Developments in Liver Transplantation for Hepatocellular Carcinoma

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Hepatocellular carcinoma (HCC) is a serious health problem worldwide because of its association with hepatitis B and C viruses. In this setting, liver transplantation (LT) has become one of the best treatments since it removes both the tumor and the underlying liver disease. Due to the improvement of imaging techniques and surveillance programs, HCC are being detected earlier at a stage at which effective treatment is feasible. The prerequisite for long term success of LT for HCC depends on tumor load and strict selection criteria with regard to the size and number of tumor nodules. The need to obtain the optimal benefit from the limited number of organs available has prompted the maintenance of selection criteria in order to list only those patients with early HCC who have a better long-term outcome after LT. The indications for LT and organ allocation system led to many controversies around the use of LT in HCC patients. This review aims at giving the latest updated developments in LT for HCC focusing on selection criteria, diagnostic tools, prognostic factors, treatment on the waiting list, role of living donor liver transplantation and adjuvant therapy, and the impact of immunosuppression on HCC recurrence after LT.
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Hepatocellular carcinoma (HCC) is an increasing health problem worldwide because of the association of HCC and hepatitis B and C viruses. Whereas historically treatment for HCC was often palliative, new curative alternatives have emerged in some cases, such as liver resection, locoregional therapies, and liver transplantation (LT). Since the beginning of LT, HCC was privileged as an indication since it would cure both the tumor and the underlying liver disease. However, early experience with LT for HCC in the 1980s was disappointing due to relatively high recurrence rates (>50%) and discouraging 5-year overall survival results ranging from 10% to 35%.[1] Since it appeared obvious that the success of LT for HCC depends on tumor load, strict selection criteria with regard to the size and number of tumor nodules (Milan criteria) allowed achieving a satisfactory long-term recurrence-free survival.[2] This evolution is mainly due to improved imaging techniques and surveillance programs, which allow HCCs to be detected earlier at a stage when effective treatment is feasible. In this context, LT for HCC currently represents 25% and 35% of the recommended treatment in Europe and the United States, respectively.[3,4] The need to obtain the optimal benefit from the limited number of organs that are available, has prompted the maintenance of selection criteria in order to list only those patients with early HCC who have the highest likelihood of survival after LT. The indications for LT and organ allocation systems led to many controversies around the use of LT in HCC patients.

The purpose of this review is to update the developments in LT for HCC, focusing on selection criteria, diagnostic tools, prognostic factors, treatment on the waiting list, role of living donor liver transplantation (LDLT) and adjuvant therapy, and impact of immunosuppression on HCC recurrence after LT.

HOW FAR CAN THE SELECTION CRITERIA BE EXTENDED?

The Milan criteria (single HCC nodule of <5 cm or with up to three nodules of <3 cm without macrovascular invasion) provide a convenient and easily reproducible way to select patients with HCC who will have a very good outcome after LT (2). In this setting, the reported 5-year survival rates range from 65%–78% and

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recurrence rates up to 11%.[5] However, there is current accumulating evidence that well-selected patients with HCC beyond the Milan criteria could benefit from LT. The University of California, San Francisco (UCSF) developed in 2001 new transplantation criteria (one tumor <6.5 cm, or two or three nodules <4.5 cm with total tumor diameter <8 cm) for HCC patients. Initially based on retrospective data from the pathology of explanted livers, UCSF demonstrated a tumor recurrence rate of 11% with a comparable 5-year survival rate of patients displaying T1/T2 tumors (72%) and those with T3 tumors (74%).[6] Over a period of 5 years, they validated prospectively these results based on pretransplant imaging in a cohort of 168 patients, including 38 patients with HCC exceeding the Milan criteria.[7] The 1- and 5-year recurrence-free probabilities were 96% and 91% and the survival without recurrence was 92% and 81%, respectively. Other studies including transplanted HCC patients within the UCSF criteria achieved comparable outcomes.[8,9] Noteworthy, except for one study where 40% (n = 185) of HCC patients were outside the Milan criteria but within the UCSF criteria,[8], the use of the latter criteria resulted in only a modest expansion of the number of eligible patients by 5%–10%.

