Hepatocellular carcinoma: recent trends in the United States. *Gastroenterology* 2004; **127**: S27-S34 [PMID: 15508094 DOI: 10.1053/j.gastro.2004.09.013]

5 **World Health Organizations**. Globocan 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012. [Cited 2014 July 24]. Available from: URL: http: //globocan.iarc.fr/Pages/fact_sheets_population.aspx

6 **Forner A**, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; **379**: 1245-1255 [PMID: 22353262 DOI: 10.1016/S0140-6736(11)61347-0S0140-6736(11)61347-0]

7 **Haslam DW**, James WP. Obesity. *Lancet* 2005; **366**: 1197-1209 [PMID: 16198769 DOI: 10.1016/S0140-6736(05)67483-1]

8 **Sun B**, Karin M. Obesity, inflammation, and liver cancer. *J Hepatol* 2012; **56**: 704-713 [PMID: 22120206 DOI: 10.1016/j.jhep.2011.09.020]

9 **Rocchini AP**. Childhood obesity and a diabetes epidemic. *N Engl J Med* 2002; **346**: 854-855 [PMID: 11893799 DOI: 10.1056/NEJM200203143461112]

10 **European Association For The Study Of The Liver**; European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. *J Hepatol* 2012; **56**: 908-943 [PMID: 22424438]

11 **Galuppo R**, McCall A, Gedaly R. The role of bridging therapy in hepatocellular carcinoma. *Int J Hepatol* 2013; **2013**: 419302 [PMID: 24455285 DOI: 10.1155/2013/419302]

12 **Mazzaferro V**, Chun YS, Poon RT, Schwartz ME, Yao FY, Marsh JW, Bhoori S, Lee SG. Liver transplantation for hepatocellular carcinoma. *Ann Surg Oncol* 2008; **15**: 1001-1007 [PMID: 18236119 DOI: 10.1245/s10434-007-9559-5]

13 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]

14 **Ulahannan SV**, Duffy AG, McNeel TS, Kish JK, Dickie LA, Rahma OE, McGlynn KA, Greten TF, Altekruse SF. Earlier presentation and application of curative treatments in hepatocellular carcinoma. *Hepatology* 2014; **60**: 1637-1644 [PMID: 24996116 DOI: 10.1002/hep.27288]

15 **Silva MF**, Sherman M. Criteria for liver transplantation for HCC: what should the limits be? *J Hepatol* 2011; **55**: 1137-1147 [PMID: 21718672 DOI: 10.1016/j.jhep.2011.05.012]

16 **Mazzaferro V**, Llovet JM, Miceli R, Bhoori S, Schiavo M, Mariani L, Camerini T, Roayaie S, Schwartz ME, Grazi GL, Adam R, Neuhaus P, Salizzoni M, Bruix J, Forner A, De Carlis L, Cillo U, Burroughs AK, Troisi R, Rossi M, Gerunda GE, Lerut J, Belghiti J, Boin I, Gugenheim J, Rochling F, Van Hoek B, Majno P. Predicting survival after liver transplantation in patients with hepatocellular carcinoma beyond the Milan criteria: a retrospective, exploratory analysis. *Lancet Oncol* 2009; **10**: 35-43 [PMID: 19058754 DOI: 10.1016/S1470-2045(08)70284-5]

17 **Rodríguez-Perálvarez M**, Luong TV, Andreana L, Meyer T, Dhillon AP, Burroughs AK. A systematic review of microvascular invasion in hepatocellular carcinoma: diagnostic and prognostic variability. *Ann Surg Oncol* 2013; **20**: 325-339 [PMID: 23149850 DOI: 10.1245/s10434-012-2513-1]

18 **Yao FY**, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394-1403 [PMID: 11391528 DOI: 10.1053/jhep.2001.24563]

19 **Yao FY**, Bass NM, Nikolai B, Davern TJ, Kerlan R, Wu V, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: analysis of survival according to the intention-to-treat principle and dropout from the waiting list. *Liver Transpl* 2002; **8**: 873-883 [PMID: 12360427 DOI: 10.1053/jlts.2002.34923]

20 **Yao FY**, Xiao L, Bass NM, Kerlan R, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: validation of the UCSF-expanded criteria based on preoperative imaging. *Am J Transplant* 2007; **7**: 2587-2596 [PMID: 17868066 DOI: 10.1111/j.1600-6143.2007.01965.x]

21 **Duffy JP**, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, Lipshutz G, Yersiz H, Lu DS, Lassman C, Tong MJ, Hiatt JR, Busuttil RW. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. *Ann Surg* 2007; **246**: 502-509; discussion 509-511 [PMID: 17717454]

22 **Chen JW**, Kow L, Verran DJ, McCall JL, Munn S, Balderson GA, Fawcett JW, Gow PJ, Jones RM, Jeffrey GP, House AK, Strasser SI. Poorer survival in patients whose explanted hepatocellular carcinoma (HCC) exceeds Milan or UCSF Criteria. An analysis of liver transplantation in HCC in Australia and New Zealand. *HPB* (Oxford) 2009; **11**: 81-89 [PMID: 19590628 DOI: 10.1111/j.1477-2574.2009.00022.x]

23 **Herrero JI**, Sangro B, Quiroga J, Pardo F, Herraiz M, Cienfuegos JA, Prieto J. Influence of tumor characteristics on the outcome of liver transplantation among patients with liver cirrhosis and hepatocellular carcinoma. *Liver Transpl* 2001; **7**: 631-636 [PMID: 11460231 DOI: 10.1053/jlts.2001.25458]

24 **Ito T**, Takada Y, Ueda M, Haga H, Maetani Y, Oike F, Ogawa K, Sakamoto S, Ogura Y, Egawa H, Tanaka K, Uemoto S. Expansion of selection criteria for patients with hepatocellular carcinoma in living donor liver transplantation. *Liver Transpl* 2007; **13**: 1637-1644 [PMID: 18044766 DOI: 10.1002/lt.21281]

25 **Kaido T**, Ogawa K, Mori A, Fujimoto Y, Ito T, Tomiyama K, Takada Y, Uemoto S. Usefulness of the Kyoto criteria as expanded selection criteria for liver transplantation for hepatocellular carcinoma. *Surgery* 2013; **154**: 1053-1060 [PMID: 24074704 DOI: 10.1016/j.surg.2013.04.056]

