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SUPPLEMENT

Place of Liver Transplantation in the Treatment of Hepatocellular Carcinoma in the Normal Liver

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Hepatocellular carcinoma (HCC) is a relatively common cancer and occurs mainly in patients with liver cirrhosis (85%-95%). A significant number of cases are, however, diagnosed in normal and noncirrhotic/nonfibrotic livers. In contrast to HCC in a cirrhotic liver, noncirrhotic hepatocellular carcinoma (NC-HCC) predominantly occurs in young and healthy female patients in their 30s, and the diagnosis is frequently made at an advanced stage in the absence of a clear etiological factor.[1-3] The same holds true for the uncommon fibrolamellar hepatocellular carcinoma (FL-HCC) variant.[1-3]

Several studies have shown that the 3-year overall survival (OS) rates with different pharmaceutical, radiological, and surgical therapies for HCC (if they are adequately performed) are approximately 60%.[4] After 3 years, the results of these treatments start to diverge substantially with respect to OS and, most importantly, with respect to disease-free survival (DFS). Long-term follow-up (5-10 years) has clearly shown that surgical resection is the only curative treatment for any kind of HCC.[2-5] With respect to very long-term DFS (>5 years), liver transplantation (LT) offers the best results.[2,4-6] In order to be successful, surgery has to be adapted to the tumor, the underlying condition of the patient, and the patient's liver. Liver resection and LT should have complementary roles rather than competing ones, and they should be associated with each other instead of being opposed.[5] Partial resection for HCC can be considered only for patients with well-compensated cirrhosis or fibrosis or with normal liver tissue. For patients with decompensated liver disease, cirrhosis, or a technically unresectable tumor, LT offers the best chance for a cure. This option indeed addresses the tumor as well as the underlying liver disease.

Despite the extensive experience with LT for the treatment of HCC in patients with cirrhosis, the experience with LT for the treatment of NC-HCC is anecdotal and is limited to situations in which resection is not possible.

The aims of this study were as follows: (1) to analyze the results from recent series of partial liver resections for NC-HCC, (2) to compare these results with the results of LT for the same condition; and (3) to propose an adaptation of the therapeutic algorithm for NC-HCC on the basis of these analyses.

MATERIALS AND METHODS

A review of the literature on resection and LT for HCC in patients with noncirrhotic livers was undertaken with the MEDLINE, Science Citation, Embase, and

Abbreviations: AFP, alpha-fetoprotein; DFS, disease-free survival; ELTR, European Liver Transplant Registry; FL-HCC, fibrolamellar hepatocellular carcinoma; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; NC-HCC, noncirrhotic hepatocellular carcinoma; NR, not reported; OS, overall survival; TNM, tumor-node-metastasis.

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Cochrane databases, and the following Medical Subject Headings keywords were used: *hepatocellular carcinoma*, *hepatocellular cancer*, *liver transplantation*, *liver resection*, and *normal liver*. The search limit was set to human studies in English between January 1995 and May 2011. One exception to the English language limit of this analysis was the inclusion of the 2006 yearly report on HCC from the Association Française de Chirurgie.[1] This monograph deals with a French multicenter survey of the largest series of patients undergoing partial liver resection for HCC in a normal liver. Unfortunately, this huge experience has never been published as a full article in the medical literature. Full texts were consulted after abstract reviews. Duplicates, registries, and repeated series from the same center were excluded from this review. Only patients whose tumor characteristics were described and for whom recurrence and outcome data were available were finally included in this study. Forty of 2859 articles were analyzed.

Twenty-six series on NC-HCC and liver resection have been published[1,7-32] (Table 1). Twenty of these articles have relevant information on outcomes. Fourteen have information on LT for NC-HCC. Although approximately 300 patients have been reported to have undergone transplantation for NC-HCC, the analysis of the literature with respect to the impact of LT on NC-HCC outcomes is particularly difficult because only 8 transplant articles (dealing with only 27 patients) contain enough detailed information to allow the analysis of risk factors for tumor recurrence. Twenty-one of these patients had FL-HCC, and only 6 had classical HCC.[33,34]