One of the limitations of the studies assessing outcome of HCC patients beyond Milan but within UCSF criteria is the radiological techniques used and the interpretation of imaging, which could lead to an under-staging in patients beyond Milan. In an "intent-to-treat" analysis, one study showed that patients outside the Milan criteria but within UCSF criteria had a 5-year survival of 46% compared to 60% for patients within the Milan criteria.[10] Although not significant, the 5-year overall and disease-free survivals were lower in patients outside Milan criteria but within UCSF criteria compared to patients within the Milan criteria. The interpretation of these results should be viewed with caution, since the study was conducted over a protracted period of time from 1985 to 1998. When the data from the last 10 years were analyzed, 34% of patients within Milan criteria and 48% beyond Milan but within UCSF criteria were understaged. On the other hand, when the data from the last 3 years were analyzed, 28% of patients within the Milan criteria and only 8.3% outside Milan but within UCSF criteria were understaged.

Both tumor size and number are important indicators of post-transplant recurrence inherent to the biology of HCC tumor that should be taken into account whenever selecting HCC patients beyond the Milan criteria for LT. This has been well described and definitely demonstrated in the "Metroticket concept (the farther you go in expansion of HCC staging criteria for selection for LT, the more you have to pay in terms of higher recurrence rates and poorer survival)."[11] This model, based on the analysis of 1,556 patients transplanted at 36 centers, provides a linear correlation between tumor diameter and recurrence throughout the observed range. The survival was directly correlated with the size of the largest tumor, number of tumors and presence of microvascular invasion (MiVI) at explant pathology examination. Patients who fell within the "up to 7 criteria" (HCC with 7 as the sum of the largest tumor diameter in cm and number of tumors) and without MiVI, achieved a 5-year overall survival of 71%. These "up to 7 criteria" were compared with Milan and UCSF criteria in a pathological study.[12] "The Metroticket" performed the best as a staging system with a 5-year recurrence rate of 4% in patients within and 51% in patients beyond those "up to 7 criteria". However, this staging system is difficult to use in practice since the MiVI cannot be accurately assessed by any preoperative work-up.

Discrepancies between radiological and pathological assessment prompted a search for more reliable morphometric data that could be used as a selection tool. The impact of total tumor volume (TTV) on patients' outcome after LT was studied recently.[13] A composite score was defined, with patients with a TTV >115 cm^3 or an alpha-fetoprotein (AFP) >400 ng/mL being outside of the criteria. When compared to the Milan and UCSF criteria, the combined TTV/AFP score provided the best prediction of outcome. More recently, the Toronto group reported a series of HCC patients who underwent LT for any size or number of tumor nodules provided that imaging studies ruled out vascular invasion, HCC was confined to the liver and HCC was not poorly differentiated on pretransplant biopsy.[14] Providing aggressive use of bridging therapy, there was no difference in the 5-year overall survival (72% *v* 70%) or disease-free survival (70% *v* 66%) in patients within and beyond the Milan criteria, respectively. This study challenged the importance of size and number of tumors as prognostic factors and emphasized that tumor differentiation may be a more important predictor of biological behavior than multifocal distribution, size, TTV, or MiVI.

The last international consensus conference on LT for HCC concluded that the Milan critera are currently the benchmark for selection of HCC patients for LT. A modest expansion of the number of potential candidates may be considered on the basis of the last studies reported here.

BENEFITS AND RISKS OF TUMOR BIOPSY

As a result of technical refinement, current imaging techniques allow the detection of small liver nodules of <1 cm. When imaging techniques are not definitely conclusive, ultrasound (US)-guided biopsy is the reference option to rule out a HCC. According to the recent guidelines published by the European and the American association for study of the liver,[15,16] a definitive diagnosis of HCC on a background of cirrhosis can be made without tissue analysis in cases of nodules >2 cm

with a characteristic imaging pattern, ie, hypervascularity in the arterial phase and washout in the delayed phase. For nodules between 1 and 2 cm, two concordant imaging techniques showing a characteristic pattern are needed to ascertain HCC in cirrhotic patients. These recommendations also might apply to patients with chronic hepatitis B and not yet fully developed cirrhosis.[17] For patients without cirrhosis, the sensitivity of imaging techniques for HCC is much lower, and the diagnosis then has to be established with a biopsy.