26 **Fujiki M**, Takada Y, Ogura Y, Oike F, Kaido T, Teramukai S, Uemoto S. Significance of des-gamma-carboxy prothrombin in selection criteria for living donor liver transplantation for hepatocellular carcinoma. *Am J Transplant* 2009; **9**: 2362-2371 [PMID: 19656125 DOI: 10.1111/j.1600-6143.2009.02783.x]

27 **DuBay D**, Sandroussi C, Sandhu L, Cleary S, Guba M, Cattral MS, McGilvray I, Ghanekar A, Selzner M, Greig PD, Grant DR. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. *Ann Surg* 2011; **253**: 166-172 [PMID: 21294289 DOI: 10.1097/SLA.0b013e31820508f1]

28 **Edmondson HA**, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. *Cancer* 1954; **7**: 462-503 [PMID: 13160935]

29 **Bertuzzo VR**, Cescon M, Ravaioli M, Grazi GL, Ercolani G, Del Gaudio M, Cucchetti A, D'Errico-Grigioni A, Golfieri R, Pinna

AD. Analysis of factors affecting recurrence of hepatocellular carcinoma after liver transplantation with a special focus on inflammation markers. *Transplantation* 2011; **91**: 1279-1285 [PMID: 21617590 DOI: 10.1097/TP.0b013e3182187cf0]

30 **Bhangui P**, Vibert E, Majno P, Salloum C, Andreani P, Zocrato J, Ichai P, Saliba F, Adam R, Castaing D, Azoulay D. Intention-to-treat analysis of liver transplantation for hepatocellular carcinoma: living versus deceased donor transplantation. *Hepatology* 2011; **53**: 1570-1579 [PMID: 21520172 DOI: 10.1002/hep.24231]

31 **Silva MA**, Hegab B, Hyde C, Guo B, Buckels JA, Mirza DF. Needle track seeding following biopsy of liver lesions in the diagnosis of hepatocellular cancer: a systematic review and meta-analysis. *Gut* 2008; **57**: 1592-1596 [PMID: 18669577 DOI: 10.1136/gut.2008.149062]

32 **Lee SG**, Hwang S, Moon DB, Ahn CS, Kim KH, Sung KB, Ko GY, Park KM, Ha TY, Song GW. Expanded indication criteria of living donor liver transplantation for hepatocellular carcinoma at one large-volume center. *Liver Transpl* 2008; **14**: 935-945 [PMID: 18581465 DOI: 10.1002/lt.21445]

33 **Fan L**, Mac MT, Frishberg DP, Fan X, Dhall D, Balzer BL, Geller SA, Wang HL. Interobserver and intraobserver variability in evaluating vascular invasion in hepatocellular carcinoma. *J Gastroenterol Hepatol* 2010; **25**: 1556-1561 [PMID: 20796155 DOI: 10.1111/j.1440-1746.2010.06304.x]

34 **Clavien PA**, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol* 2012; **13**: e11-e22 [PMID: 22047762]

35 **McHugh PP**, Gilbert J, Vera S, Koch A, Ranjan D, Gedaly R. Alpha-fetoprotein and tumour size are associated with microvascular invasion in explanted livers of patients undergoing transplantation with hepatocellular carcinoma. *HPB* (Oxford) 2010; **12**: 56-61 [PMID: 20495646 DOI: 10.1111/j.1477-2574.2009.00128.x]

36 **Eguchi S**, Takatsuki M, Hidaka M, Soyama A, Tomonaga T, Muraoka I, Kanematsu T. Predictor for histological microvascular invasion of hepatocellular carcinoma: a lesson from 229 consecutive cases of curative liver resection. *World J Surg* 2010; **34**: 1034-1038 [PMID: 20127241 DOI: 10.1007/s00268-010-0424-5]

37 **Pawlik TM**, Delman KA, Vauthey JN, Nagorney DM, Ng IO, Ikai I, Yamaoka Y, Belghiti J, Lauwers GY, Poon RT, Abdalla EK. Tumor size predicts vascular invasion and histologic grade: Implications for selection of surgical treatment for hepatocellular carcinoma. *Liver Transpl* 2005; **11**: 1086-1092 [PMID: 16123959 DOI: 10.1002/lt.20472]

38 **Kaibori M**, Ishizaki M, Matsui K, Kwon AH. Predictors of microvascular invasion before hepatectomy for hepatocellular carcinoma. *J Surg Oncol* 2010; **102**: 462-468 [PMID: 20872949 DOI: 10.1002/jso.21631]

39 **Sumie S**, Kuromatsu R, Okuda K, Ando E, Takata A, Fukushima N, Watanabe Y, Kojiro M, Sata M. Microvascular invasion in patients with hepatocellular carcinoma and its predictable clinicopathological factors. *Ann Surg Oncol* 2008; **15**: 1375-1382 [PMID: 18324443 DOI: 10.1245/s10434-008-9846-9]

40 **Kim BK**, Han KH, Park YN, Park MS, Kim KS, Choi JS, Moon BS, Chon CY, Moon YM, Ahn SH. Prediction of microvascular invasion before curative resection of hepatocellular carcinoma. *J Surg Oncol* 2008; **97**: 246-252 [PMID: 18095300 DOI: 10.1002/jso.20953]

41 **Esnaola NF**, Lauwers GY, Mirza NQ, Nagorney DM, Doherty D, Ikai I, Yamaoka Y, Regimbeau JM, Belghiti J, Curley SA, Ellis LM, Vauthey JN. Predictors of microvascular invasion in patients with hepatocellular carcinoma who are candidates for orthotopic liver transplantation. *J Gastrointest Surg* 2002; **6**: 224-232; discussion 232 [PMID: 11992808]

42 **Witjes CD**, Willemssen FE, Verheij J, van der Veer SJ, Hansen BE, Verhoef C, de Man RA, Ijzermans JN. Histological differentiation grade and microvascular invasion of hepatocellular carcinoma predicted by dynamic contrast-enhanced MRI. *J Magn Reson Imaging* 2012; **36**: 641-647 [PMID: 22532493 DOI: 10.1002/jmri.23681]