The number of reported patients, the inclusion of patients with viral hepatitis and/or alcoholic liver disease, the OS, DFS, and recurrence rates, the operative mortality, the risk factors influencing survival, and tumor recurrence were analyzed. The literature review of the transplant experience for NC-HCC was completed for the 2010 consensus conference on LT for HCC (Zurich, Switzerland) with data obtained from a recent analysis of 105 liver recipients entered into the audited European Liver Transplant Registry (ELTR). The ELTR series included 62 patients (7 had FL-HCC) who underwent primary LT for NC-HCC and 43 patients (4 had FL-HCC) who underwent rescue LT for recurrence after partial liver resection. The preliminary results of this analysis, which have been published in abstract form,[35] are included in this article with the permission of the primary study investigators (H.M. and R.J.P.), who were part of the consensus conference committee. The detailed results of this study, including all characteristics of the studied patients, are currently under final analysis by the European Society for Organ Transplantation/ELTR boards. Because the tumor characteristics of the NC-HCC and FL-HCC patients who underwent LT were similar (except for the tumor size and the Milan inclusion criteria), the results for NC-HCC and FL-HCC were considered together in the European Society for Organ Transplantation/ELTR study in order to allow a more conclusive statistical analysis.

RESULTS

Liver Resection[7-13,15-32] (Table 1)

The articles reviewed for information on partial liver resection for NC-HCC include 2263 patients; the numbers of patients in these series range from 20 to 254.[7-13,15-32] The results of the French multicenter study,[1] which includes the world's largest series of resections for HCC arising in normal livers (ie, nonfibrotic and noncirrhotic), are discussed separately. The larger studies come from regions with high rates of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. The interpretation of the literature on liver resection for NC-HCC is strongly confounded by differences in the inclusion criteria. Almost no studies have dealt with HCC in strictly normal livers. Some studies have included only patients with noncirrhotic and nonfibrotic livers without underlying viral hepatitis or alcohol abuse; most reports, however, have included many patients with viral hepatitis or evidence of alcohol abuse. Moreover, almost no information about the increasing risk factors of steatosis and/or steatohepatitis is available in these series. In these reports, the rates of HBV and HCV infections ranged from 4.8% to 70% and from 2.5% to 68%, respectively; the incidence of alcohol intake varied from 7.1% to 70%. It is, therefore, difficult to compare the data in these various reports because of the different rates of the risk factors. This observation is very important because it has been estimated that approximately 30% of HCV-associated HCCs develop before cirrhosis is established. Thus, the presence of HCV and HBV infections certainly influences recurrence after resection as well as survival.

Patients with NC-HCC present late, so they usually have large tumors. The mean/median sizes of the tumors in the various studies ranged from 8 to 14 cm. In most cases, the diagnosis was made when clinical symptoms and signs related to the tumor mass (eg, pain, discomfort, and a palpable mass) occurred. The preserved liver function allowed more extensive liver resections in these patients and made the achievement of R0 resection (macro- and microscopic tumor-free resection margin) likely. Over the past few decades, because of better selection criteria and surgical techniques, the results of partial liver resection have steadily and markedly improved. Computed tomography–assisted liver volumetry, preoperative portal vein embolization, anatomical surgery, intraoperative ultrasound-guided surgery, and parenchymal transection with (intermittent) inflow occlusion or even total vascular exclusion have all played important roles in safely extending the boundaries of partial liver resection.[33-36] Extensive liver resection, which leaves up to 20% of the normal functional liver volume, can be performed quite safely in these patients; this is evidenced by the low operative mortality rate, which ranges from 0% to 6.4%. The 1- and 5-year OS rates

TABLE 1. Literature Review of HCC Patients Without Cirrhosis Who Were Treated With Hepatic Resection