In the era of allocation policy based on the MELD score (defined by International Normalized Ratio [INR], total bilirubin, and creatinine values), it is paramount to get a correct diagnosis of HCC, especially for patients with stage II disease (one nodule 2–5 cm or two to three nodules all <3 cm) who will get extra MELD points. Indeed, these patients, who often have a low physiological MELD score, are unlikely to receive a transplant before excessive tumor progression if they have not received extra points. On the other hand, several studies comparing pretransplant imaging diagnoses to pathology of explanted livers showed that the non-invasive diagnosis of stage I and II HCC is associated with a significant false positive rate.[18–20] This led to a dramatic incorrect organ allocation in 7%–20% of these patients.

Overall, the specificity and the positive predictive value of a tumor biopsy is 100%. The sensitivity varies between 66% and 90%, except for biopsy results obtained with the 21- to 22-gauge needle (sensitivity: 67%) and for nodules smaller than 1 cm (sensitivity: 83%).[21,22] Tumor biopsy is then an excellent method to rule in the diagnosis of HCC. However, to rule out the diagnosis, tumor biopsy is less reliable, especially for nodules <1 cm. In contrast, in patients with lesions between 1 and 2 cm, a single imaging modality showing the typical vascular pattern has a 100% specificity and sensitivity between 47%–65%. Therefore, 40%–60% of patients with a nodule between 1 and 2 cm will still need a biopsy. Furthermore, if a diagnosis of HCC remains uncertain based on imaging techniques, the likelihood that it can be definitely established by US-guided biopsy is high. Of note, the negative predictive value of biopsy remains low (14%).[23]

Percutaneous biopsy of HCC carries a potential risk of tumor seeding along the needle tract of 2.7% with a median time interval between biopsy and seeding of 17 months (range, 3–48 months).[17] Rarely, peritoneal dissemination distant from the puncture site has been reported.[23] Risk factors for needle tract seeding have not been clearly identified, although one study has suggested that this risk could be increased (up to 12%) after radiofrequency ablation, possibly because of the larger diameter of the needle.[24] Finally, bleeding risk is reported only in few studies and occurred in 0%–6.3% of all biopsies.[17]

Tumor biopsy is thus a safe procedure with excellent sensitivity and specificity. It increases dramatically the accuracy of pretransplant diagnosis in patients with cirrhosis in whom radiological findings of the lesion are not typical.

MOLECULAR PROFILING OF HCC FOR LT

Molecular Profiling for LT

Recent technological advances in transcriptomics and proteomics have made it possible to study expression profiles in patient tissues at the mRNA and protein level. Identification of differential activation of various molecular pathways is increasingly being applied to practical advantage in LT, such as identifying hepatitis recurrence, acute cellular rejection, post-transplant liver inflammation, and progression to HCC on the transplant waiting list.[25–27]

Molecular Profiling for HCC

Molecular tumor classification is being used increasingly to identify tumor subsets that are similar when studied by standard histological techniques but which have quite different biological behaviors, growth rates, differentiation potentials, and abilities to invade the portal vein and otherwise to metastasize. The classification of molecular profiles has been based on several factors, including patient survival, HCC growth rate, identification of specific growth-associated signaling pathways, angiogenesis pathways, and increasingly with pathway activation in relation to the action of the burgeoning number of targeted therapies.[28–33]

Molecular Profiling for HCC Treated by LT

Evidence From Transplanted HCC

Initial molecular HCC profiling was done retrospectively. However, increasingly, as expression patterns associated with better or worse survival are emerging, these patterns will be used in patient selection for LT.[34–37]

Predictors of Portal Vein Thrombosis and Metastases

Micro- and macrovascular invasion by HCC, especially of the portal vein, is a major predictor of HCC recurrence and metastasis and poor survival post LT.[38–40] Recent work has focused on identifying biochemical and genetic signatures of HCCs that invade the portal vein, without having to await post-transplantation pathological examination.[41–43]

Microenvironmental Influences on HCC Biology

It has become increasingly evident, both from clinical and molecular profiling and microarray analysis,

that the non-tumor tissue of livers bearing HCCs is a rich source of prognostic information concerning HCC recurrence and metastasis through growth pathway deregulation, as well as the stress pathways, and provides increasing support for the idea that the microenvironment of the tumor is involved in tumor behavior.[44-47]