43 **Kornberg A**, Küpper B, Thrum K, Katenkamp K, Steenbeck J, Sappler A, Habrecht O, Gottschild D. Increased 18F-FDG uptake of hepatocellular carcinoma on positron emission tomography independently predicts tumor recurrence in liver transplant patients. *Transplant Proc* 2009; **41**: 2561-2563 [PMID: 19715974]

44 **Chou CT**, Chen RC, Lee CW, Ko CJ, Wu HK, Chen YL. Prediction of microvascular invasion of hepatocellular carcinoma by pre-operative CT imaging. *Br J Radiol* 2012; **85**: 778-783 [PMID: 21828149]

45 **Hameed B**, Mehta N, Sapisochin G, Roberts JP, Yao FY. Alpha-fetoprotein level & gt; 1000 ng/mL as an exclusion criterion for liver transplantation in patients with hepatocellular carcinoma meeting the Milan criteria. *Liver Transpl* 2014; **20**: 945-951 [PMID: 24797281 DOI: 10.1002/lt.23904]

46 **Duvoux C**, Roudot-Thoraval F, Decaens T, Pessione F, Badran H, Piardi T, Francoz C, Compagnon P, Vanlemmens C, Dumortier J, Dharancy S, Gugenheim J, Bernard PH, Adam R, Radenne S, Muscari F, Conti F, Hardwigsen J, Pageaux GP, Chazouillères O, Salame E, Hilleret MN, Lebray P, Abergel A, Debette-Gratien M, Kluger MD, Mallat A, Azoulay D, Cherqui D. Liver transplantation for hepatocellular carcinoma: a model including α-fetoprotein improves the performance of Milan criteria. *Gastroenterology* 2012; **143**: 986-994.e3; quiz e14-15 [PMID: 22750200]

47 **Vibert E**, Azoulay D, Hoti E, Iacopinelli S, Samuel D, Salloum C, Lemoine A, Bismuth H, Castaing D, Adam R. Progression of alphafetoprotein before liver transplantation for hepatocellular carcinoma in cirrhotic patients: a critical factor. *Am J Transplant* 2010; **10**: 129-137 [PMID: 20070666]

48 **Hamamura K**, Shiratori Y, Shiina S, Imamura M, Obi S, Sato S, Yoshida H, Omata M. Unique clinical characteristics of patients with hepatocellular carcinoma who present with high plasma des-gamma-carboxy prothrombin and low serum alpha-fetoprotein. *Cancer* 2000; **88**: 1557-1564 [PMID: 10738213]

49 **Marrero JA**, Feng Z, Wang Y, Nguyen MH, Befeler AS, Roberts LR, Reddy KR, Harnois D, Llovet JM, Normolle D, Dalhgren J, Chia D, Lok AS, Wagner PD, Srivastava S, Schwartz M. Alpha-fetoprotein, des-gamma carboxyprothrombin, and lectin-bound alpha-fetoprotein in early hepatocellular carcinoma. *Gastroenterology* 2009; **137**: 110-118 [PMID: 19362088]

50 **Shirabe K**, Itoh S, Yoshizumi T, Soejima Y, Taketomi A, Aishima S, Maehara Y. The predictors of microvascular invasion in candidates for liver transplantation with hepatocellular carcinoma-with special reference to the serum levels of des-gamma-carboxy prothrombin. *J Surg Oncol* 2007; **95**: 235-240 [PMID: 17323337 DOI: 10.1002/jso.20655]

51 **Shirabe K**, Toshima T, Kimura K, Yamashita Y, Ikeda T, Ikegami T, Yoshizumi T, Abe K, Aishima S, Maehara Y. New scoring system for prediction of microvascular invasion in patients with hepatocellular carcinoma. *Liver Int* 2014; **34**: 937-941 [PMID: 24393295 DOI: 10.1111/liv.12459]

52 **Koike Y**, Shiratori Y, Sato S, Obi S, Teratani T, Imamura M, Yoshida H, Shiina S, Omata M. Des-gamma-carboxy prothrombin as a useful predisposing factor for the development of portal venous invasion in patients with hepatocellular carcinoma: a prospective analysis of 227 patients. *Cancer* 2001; **91**: 561-569 [PMID: 11169939 DOI: 10.1002/1097-0142(20010201)91:3<561::AID-CNCR1035>3.0.CO;2-N]

53 **Inagaki Y**, Tang W, Makuuchi M, Hasegawa K, Sugawara Y, Kokudo N. Clinical and molecular insights into the hepatocellular carcinoma tumour marker des-γ-carboxyprothrombin. *Liver Int* 2011; **31**: 22-35 [PMID: 20874725 DOI: 10.1111/j.1478-3231.2010.02348.x]

54 **Pinato DJ**, Stebbing J, Ishizuka M, Khan SA, Wasan HS, North BV, Kubota K, Sharma R. A novel and validated prognostic index in hepatocellular carcinoma: the inflammation based index (IBI). *J Hepatol* 2012; **57**: 1013-1020 [PMID: 22732513 DOI: 10.1016/j.jhep.2012.06.022]

55 **Oh BS**, Jang JW, Kwon JH, You CR, Chung KW, Kay CS, Jung HS, Lee S. Prognostic value of C-reactive protein and neutrophil-to-lymphocyte ratio in patients with hepatocellular carcinoma. *BMC Cancer* 2013; **13**:

78 [PMID: 23409924 DOI: 10.1186/1471-2407-13-78]
56 **Parisi I**, Tsochatzis E, Wijewantha H, Rodríguez-Perálvarez M, De Luca L, Manousou P, Fatourou E, Pieri G, Papastergiou V, Davies N, Yu D, Luong T, Dhillon AP, Thorburn D, Patch D, O'Beirne J, Meyer T, Burroughs AK. Inflammation-based scores do not predict post-transplant recurrence of hepatocellular carcinoma in patients within Milan criteria. *Liver Transpl* 2014; **20**: 1327-1335 [PMID: 25088400 DOI: 10.1002/lt.23969]
57 **Lai Q**, Castro Santa E, Rico Juri JM, Pinheiro RS, Lerut J. Neutrophil and platelet-to-lymphocyte ratio as new predictors of dropout and recurrence after liver transplantation for hepatocellular cancer. *Transpl Int* 2014; **27**: 32-41 [PMID: 24118272 DOI: 10.1111/tri.12191]
58 **Briceño J**, Cruz-Ramírez M, Prieto M, Navasa M, Ortiz de Urbina J, Orti R, Gómez-Bravo MÁ, Otero A, Varo E, Tomé S, Clemente G, Bañares R, Bárcena R, Cuervas-Mons V, Solórzano G, Vinaixa C, Rubín A, Colmenero J, Valdivieso A, Ciria R, Hervás-Martínez C, de la Mata M. Use of artificial intelligence as an innovative donor-recipient matching model for liver transplantation: results from a multicenter Spanish study. *J Hepatol* 2014; **61**: 1020-1028 [PMID: 24905493 DOI: 10.1016/j.jhep.2014.05.039]
59 **Wiesner RH**. Patient selection in an era of donor liver shortage: current US policy. *Nat Clin Pract Gastroenterol Hepatol* 2005; **2**: 24-30 [PMID: 16265097 DOI: 10.1038/ncpgasthep0070]
60 **Wiesner RH**, Freeman RB, Mulligan DC. Liver transplantation for hepatocellular cancer: the impact of the MELD allocation policy. *Gastroenterology* 2004; **127**: S261-S267 [PMID: 15508092 DOI: 10.1053/j.gastro.2004.09.040]
61 **Sharma P**, Balan V, Hernandez JL, Harper AM, Edwards EB, Rodriguez-Luna H, Byrne T, Vargas HE, Mulligan D, Rakela J, Wiesner RH. Liver transplantation for hepatocellular carcinoma: the MELD impact. *Liver Transpl* 2004; **10**: 36-41 [PMID: 14755775]
62 **Park SJ**, Freise CE, Hirose R, Kerlan RK, Yao FY, Roberts JP, Vagefi PA. Risk factors for liver transplant waitlist dropout in patients with hepatocellular carcinoma. *Clin Transplant* 2012; **26**: E359-E364 [PMID: 22693962 DOI: 10.1111/j.1399-0012.2012.01668.x]
63 **Piscaglia F**, Camaggi V, Ravaioli M, Grazi GL, Zanello M, Leoni S, Ballardini G, Cavrini G, Pinna AD, Bolondi L. A new priority policy for patients with hepatocellular carcinoma awaiting liver transplantation within the model for end-stage liver disease system. *Liver Transpl* 2007; **13**: 857-866 [PMID: 17539006 DOI: 10.1002/lt.21155]
64 **Schlansky B**, Chen Y, Scott DL, Austin D, Naugler WE. Waiting time predicts survival after liver transplantation for hepatocellular carcinoma: a cohort study using the United Network for Organ Sharing registry. *Liver Transpl* 2014; **20**: 1045-1056 [PMID: 24838471 DOI: 10.1002/lt.23917]
65 **Vitale A**, Volk ML, De Feo TM, Burra P, Frigo AC, Ramirez Morales R, De Carlis L, Belli L, Colledan M, Fagiuoli S, Rossi G, Andorno E, Baccarani U, Regalia E, Vivarelli M, Donataccio M, Cillo U. A method for establishing allocation equity among patients with and without hepatocellular carcinoma on a common liver transplant waiting list. *J Hepatol* 2014; **60**: 290-297 [PMID: 24161408 DOI: 10.1016/j.jhep.2013.10.010]
66 **Yamashiki N**, Tateishi R, Yoshida H, Shiina S, Teratani T, Sato S, Mine N, Kondo Y, Kawabe T, Omata M. Ablation therapy in containing extension of hepatocellular carcinoma: a simulative analysis of dropout from the waiting list for liver transplantation. *Liver Transpl* 2005; **11**: 508-514 [PMID: 15838878 DOI: 10.1002/lt.20392]
67 **Nicolini D**, Svegliati-Baroni G, Candelari R, Mincarelli C, Mandolesi A, Bearzi I, Mocchegiani F, Vecchi A, Montalti R, Benedetti A, Risaliti A, Vivarelli M. Doxorubicin-eluting bead vs conventional transcatheter arterial chemoembolization for hepatocellular carcinoma before liver transplantation. *World J Gastroenterol* 2013; **19**: 5622-5632 [PMID: 24039354 DOI: 10.3748/wjg.v19.i34.5622]
68 **De Luna W**, Sze DY, Ahmed A, Ha BY, Ayoub W, Keeffe EB, Cooper A, Esquivel C, Nguyen MH. Transarterial chemoinfusion for hepatocellular carcinoma as downstaging therapy and a bridge toward liver transplantation. *Am J Transplant* 2009; **9**: 1158-1168 [PMID: 19344435 DOI: 10.1111/j.1600-6143.2009.02576.x]
69 **Graziadei IW**, Sandmueller H, Waldenberger P, Koenigsrainer A, Nachbaur K, Jaschke W, Margreiter R, Vogel W. Chemoembolization followed by liver transplantation for hepatocellular carcinoma impedes tumor progression while on the waiting list and leads to excellent outcome. *Liver Transpl* 2003; **9**: 557-563 [PMID: 12783395 DOI: 10.1053/jlts.2003.50106]
70 **Hayashi PH**, Ludkowski M, Forman LM, Osgood M, Johnson S, Kugelmas M, Trotter JF, Bak T, Wachs M, Kam I, Durham J, Everson GT. Hepatic artery chemoembolization for hepatocellular carcinoma in patients listed for liver transplantation. *Am J Transplant* 2004; **4**: 782-787 [PMID: 15084175 DOI: 10.1111/j.1600-6143.2004.00413.x]
71 **Dharancy S**, Boitard J, Decaens T, Sergent G, Boleslawski E, Duvoux C, Vanlemmens C, Meyer C, Gugenheim J, Durand F, Boillot O, Declerck N, Louvet A, Canva V, Romano O, Ernst O, Mathurin P, Pruvot FR. Comparison of two techniques of transarterial chemoembolization before liver transplantation for hepatocellular carcinoma: a case-control study. *Liver Transpl* 2007; **13**: 665-671 [PMID: 17427172 DOI: 10.1002/lt.21109]
72 **Cescon M**, Cucchetti A, Ravaioli M, Pinna AD. Hepatocellular carcinoma locoregional therapies for patients in the waiting list. Impact on transplantability and recurrence rate. *J Hepatol* 2013; **58**: 609-618 [PMID: 23041304 DOI: 10.1016/j.jhep.2012.09.021S0168-8278(12)00752-0]
73 **Llovet JM**, Mas X, Aponte JJ, Fuster J, Navasa M, Christensen E, Rodés J, Bruix J. Cost effectiveness of adjuvant therapy for hepatocellular carcinoma during the waiting list for liver transplantation. *Gut* 2002; **50**: 123-128 [PMID: 11772979 DOI: 10.1136/gut.50.1.123]
74 **Kim DJ**, Clark PJ, Heimbach J, Rosen C, Sanchez W, Watt K, Charlton MR. Recurrence of hepatocellular carcinoma: importance of mRECIST response to chemoembolization and tumor size. *Am J Transplant* 2014; **14**: 1383-1390 [PMID: 24801862 DOI: 10.1111/ajt.12684]
75 **Millonig G**, Graziadei IW, Freund MC, Jaschke W, Stadlmann S, Ladurner R, Margreiter R, Vogel W. Response to preoperative chemoembolization correlates with outcome after liver transplantation in patients with hepatocellular carcinoma. *Liver Transpl* 2007; **13**: 272-279 [PMID: 17256758 DOI: 10.1002/lt.21033]
76 **Decaens T**, Roudot-Thoraval F, Bresson-Hadni S, Meyer C, Gugenheim J, Durand F, Bernard PH, Boillot O, Boudjema K, Calmus Y, Hardwigsen J, Ducerf C, Pageaux GP, Dharancy S, Chazouilleres O, Dhumeaux D, Cherqui D, Duvoux C. Impact of pretransplantation transarterial chemoembolization on survival and recurrence after liver transplantation for hepatocellular carcinoma. *Liver Transpl* 2005; **11**: 767-775 [PMID: 15973710 DOI: 10.1002/lt.20418]
77 **Baccarani U**, Adani GL, Serraino D, Lorenzin D, Gambato M, Buda A, Zanus G, Vitale A, Piselli P, De Paoli A, Bresadola V, Risaliti A, Toniutto P, Cillo U, Bresadola F, Burra P. De novo tumors are a major cause of late mortality after orthotopic liver transplantation. *Transplant Proc* 2009; **41**: 1303-1305 [PMID: 19460546 DOI: 10.1016/j.transproceed.2009.03.079]
78 **Yao FY**, Bass NM, Nikolai B, Merriman R, Davern TJ, Kerlan R, Ascher NL, Roberts JP. 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 Transpl* 2003; **9**: 684-692 [PMID: 12827553 DOI: 10.1053/jlts.2003.50147]
79 **De Giorgio M**, Vezzoli S, Cohen E, Armellini E, Lucà MG, Verga G, Pinelli D, Nani R, Valsecchi MG, Antolini L, Colledan M, Fagiuoli S, Strazzabosco M. Prediction of progression-free survival in patients presenting with hepatocellular carcinoma within the Milan criteria. *Liver Transpl* 2010; **16**: 503-512 [PMID: 20373461 DOI: 10.1002/lt.22039]
80 **Cucchetti A**, Cescon M, Bigonzi E, Piscaglia F, Golfieri R, Ercolani G, Cristina Morelli M, Ravaioli M, Daniele Pinna A. Priority of candidates with hepatocellular carcinoma awaiting liver