Study	Patients (n)	5-Year Survival (%) OS	DFS	Recurrence Rate (%)	Median Interval (Months)	Risk Factors
Sasaki et al.[7] (1992)	48	68	54	44	NR	NR
Bismuth et al.[8] (1995)	68	40	33	59	NR	NR
Smalley et al.[9] (1988)	29	25				High histological grade, severe necrosis, hepatomegaly, hemoperitoneum, and adjacent organ involvement
Fong et al.[10] (1999)	54	42		66	20	Tumor size, AFP level >2000 ng/mL, and vascular invasion
Poon et al.[11] (2000)	155	46	35	51	NR	
Shimada et al.[12] (2000)	65	65	40		NR	NR
Nagasue et al.[13] (2001)	126	50	31		NR	Portal vein invasion, HCV infection, blood loss, intrahepatic metastases, and resection margin
Belghiti et al.[15] (2002)	53	50				Vascular invasion, poor differentiation, and tumor diameter
Chen et al.[16] (2003)	254	36	24	57	12	Multiple tumors, blood transfusion, resection margin, and liver function
Grazi et al.[17] (2003)	135	51	46	30	28	Blood transfusion and age >60 years
Verhoef et al.[18] (2004)	22	68	56			Microvascular/macrovascular invasion and lymph node invasion
Chang et al.[19] (2004)	222	53	37	59	52	Advanced TNM stage
Lang et al.[20] (2005)	83	30		63	25	Vascular invasion
Dupont-Bierre et al.[21] (2005)	88	44		41	25	Multiple tumors, macroscopic vascular invasion, and nonuse of adjuvant ^{131}I-iodized oil
Laurent et al.[22] (2005)	108	29	43	52	7	Blood transfusion, absence of tumor capsules, satellite nodules, and resection margin <1 cm
Cherqui et al.[1] (2006)	586	53	40	60	>12	Tumor size >5 cm, number of tumors, microvascular/macrovascular invasion, poor differentiation, and R0 resection
Capussotti et al.[23] (2006)	47	34	31			Tumor size >10 cm, satellite nodules, and resection margin
Eguchi et al.[24] (2006)	29	65	56			NR
Taura et al.[25] (2007)	127	81		56	60	Tumor burden, vascular invasion, and AFP level
Hubert et al.[26] (2007)	29	71	59	38	42	Age >50 years, poor differentiation, and satellite nodules
Bège et al.[27] (2007)	116	40	33	65	79	Resection margin, vascular invasion, and HBV infection
Lubrano et al.[28] (2008)	20	64	58	40	NR	Resection margin and perioperative cytolysis
Rayya et al.[29] (2008)	54	48		27	24	NR
Xu et al.[30] (2008)	96	48	33	73	57	TNM staging
Sotiropoulos et al.[31] (2009)	92	40	25	62	28	Resection margin, vascular invasion, and TNM staging
Smoot et al.[32] (2011)	143	38	42	58	27	Multiple tumors (≥2), poor differentiation grade, age >65 years, blood transfusion, and male sex

after liver resection for NC-HCC range from 62% to 97% and from 25% to 81%, respectively. The 1- and 5-year DFS rates range from 49% to 84% and from 24% to 59%, respectively. The enhanced feasibility of large liver resections and the longer survival times have shifted the attention of the liver community from (early) perioperative mortality to (late) tumor recurrence. The reported rates of tumor recurrence, which most frequently occurs in the liver (but less than in patients with cirrhosis), range from 30% to 73%. These worrisome numbers might be even higher because systematic long-term follow-up is missing in most reports. The early diagnosis of tumor recurrence is important because it may allow repeat resection with good long-term outcomes in up to 30% of patients. Tumor recurrence, especially within 1 year,

is predictive of poor OS and is a major cause of death. It remains unanswered whether recurrence is due to de novo cancer in a diseased liver (especially in HBV- and HCV-infected patients) or to the evolution of micrometastases. Several factors, such as daughter or satellite nodules, multiple tumors, microvascular/macrovascular invasion, R1 (microscopic tumor invasion of resection margin) resection, and a short interval (usually 1 year) between resection and appearance, are predictive of recurrence and, therefore, favor the latter hypothesis.

R0 resection has the greatest impact on OS and DFS. Other clinical and pathological factors that significantly influence OS and DFS are intrahepatic metastases (also called daughter or satellite nodules or multiple tumors), tumor capsule and lymph node involvement, microvascular/macrovascular invasion, the absence of a tumor capsule, perioperative blood loss, and blood product use. The significant impact of blood transfusions on outcomes, which has been observed by several Western and Eastern groups, underlines the importance of adequate surgical techniques. Blood transfusions may be a surrogate marker of other factors, such as larger tumors requiring larger resections or the presence of an underlying liver disease with an associated coagulopathy; the effects of blood transfusions could also be related to an immunomodulatory effect that possibly stimulates tumor growth. Although an age greater than 60 or 65 years, elevated preoperative levels of aminotransferases, resection margins < 1 cm, poor tumor differentiation, HBV and HCV infections, elevated alpha-fetoprotein (AFP) levels, and the nonuse of adjuvant, intra-arterial ^{131}I-iodized oil injections have all been correlated with unfavorable outcomes, they seem to have less prognostic value. Interestingly, the tumor size has not been a predictor of survival in several studies.