Choice of Therapies and Response Prediction and Clinical Trial Subset Analyses

The advent of molecularly targeted therapies for treatment of many tumor types has focused attention on prediction of responses in individual patients (personalized medicine), given the idea that a drug targeting a specific pathway is likely to work or inhibit a specific tumor, provided that pathway is intact and not activated by mutations that might make that tumor resistant to the targeting agent.[48] Increasing evidence for the predictive usefulness of identifying normal and mutation-associated pathways that might predict drug response has been found for colon cancer, lung cancer, and melanoma. However, the evidence for prediction of a response to targeted therapies in HCC has been slower to emerge, with suggestive evidence only so far, relating possible sorafenib benefit and tumor phospho-ERK status[49,50] and likewise for the prolonged survival associated with bevacizumab plus erlotinib.[51] Multiple new agents are currently being evaluated in clinical trials for HCC, which target specific pathways, including vascular endothelial growth factor and its receptor (VEGF/VEGFR), epidermal growth factor and its receptor (EGF/EGFR), insulin-like growth factor and its receptor (IGF1/IGF1R), phospho-inositol 3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR), apoptosis, autophagy, ubiquitin, and hepatic stem cell pathways, and correlation and prediction studies relating specific pathway inhibitor effects to expression of their targets in HCC tissue are currently under way. Future clinical trial patients also will need to be stratified according to their tumor molecular profiles.

IMPACT OF MACRO- AND MICROVASCULAR INVASION

It is well known that macroscopic vascular invasion in major vessels is a poor prognostic factor after LT for HCC and is regarded as a contraindication to LT.[52] However, the significance of MiVI as a predictor of poor outcome is still controversial.[52]

Many reports described that the combination of large tumor size, histologic grade (poor differentiation), and MiVI was the strongest factor related to recurrence and poor outcome after LT.[53,54] Furthermore, MiVI was shown to be correlated with the presence of satellite nodules and poor outcome after LT.[54] A prospective study showed that MiVI is significantly more common with large tumors (38% in tumors <4 cm and 60% in tumors >4 cm) and influences survival rates.[55]

Although the risk of HCC recurrence seems to be higher in patients with MiVI, not all patients with MiVI will have recurrence after LT. Some studies were unable to correlate poor results with MiVI, though MiVI correlated negatively with patient outcome. Lee et al found that the number of tumor nodules and the presence of MiVI did not affect tumor recurrence after LT.[56] Currently, diagnosis of MiVI in HCC patients before LT remains a problem due to the lack of highly specific and sensitive markers. Only one study showed the potential usefulness of ^{18}F-FDG (fluoro-deoxyglucose) uptakes on positron emission tomography for predicting MiVI.[57] This should be balanced with MiVI and satellite nodules detected on other preoperative imaging. Large multicenter studies are still needed to assess precisely the predictive value of imaging modalities for MiVI.

There is increasing evidence for the importance of circulating tumor cells in the progression of HCC.[58] The identification of local and circulating stem cells in HCC patients could be used as markers for the diagnosis and treatment of HCC. Recently one study showed that the identification of $CD45^{-}CD90^{+}$ cancer stem cells in both tumor tissues and circulation could be used as a marker and as a target for the diagnosis and therapy of HCC patients.[59] However, the correlation between circulating stem cells detection and MiVI has not been demonstrated yet.

Therefore, MiVI may be an independent risk factor for recurrence and poor outcome in LT. It is more likely to be present in large (>3 cm), multinodular, and histologic high-grade (poorly differentiated) tumors. However, it is still impossible to detect MiVI by conventional imaging methods and there is no widely recognized biomarker for predicting MiVI.

DO PATIENTS BENEFIT FROM BRIDGE THERAPIES ON THE WAITING LIST?

The term "bridge strategies" is reserved for patients on the waiting list who underwent a locoregional treatment so that they can "wait" until they receive a graft.[60] This strategy can be effective either by minimizing the dropout rate from the waiting list or because it improves the outcomes of LT. In this setting, several strategies can be adopted: transarterial chemoembolization (TACE), radiofrequency ablation (RFA), radioembolization, or resection.