transplantation can be reduced after successful bridge therapy. *Liver Transpl* 2011; **17**: 1344-1354 [PMID: 21837731 DOI: 10.1002/lt.22397]

81 **Mehta N**, Dodge JL, Goel A, Roberts JP, Hirose R, Yao FY. Identification of liver transplant candidates with hepatocellular carcinoma and a very low dropout risk: implications for the current organ allocation policy. *Liver Transpl* 2013; **19**: 1343-1353 [PMID: 24285611 DOI: 10.1002/lt.23753]

82 **Xu XS**, Liu C, Qu K, Song YZ, Zhang P, Zhang YL. Liver transplantation versus liver resection for hepatocellular carcinoma: a meta-analysis. *Hepatobiliary Pancreat Dis Int* 2014; **13**: 234-241 [PMID: 24919605 DOI: 10.1016/S1499-3872(14)60037-0]

83 **Hu Z**, Zhou J, Xu X, Li Z, Zhou L, Wu J, Zhang M, Zheng S. Salvage liver transplantation is a reasonable option for selected patients who have recurrent hepatocellular carcinoma after liver resection. *PLoS One* 2012; **7**: e36587 [PMID: 22574187 DOI: 10.1371/journal.pone.0036587]

84 **Fuks D**, Dokmak S, Paradis V, Diouf M, Durand F, Belghiti J. Benefit of initial resection of hepatocellular carcinoma followed by transplantation in case of recurrence: an intention-to-treat analysis. *Hepatology* 2012; **55**: 132-140 [PMID: 21932387 DOI: 10.1002/hep.24680]

85 **Lei JY**, Yan LN, Wang WT. Transplantation vs resection for hepatocellular carcinoma with compensated liver function after downstaging therapy. *World J Gastroenterol* 2013; **19**: 4400-4408 [PMID: 23885153 DOI: 10.3748/wjg.v19.i27.4400]

86 **Wang HQ**, Yang J, Yan LN, Zhang XW, Yang JY. Liver resection in hepatitis B related-hepatocellular carcinoma: clinical outcomes and safety in elderly patients. *World J Gastroenterol* 2014; **20**: 6620-6625 [PMID: 24914386 DOI: 10.3748/wjg.v20.i21.6620]

87 **Adam R**, Azoulay D, Castaing D, Eshkenazy R, Pascal G, Hashizume K, Samuel D, Bismuth H. Liver resection as a bridge to transplantation for hepatocellular carcinoma on cirrhosis: a reasonable strategy? *Ann Surg* 2003; **238**: 508-518; discussion 518-519 [PMID: 14530722]

88 **Goel A**, Mehta N, Guy J, Fidelman N, Yao F, Roberts J, Terrault N. Hepatic artery and biliary complications in liver transplant recipients undergoing pretransplant transarterial chemoembolization. *Liver Transpl* 2014; **20**: 1221-1228 [PMID: 25045002 DOI: 10.1002/lt.23945]