The rationale for using TACE as a neoadjuvant therapy prior to LT is twofold: to control tumor growth while the patient is on the waiting list and to induce significant tumor necrosis, which may reduce tumor dissemination during LT. Overall it has been shown that TACE does not improve overall survival after LT neither for early nor for advanced HCC.[61] However,

this procedure does not increase the complication rates after LT. A retrospective case control study investigated the results of TACE on outcome after LT.[62] In this study, there was no difference in the 5-year survival rate (69% with TACE *v* 64% without TACE) but recurrences were less frequent after TACE (13% *v* 23%). It appears therefore that TACE is not harmful and may reduce dropout rates from the waiting list.

In pathological studies, the results of RFA appear to be superior to TACE in term of local tumor control.[63,64] Mazzaferro et al showed in patients who underwent RFA as a bridge treatment to LT that tumor size >3 cm or the presence of large abutting vessels results in a drop in the rate of complete tumor necrosis to 50% or less.[65] RFA appears then to be safe as a bridging therapy for HCC less than 3 cm in size. However, its ability to decrease the dropout rates still needs to be proven in further prospective trials.

Radioembolization represents 5%–10% of bridging locoregional treatment in the organ procurement and transplant network registry, but data available on its impact are scarce and further experience is needed.[60] In a recent study looking at the radiopathological correlation of HCC treated with internal radiation using yttrium-90 microspheres, all targeted lesions had some histologic necrosis and 60% of them showed complete necrosis.[64]

In compensated cirrhotic patients with HCC and a long anticipated time on the waiting list (ie, longer than 1 year),[66] liver resection followed by listing for LT could be applied.[60] The decision for resection depends on liver function and the size and location of the tumor. This strategy allows control of the tumor and a better assessment of its pathological features. In case of poor prognostic factors (poor differentiation, MiVI, absence of capsule), a pre-emptive LT could be advised (ie, before recurrence but after sufficient observation). If the tumor does not show any risk factors for recurrence, LT may be postponed and offered only in cases of tumor recurrence (salvage procedure). Liver resection for small solitary HCC in compensated cirrhosis yields an overall survival rate comparable to LT.[67] Despite a significant recurrence rate, close imaging monitoring after liver resection allows salvage LT in two thirds of the patients with recurrence in intent-to-treat analysis.[67] Recently, Fuks et al evaluated liver resection for HCC as first-line treatment in transplantable patients within the Milan criteria followed by salvage LT in case of recurrence and compared them to a group of patients within the Milan criteria who underwent LT only.[68] In both groups, 5-year overall and disease-free survivals were similar (60% *v* 77% and 56% *v* 40%, respectively). The predictive factors for nontransplantability due to recurrence beyond Milan criteria after liver resection included MiVI, satellite nodules, tumor size >3 cm, poor differentiation, and liver cirrhosis. Therefore, salvage LT should be restricted to patients with favorable oncological factors found on tissue analysis after liver resection.

Bridging strategies with locoregional treatments are probably beneficial in patients when a long waiting time is likely because it decreases dropout rates without impairing post-transplant outcomes. This strategy seems to be indicated for T2 tumors (solitary tumor with vascular invasion or multiple tumors none more than 5 cm) and patients likely to wait longer than 6 months.[60] Pathological studies suggest that there is a marginal advantage for RFA in terms of local ablation. Newer strategies combining TACE and RFA or using yttrium-90 may be promising. Finally, liver resection followed by salvage LT in case of recurrence should be restricted to patients with favorable oncological factors.

WHAT IS THE ROLE OF LDLT FOR HCC?

Even in countries with adequate access to deceased donor liver transplantation (DDLT), it is well established that LDLT is appropriate due to organ shortage, increasing waiting lists, and the expectation that many patients listed for LT will die while waiting for a suitable organ.[69] In this setting, donor safety is of paramount importance and must be a priority knowing that the incidence of operative mortality and morbidity ranges between 0.15%–0.50% and 30%–40%, respectively, when using the right hemi-liver for adult-to-adult LDLT.[70]

If we accept that HCC within accepted criteria for LT is an indication for DDLT, those criteria also should be applied for LDLT. One strong argument in favor of LDLT is that living liver donors, by reducing the number of recipients on the deceased donor waiting list, potentially advantage each person remaining on the waiting list. However, patients with HCC beyond the accepted criteria for LT raise some ethical concerns. To analyze the appropriateness of LDLT, the concept of double equipoise could be used.[71] It describes the balance between the recipient's survival benefit with or without a live donor transplant and the probability of donor mortality risk.[72–75] This balance should be explicitly defined and agreed upon by all parties, including the recipient, donor, surgical team, and society.

The next issue is to know whether it is justified to use different transplant criteria for DDLT and LDLT in HCC patients. Six published studies compared DDLT and LDLT for HCC, including a report from a multicenter consortium of LDLT centers in the United States (Table 1).[76–81] Despite higher recurrence rates in three studies, the overall survival rates of LDLT for HCC compared to DDLT in all studies were not inferior, although one could argue that this difference would eventually translate into a lower long-term survival in the LDLT groups. Given that LDLT is offered on a faster

Table 1. Recurrence and Survival Data After DDLT and LDLT for HCC

Authors (year)	No. of Patients	Recurrence Rate	DFS	Overall Survival
Kulik et al (2004)[79]	LDLT 63	27%	n/a	n/a
Hwang et al (2005)[78]	LDLT 237	n/a	80%	73.2%*
	DDLT 75		80%	61.1%*
Fisher et al (2007)[77]	LDLT 58	29%*	58%	67%
	DDLT 34	0%*	62%	63%
Lo et al (2007)[80]	LDLT 43	29%*	n/a	80%
	DDLT 17	0%*		94%
Di Sandro et al (2009)[76]	LDLT 25	4%	95.5%	77.3%
	DDLT 154	10.5%	90.5%	82.8%
Vakili et al (2009)[81]	LDLT 28	28.6%*	n/a	80%
	DDLT 74	12.1%*		70%

Abbreviations: HCC, hepatocellular carcinoma; DFS, disease-free survival; LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; n/a, not available.
*$P < .05$.

track than DDLT, it is conceivable that many LDLT recipients did not have sufficient waiting time to declare the biologic behavior of their HCC. In contrast, patients who await DDLT and who have a biologically aggressive HCC are likely to progress and then to drop-out from the waiting list, leaving only patients with less aggressive HCC having access to DDLT. Of note, neither the waiting time nor the type of graft (DDLT *v* LDLT) was identified as a risk factor for HCC recurrence. Therefore, prior treatment and HCC tumor biology seem to be more important determinants of the recurrence risk than the type of graft that the patient receives.

Then the question arises as to whether LDLT should be offered for HCC patients in whom tumor stage prevents the use of DDLT. Offering LDLT only for selected patients with advanced HCC cases is based on respect for the principles of donor autonomy and fairness. Since other listed patients are not adversely affected by this process, the required "acceptable" survival may be lower than the expected survival for other deceased donor indications. Such policy requires rigorous safeguards to ensure that the pressure to treat recipients does not result in donor coercion, increased risk-taking by the donor surgical team, or donor depression after a poor LDLT outcome; and establishment of a minimum survival expectation. On this difficult question, the jury of the international consensus conference on LT for HCC stated that there are currently no high-quality data to endorse or ban the use of different criteria for DDLT and LDLT for HCC. Centers choosing to use different LT criteria for HCC must carefully weigh respect for donor autonomy with the responsibility to protect the donor. Each center must explicitly state its policy regarding living donation for HCC patients with a poorer prognosis.[82,83]

WHAT IS THE IMPACT OF IMMUNOSUPPRESSION ON HCC RECURRENCE AFTER LT?

Despite the careful selection of patients with HCC for LT, 10%–20% of liver transplant recipients who have HCC in the native liver develop tumor recurrence after transplantation.[3] In this setting, the main concern comes from immunosuppressant therapy, which inhibits the tumor-suppressive properties of the immune system and, therefore, may increase the likelihood of HCC recurrence after LT. Indirect evidence of a favoring effect of immunosuppressant on tumor genesis comes from the observation that the incidence of malignancies is significantly higher in organ recipients than in the general population.[84] The calcineurin inhibitors (CNIs), namely, cyclosporine and tacrolimus, represent the main pharmacological immunosuppressants used in organ transplantation. These agents affect T-cell recognition of alloantigen and signal transduction via the calcium-dependent calcineurin pathway. Besides inhibiting interleukin (IL)-2 expression, they increase transforming growth factor (TGF)-β1, a potent inhibitor of IL-2–stimulated T-cell proliferation. Unfortunately, TGF-β1 depresses the natural killer cell–mediated anti-tumor immune response, and is implicated in the development of the metastatic process.[85] A newer category of immunosuppressant drugs, the mTOR inhibitors, have raised a high degree of interest. Indeed, these drugs are associated with strong immunosuppressant activity, due to the blocking of IL-2 stimulation of lymphocyte proliferation, and have a potential anti-cancer effect, which has been demonstrated in the experimental setting. The anti-cancer effect is mainly related to the impairment of VEGF production and the blockage of VEGF-induced vascular endothelial cell stimulation.[86]