89 **Pompili M**, Francica G, Ponziani FR, Iezzi R, Avolio AW. Bridging and downstaging treatments for hepatocellular carcinoma in patients on the waiting list for liver transplantation. *World J Gastroenterol* 2013; **19**: 7515-7530 [PMID: 24282343 DOI: 10.3748/wjg.v19.i43.7515]

90 **Huo TI**, Huang YH, Su CW, Lin HC, Chiang JH, Chiou YY, Huo SC, Lee PC, Lee SD. Validation of the HCC-MELD for dropout probability in patients with small hepatocellular carcinoma undergoing locoregional therapy. *Clin Transplant* 2008; **22**: 469-475 [PMID: 18318736 DOI: 10.1111/j.1399-0012.2008.00811.xCTR811]

91 **Atabani SF**, Smith C, Atkinson C, Aldridge RW, Rodriguez-Perálvarez M, Rolando N, Harber M, Jones G, O'Riordan A, Burroughs AK, Thorburn D, O'Beirne J, Milne RS, Emery VC, Griffiths PD. Cytomegalovirus replication kinetics in solid organ transplant recipients managed by preemptive therapy. *Am J Transplant* 2012; **12**: 2457-2464 [PMID: 22594993 DOI: 10.1111/j.1600-6143.2012.04087.x]

92 **Feng K**, Ma KS. Value of radiofrequency ablation in the treatment of hepatocellular carcinoma. *World J Gastroenterol* 2014; **20**: 5987-5998 [PMID: 24876721 DOI: 10.3748/wjg.v20.i20.5987]

93 **Mearini L**. High intensity focused ultrasound, liver disease and bridging therapy. *World J Gastroenterol* 2013; **19**: 7494-7499 [PMID: 24282341 DOI: 10.3748/wjg.v19.i43.7494]

94 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514]

95 **Castelli G**, Burra P, Giacomin A, Vitale A, Senzolo M, Cillo U, Farinati F. Sorafenib use in the transplant setting. *Liver Transpl* 2014; **20**: 1021-1028 [PMID: 24809799 DOI: 10.1002/lt.23911]

96 **Vitale A**, Volk ML, Pastorelli D, Lonardi S, Farinati F, Burra P, Angeli P, Cillo U. Use of sorafenib in patients with hepatocellular carcinoma before liver transplantation: a cost-benefit analysis while awaiting data on sorafenib safety. *Hepatology* 2010; **51**: 165-173 [PMID: 19877181 DOI: 10.1002/hep.23260]

97 **Saidi RF**, Shah SA, Rawson AP, Grossman S, Piperdi B, Bozorgzadeh A. Treating hepatocellular carcinoma with sorafenib in liver transplant patients: an initial experience. *Transplant Proc* 2010; **42**: 4582-4584 [PMID: 21168742 DOI: 10.1016/j.transproced.2010.09.147]

98 **Hoffmann K**, Glimm H, Radeleff B, Richter G, Heining C, Schenkel I, Zahlten-Hinguranage A, Schirrmacher P, Schmidt J, Büchler MW, Jaeger D, von Kalle C, Schemmer P. Prospective, randomized, double-blind, multi-center, Phase III clinical study on transarterial chemoembolization (TACE) combined with Sorafenib versus TACE plus placebo in patients with hepatocellular cancer before liver transplantation - HeiLivCa [ISRCTN24081794]. *BMC Cancer* 2008; **8**: 349 [PMID: 19036146 DOI: 10.1186/1471-2407-8-3491471-2407-8-349]

99 **Kulik L**, Vouche M, Koppe S, Lewandowski RJ, Mulcahy MF, Ganger D, Habib A, Karp J, Al-Saden P, Lacouture M, Cotliar J, Abecassis M, Baker T, Salem R. Prospective randomized pilot study of Y90+/-sorafenib as bridge to transplantation in hepatocellular carcinoma. *J Hepatol* 2014; **61**: 309-317 [PMID: 24681342 DOI: 10.1016/j.jhep.2014.03.023]

100 **Bruix J**, Sherman M. Management of hepatocellular carcinoma. *Hepatology* 2005; **42**: 1208-1236 [PMID: 16250051 DOI: 10.1002/hep.20933]

101 **Chen K**, Man K, Metselaar HJ, Janssen HL, Peppelenbosch MP, Pan Q. Rationale of personalized immunosuppressive medication for hepatocellular carcinoma patients after liver transplantation. *Liver Transpl* 2014; **20**: 261-269 [PMID: 24376158 DOI: 10.1002/lt.23806]

102 **Wiesner RH**, Fung JJ. Present state of immunosuppressive therapy in liver transplant recipients. *Liver Transpl* 2011; **17** Suppl 3: S1-S9 [PMID: 21850697 DOI: 10.1002/lt.22410]

103 **Hanahan D**, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011; **144**: 646-674 [PMID: 21376230 DOI: 10.1016/j.cell.2011.02.013]

104 **Kim R**, Emi M, Tanabe K. Cancer immunoediting from immune surveillance to immune escape. *Immunology* 2007; **121**: 1-14 [PMID: 17386080 DOI: 10.1111/j.1365-2567.2007.02587.x]

105 **Teng MW**, Swann JB, Koebel CM, Schreiber RD, Smyth MJ. Immune-mediated dormancy: an equilibrium with cancer. *J Leukoc Biol* 2008; **84**: 988-993 [PMID: 18515327 DOI: 10.1189/jlb.1107774]

106 **Rodríguez-Perálvarez M,** De la Mata M, Burroughs AK. Liver transplantation: immunosuppression and oncology. *Curr Opin Organ Transplant* 2014; **19**: 253 [DOI: 10.1097/MOT.0000000000000069]

107 **Schulz TF**. Cancer and viral infections in immunocompromised individuals. *Int J Cancer* 2009; **125**: 1755-1763 [PMID: 19588503 DOI: 10.1002/ijc.24741]

108 **Mbulaiteye SM**, Clarke CA, Morton LM, Gibson TM, Pawlish K, Weisenburger DD, Lynch CF, Goodman MT, Engels EA. Burkitt lymphoma risk in US solid organ transplant recipients. *Am J Hematol* 2013; **88**: 245-250 [PMID: 23386365 DOI: 10.1002/ajh.23385]