Table 2. Studies Investigating HCC Recurrence After LT in Patients Receiving Sirolimus as Immunosuppression

Authors	Year	Type of Study	Patients (n)	Outcomes
Zhou et al[95]	2008	Retrospective cohort	73	6-month recurrence rate: 4% *v* 20%*
Zimmerman et al[96]	2008	Retrospective cohort	97	5-year DFS: 79% *v* 54%*
Chinnakotla et al[91]	2009	Case control	227	5-year DFS: 80% *v* 59%*
Toso et al[92]	2007	Retrospective cohort	70	Recurrence 6% for Milan *v* 17% over Milan
Vivarelli et al[94]	2010	Matched cohort	62	3-year DFS: 86% *v* 56%*
Toso et al[93]	2010	Retrospective cohort	2491	Patient survival: hazard ratio = 0.53

Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; DFS, disease-free survival.
*Patients treated with sirolimus versus calineurin inhibitors.

Experimental data provided good evidence that CNIs promote cellular growth of malignant cells by enhancing cancer cell invasions and by inhibiting DNA repair.[87,88] On the other hand, mTOR inhibitors like sirolimus inhibit HCC hepatoma cell proliferation in vitro and downregulate VEGF expression. In animal models, rats receiving sirolimus had significantly longer survival and developed smaller tumors and fewer extrahepatic metastases compared to controls.[89,90]

In the last 5 years, clinical studies investigated whether mTOR inhibitors affect the post-transplant recurrence rate of HCC.[91-96] As reported in Table 2 these studies showed significant benefit on HCC recurrence rates after LT in patients receiving sirolimus as immunosuppressant. However, because none of these studies were randomized, there is a significant potential for selection, treatment, or reporting bias towards more positive findings of sirolimus. Recently, five of these six studies with a total of 2,950 patients were included in a meta-analysis.[97] The pooled results showed that in comparison with sirolimus-free regimens, sirolimus-based regimens decreased tumor recurrence (odds ratio [OR], 0.42; 95% confidence interval [CI], 0.21–0.83) and improved 5-year overall survival (OR, 2.47; 95% CI, 01.72–3.55). However, as stated by the authors themselves, since none of the included studies performed a statistical analysis of the cause of death, this meta-analysis could not determine whether the survival improvement was due to sirolimus itself or to the CNI reduction in the protocol considering the nephrotoxicity and other side effects of CNIs. The other limitations of this meta-analysis are the lack of randomized controlled trials (RCTs) included in the meta-analysis resulting in a potential selection bias; the lack of subgroup analyses based on potential confounding factors; and the fact that the analyses of each endpoint were based on only two or three of the included studies because of missing data.

Although retrospective and uncontrolled studies favor the use of mTOR inhibitors in LT for HCC patients, confirmatory data from a hypothesis-driven RCT are still missing. Up to now, no recommendation can be made for choosing any type or dose of immunosuppressant therapy to influence the incidence or the prognosis of HCC recurrence after LT. The SiLVER05 multicenter RCT studying the potential benefits of sirolimus in this setting will help to answer definitively this question.[98]

IS THERE A PLACE FOR ADJUVANT THERAPY AFTER LT FOR HCC?

Efforts to decrease post-transplant liver recurrence rates and to further improve overall survival have included anti-tumoral adjuvant treatment after LT for HCC. Adjuvant therapy may achieve this goal through the elimination of undetectable micrometastases present at the time of the transplantation. However, because of possible adverse effects, the potential benefits of adjuvant therapy must be weighed against the potential risks. Furthermore, it should be kept in mind that the use of frequent combined neoadjuvant or intraoperative therapies makes the assessment of the post-transplant adjuvant therapy more difficult. For example, some patients may receive chemoembolization or local treatment such as RFA before LT.