109 **Grulich AE**, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. *Lancet* 2007; **370**: 59-67 [PMID: 17617273 DOI: 10.1016/S0140-6736(07)61050-2]

110 **Manousou P**, Cholongitas E, Samonakis D, Tsochatzis E, Corbani A, Dhillon AP, Davidson J, Rodríguez-Perálvarez M, Patch D, O'Beirne J, Thorburn D, Luong T, Rolles K, Davidson B, McCormick PA, Hayes P, Burroughs AK. Reduced fibrosis in

recurrent HCV with tacrolimus, azathioprine and steroids versus tacrolimus: randomised trial long term outcomes. *Gut* 2014; **63**: 1005-1013 [PMID: 24131637 DOI: 10.1136/gutjnl-2013-305606]

111 **Karran P**, Attard N. Thiopurines in current medical practice: molecular mechanisms and contributions to therapy-related cancer. *Nat Rev Cancer* 2008; **8**: 24-36 [PMID: 18097462 DOI: 10.1038/nrc2292]

112 **Smith MA**, Irving PM, Marinaki AM, Sanderson JD. Review article: malignancy on thiopurine treatment with special reference to inflammatory bowel disease. *Aliment Pharmacol Ther* 2010; **32**: 119-130 [PMID: 20412066 DOI: 10.1111/j.1365-2036.2010.04330.x]

113 **Robson R**, Cecka JM, Opelz G, Budde M, Sacks S. Prospective registry-based observational cohort study of the long-term risk of malignancies in renal transplant patients treated with mycophenolate mofetil. *Am J Transplant* 2005; **5**: 2954-2960 [PMID: 16303010 DOI: 10.1111/j.1600-6143.2005.01125.x]

114 **O'Neill JO**, Edwards LB, Taylor DO. Mycophenolate mofetil and risk of developing malignancy after orthotopic heart transplantation: analysis of the transplant registry of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant* 2006; **25**: 1186-1191 [PMID: 17045930 DOI: 10.1016/j.healun.2006.06.010]

115 **Turner AP**, Knechtle SJ. Induction immunosuppression in liver transplantation: a review. *Transpl Int* 2013; **26**: 673-683 [PMID: 23651083 DOI: 10.1111/tri.12100]

116 **Maluccio M**, Sharma V, Lagman M, Vyas S, Yang H, Li B, Suthanthiran M. Tacrolimus enhances transforming growth factor-beta1 expression and promotes tumor progression. *Transplantation* 2003; **76**: 597-602 [PMID: 12923450 DOI: 10.1097/01.TP.0000081399.75231.3B]

117 **Datta D**, Contreras AG, Basu A, Dormond O, Flynn E, Briscoe DM, Pal S. Calcineurin inhibitors activate the proto-oncogene Ras and promote protumorigenic signals in renal cancer cells. *Cancer Res* 2009; **69**: 8902-8909 [PMID: 19903851 DOI: 10.1158/0008-5472.CAN-09-1404]

118 **Vivarelli M**, Cucchetti A, Piscaglia F, La Barba G, Bolondi L, Cavallari A, Pinna AD. Analysis of risk factors for tumor recurrence after liver transplantation for hepatocellular carcinoma: key role of immunosuppression. *Liver Transpl* 2005; **11**: 497-503 [PMID: 15838913 DOI: 10.1002/lt.20391]

119 **Vivarelli M**, Cucchetti A, La Barba G, Ravaioli M, Del Gaudio M, Lauro A, Grazi GL, Pinna AD. Liver transplantation for hepatocellular carcinoma under calcineurin inhibitors: reassessment of risk factors for tumor recurrence. *Ann Surg* 2008; **248**: 857-862 [PMID: 18948815 DOI: 10.1097/SLA.0b013e3181896278]

120 **Rodríguez-Perálvarez M**, Tsochatzis E, Naveas MC, Pieri G, García-Caparrós C, O'Beirne J, Poyato-González A, Ferrín-Sánchez G, Montero-Álvarez JL, Patch D, Thorburn D, Briceño J, De la Mata M, Burroughs AK. Reduced exposure to calcineurin inhibitors early after liver transplantation prevents recurrence of hepatocellular carcinoma. *J Hepatol* 2013; **59**: 1193-1199 [PMID: 23867318 DOI: 10.1016/j.jhep.2013.07.012]

121 **Villanueva A**, Chiang DY, Newell P, Peix J, Thung S, Alsinet C, Tovar V, Roayaie S, Minguez B, Sole M, Battiston C, Van Laarhoven S, Fiel MI, Di Feo A, Hoshida Y, Yea S, Toffanin S, Ramos A, Martignetti JA, Mazzaferro V, Bruix J, Waxman S, Schwartz M, Meyerson M, Friedman SL, Llovet JM. Pivotal role of mTOR signaling in hepatocellular carcinoma. *Gastroenterology* 2008; **135**: 1972-1983, 1983.e1-11 [PMID: 18929564 DOI: 10.1053/j.gastro.2008.08.008]

122 **Gaumann A**, Schlitt HJ, Geissler EK. Immunosuppression and tumor development in organ transplant recipients: the emerging dualistic role of rapamycin. *Transpl Int* 2008; **21**: 207-217 [PMID: 18069922]

123 **Schumacher G**, Oidtmann M, Rueggeberg A, Jacob D, Jonas S, Langrehr JM, Neuhaus R, Bahra M, Neuhaus P. Sirolimus inhibits growth of human hepatoma cells alone or combined with tacrolimus, while tacrolimus promotes cell growth. *World J Gastroenterol* 2005; **11**: 1420-1425 [PMID: 15770715 DOI: 10.3748/wjg.v11.i10.1420]

124 **De Simone P**, Nevens F, De Carlis L, Metselaar HJ, Beckebaum S, Saliba F, Jonas S, Sudan D, Fung J, Fischer L, Duvoux C, Chavin KD, Koneru B, Huang MA, Chapman WC, Foltys D, Witte S, Jiang H, Hexham JM, Junge G. Everolimus with reduced tacrolimus improves renal function in de novo liver transplant recipients: a randomized controlled trial. *Am J Transplant* 2012; **12**: 3008-3020 [PMID: 22882750 DOI: 10.1111/j.1600-6143.2012.04212.x]

125 **Zhou J**, Wang Z, Wu ZQ, Qiu SJ, Yu Y, Huang XW, Tang ZY, Fan J. Sirolimus-based immunosuppression therapy in liver transplantation for patients with hepatocellular carcinoma exceeding the Milan criteria. *Transplant Proc* 2008; **40**: 3548-3553 [PMID: 19100435]

126 **Vivarelli M**, Dazzi A, Zanello M, Cucchetti A, Cescon M, Ravaioli M, Del Gaudio M, Lauro A, Grazi GL, Pinna AD. Effect of different immunosuppressive schedules on recurrence-free survival after liver transplantation for hepatocellular carcinoma. *Transplantation* 2010; **89**: 227-231 [PMID: 20098287]

127 **Campsen J**, Zimmerman MA, Trotter JF, Wachs M, Bak T, Steinberg T, Kam I. Clinically recurrent primary sclerosing cholangitis following liver transplantation: a time course. *Liver Transpl* 2008; **14**: 181-185 [PMID: 18236392 DOI: 10.1002/lt.21420]

128 **Chinnakotla S**, Davis GL, Vasani S, Kim P, Tomiyama K, Sanchez E, Onaca N, Goldstein R, Levy M, Klintmalm GB. Impact of sirolimus on the recurrence of hepatocellular carcinoma after liver transplantation. *Liver Transpl* 2009; **15**: 1834-1842 [PMID: 19938137 DOI: 10.1002/lt.21953]

129 **Toso C**, Merani S, Bigam DL, Shapiro AM, Kneteman NM. Sirolimus-based immunosuppression is associated with increased survival after liver transplantation for hepatocellular carcinoma. *Hepatology* 2010; **51**: 1237-1243 [PMID: 20187107 DOI: 10.1002/hep.23437]

130 **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 [PMID: 23278125 DOI: 10.1111/apt.12185]

131 **Liang W**, Wang D, Ling X, Kao AA, Kong Y, Shang Y, Guo Z, He X. Sirolimus-based immunosuppression in liver transplantation for hepatocellular carcinoma: a meta-analysis. *Liver Transpl* 2012; **18**: 62-69 [PMID: 21964956 DOI: 10.1002/lt.22441]

132 **Schnitzbauer AA**, Zuelke C, Graeb C, Rochon J, Bilbao I, Burra P, de Jong KP, Duvoux C, Kneteman NM, Adam R, Bechstein WO, Becker T, Beckebaum S, Chazouillères O, Cillo U, Colledan M, Fändrich F, Gugenheim J, Hauss JP, Heise M, Hidalgo E, Jamieson N, Königsrainer A, Lamby PE, Lerut JP, Mäkisalo H, Margreiter R, Mazzaferro V, Mutzbauer I, Otto G, Pageaux GP, Pinna AD, Pirenne J, Rizell M, Rossi G, Rostaing L, Roy A, Turrion VS, Schmidt J, Troisi RI, van Hoek B, Valente U, Wolf P, Wolters H, Mirza DF, Scholz T, Steininger R, Soderdahl G, Strasser SI, Jauch KW, Neuhaus P, Schlitt HJ, Geissler EK. 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 [PMID: 20459775]

133 **Asrani SK**, Wiesner RH, Trotter JF, Klintmalm G, Katz E, Maller E, Roberts J, Kneteman N, Teperman L, Fung JJ, Millis JM. De novo sirolimus and reduced-dose tacrolimus versus standard-dose tacrolimus after liver transplantation: the 2000-2003 phase II prospective randomized trial. *Am J Transplant* 2014; **14**: 356-366 [PMID: 24456026 DOI: 10.1111/ajt.12543]

134 **Watt KD**, Dierkhising R, Heimbach JK, Charlton MR. Impact of sirolimus and tacrolimus on mortality and graft loss in liver transplant recipients with or without hepatitis C virus: an analysis of the Scientific Registry of Transplant Recipients Database. *Liver Transpl* 2012; **18**: 1029-1036 [PMID: 22641474 DOI: 10.1002/lt.23479]

135 **Jin YP**, Valenzuela NM, Ziegler ME, Rozengurt E, Reed EF. Everolimus inhibits anti-HLA I antibody-mediated endothelial cell signaling, migration and proliferation more potently than sirolimus. *Am J Transplant* 2014; **14**: 806-819 [PMID: 24580843 DOI: 10.1111/ajt.12669]

136 **Laplante M**, Sabatini DM. mTOR signaling in growth control and disease. *Cell* 2012; **149**: 274-293 [PMID: 22500797]
137 **Yan J**, Tan C, Gu F, Jiang J, Xu M, Huang X, Dai Z, Wang Z, Fan J, Zhou J. Sorafenib delays recurrence and metastasis after liver transplantation in a rat model of hepatocellular carcinoma with high expression of phosphorylated extracellular signal-regulated kinase. *Liver Transpl* 2013; **19**: 507-520 [PMID: 23408515 DOI: 10.1002/lt.23619]
138 **Shetty K**, Dash C, Laurin J. Use of adjuvant sorafenib in liver transplant recipients with high-risk hepatocellular carcinoma. *J Transplant* 2014; **2014**: 913634 [PMID: 24818010 DOI: 10.1155/2014/913634]
139 **Lei JY**, Wang WT, Yan LN. Up-to-seven criteria for hepatocellular carcinoma liver transplantation: a single center analysis. *World J Gastroenterol* 2013; **19**: 6077-6083 [PMID: 24106409 DOI: 10.3748/wjg.v19.i36.6077]
140 **D'Amico F**, Schwartz M, Vitale A, Tabrizian P, Roayaie S, Thung S, Guido M, del Rio Martin J, Schiano T, Cillo U. Predicting recurrence after liver transplantation in patients with hepatocellular carcinoma exceeding the up-to-seven criteria. *Liver Transpl* 2009; **15**: 1278-1287 [PMID: 19790142 DOI: 10.1002/lt.21842]
141 **de Ataide EC**, Garcia M, Mattosinho TJ, Almeida JR, Escanhoela CA, Boin IF. Predicting survival after liver transplantation using up-to-seven criteria in patients with hepatocellular carcinoma. *Transplant Proc* 2012; **44**: 2438-2440 [PMID: 23026614]

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