Taking into consideration these limitations, eight nonrandomized studies suggested a very modest benefit from adjuvant chemotherapy.[99-106] Four RCTs assessing adjuvant monotherapy or combined chemotherapy failed to demonstrate any benefit.[107-110] More recently, an RCT testing a monoclonal antibody reported encouraging preliminary results.[111] As listed in Table 3, two randomized studies using the single-agent doxorubicin during LT did not demonstrate any significant benefit.[108,109] In the RCT from Li et al,[107] epirubicin was administrated in both groups and an adenovirus-mediated delivery of herpes simplex virus thymidine kinase therapy injected in the peritoneum in the experimental group was evaluated. Epirubicin alone did not show any survival benefit in advanced HCC patients. Interpretation of the results of the virus-mediated thymidine

Table 3. Randomized Controlled Trials Assessing Adjuvant Therapies After LT for HCC

Authors (year)	Treatment	Treated Patients/ Controls (n)	Follow-up (years)	DFS (treated patients/controls)	Overall Survival (treated patients/ controls)
Pokorny et al (2005)[108]	Doxorubicin	34/28 (outside Milan)	5	43%/53% (NS)	38%/40% (NS)
Söderhahl et al (2006)[109]	Doxorubicin	19/27 (outside Milan)	3	63%/50% (NS)	63%/70% (NS)
Li et al (2007)[107]	Epirubicin in both groups + thymidine kinase in peritoneum	23/22 (outside Milan)	3	43%/9% ($P = .001$)	69%/20% ($P = .001$)
Xu et al (2007)[111]	Licartin	30/30 (outside Milan)	1	57%/27% ($P = .017$)	82%/62% ($P = .001$)
Zhang et al (2011)[110]	FOLFOX	29/29 (outside Milan)	3	48%/51% (NS)	79%/62% (NS)

Abbreviations: HCC, hepatocellular carcinoma; LT, liver transplantation; DFS, disease-free survival; FOLFOX, oxaliplatin + leucoverin + fluorouracil; NS, not significant.

kinase therapy in such a patient population and with a very small sample size is very difficult. Similarly FOLFOX did not show any benefit on 3-year disease-free or overall survival in HCC patients beyond the Milan criteria.[110] Licartin, an iodine 131–radiolabeled murine monoclonal antibody that specifically binds to HCC cells expressing an HCC-specific molecule (HAb18G/CD147), was tested in a small placebo-controlled, randomized, double-blind study in China.[111] Only a small number of HCC patients beyond Milan criteria were included and the 1-year follow-up was short. However, the benefit on recurrence rate and overall survival is encouraging but needs to be confirmed at long-term. In summary, results from controlled studies are mixed, negative, inconclusive, or require confirmation. As recommended by the last international consensus conference on LT for HCC, the current evidence does not justify the routine use of adjuvant anti-tumor therapy after LT for HCC outside of a controlled clinical trial.[82]

Some hope has been placed in sorafenib. Sorafenib is a multi-targeted tyrosine kinase inhibitor, which was shown to have an anti-tumoral effect in patients with advanced unresectable HCC.[112] It is currently being studied as adjuvant therapy after resection or ablation of HCC in a multicenter phase III trial (STORM trial [Sorafenib as adjuvant Treatment in the prevention of Recurrence of Hepatocellular Carcinoma]).

CONCLUSION

In less than 20 years, LT for HCC rapidly developed from a highly disappointing and controversial procedure to one of the most successful treatments in oncology. The results of LT for HCC continue to improve with time, and outcome is only marginally worse than for end-stage liver disease itself. A better understanding of tumor biology and prognostic factors has allowed the better selection of HCC patients who can benefit from LT. Undoubtedly, an increasing number of HCC patients will have access to LT due to the acceptance of extended selection criteria, earlier detection of tumor, control of tumor load while patients wait for a graft, use of living donor, tailored immunosuppression and adjuvant therapies. In the context of organ shortage, this success of LT for HCC is not without its ethical problems with respect to patients with end-stage liver disease and should prompt an increase in the pool of donor organs.

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