The French multicenter NC-HCC study, which includes 586 patients, identified the tumor size (>5 cm), the number of tumors, microvascular/macrovascular invasion, poor tumor differentiation, and R0 resection as significant negative prognostic factors.[1] The 5-year OS rate was 53%. The 5- and 10-year DFS rates were 40% and 30%, respectively. Unfortunately, this high-volume study suffers from incomplete data for many patients.

The very recently published retrospective study of the larger Mayo Clinic series, which includes 143 well-documented NC-HCC patients undergoing partial liver resection, is particularly interesting in the context of this consensus conference publication.[32] The median DFS time was 2.4 years; the 5-year OS and DFS rates were 38% and 42%, respectively. Despite a mean tumor diameter of 10.3 cm, macrovascular invasion and microvascular invasion were present in only 13% and 8% of the cases, respectively. This finding suggests that vascular invasion may be a delayed feature of the intrahepatic growth of HCC in a noncirrhotic liver. The presence of 2 or more tumors (and thus not the tumor diameter) was the only independent predictor of tumor recurrence. Multiple tumors, male sex, an age >65 years, and a high histological grade were predictors of OS. Because 75% of the recurrences occurred in the liver, we can rightly address whether LT would have been a better treatment for the high-risk patients.[32]

The aforementioned risk criteria and considerations could be used preoperatively to identify which patients would most likely benefit from surgery and eventually from primary or salvage transplantation and which ones would be suitable candidates for adjuvant therapy.

In summary, the occurrence and presentation of NC-HCC are well documented, and liver resection is currently still the preferred therapeutic option whenever it is technically feasible. These young patients usually tend to present late with large tumors, and because of their relatively good liver function, they are able to tolerate extensive liver resections. Extensive operations can nowadays be performed safely with acceptable long-term OS. Several risk factors that have an impact on OS and DFS have been identified. Tumor recurrence after resection continues to be a major problem, and this indicates that there may be a place for adjuvant treatment and/or LT in the treatment of these patients.

LT[37-42] (Table 2)

In 1999, Houben and McCall[33] published the reported experience with LT for HCC in patients without an underlying disease (1966-1998). One hundred twenty-six LT procedures were reported in 16 articles. The results were very poor: the 5-year OS rates for NC-HCC and FL-HCC patients were 11.2% and 39.4%, respectively. This analysis unfortunately could not identify any prognostic factors. The authors concluded that LT should not be proposed for patients with NC-HCC and should be proposed only for very select patients with FL-HCC. These conclusions clearly influenced the LT community because patients with NC-HCC are currently only rarely considered for LT. The reasons for this are multiple: (1) the reluctance of liver surgeons to take into consideration the possibility of LT as an initial therapeutic option; (2) the common scenario in which these tumors are already beyond the Milan criteria (designed for patients with HCC and cirrhosis) at presentation; (3) the fear that LT followed by immunosuppression will favor tumor recurrence; (4) the notion of utility, which restricts transplantation in an era of organ shortages to those patients who will benefit the most from LT (ie, those presenting with liver failure and less advanced tumors); and (5) the fact that patients with NC-HCC do not benefit from an exception status in the Model for End-Stage Liver Disease–based liver allocation system.

The high incidence of tumor recurrence after extended resection and the (sparse) reports of long-term DFS after LT for tumor recurrence after liver resection challenge the concept that liver resection is

TABLE 2. Literature Review of HCC Patients Without Cirrhosis Who Were Treated With LT

Study	Patients (n)	5-Year Survival (%) OS	5-Year Survival (%) DFS	Recurrence Rate (%)	Risk Factors
Houben and McCall[37] (1999)	126	FL-HCC: 39.4 NC-HCC: 11.2		>50 >50	NR NR
Pichlmayr et al. (1995)[40]*	8	49		38	>1 tumor and lymph node invasion
Figueras et al. (1999)[41]	5	60		20	NR
Schlitt et al. (1999)[42]	25	27		NR	
Pinna et al.[43] (1997)*	13	36.3	30.8	69.2	Tumor stage, macrovascular invasion, and lymph node invasion
El-Gazzaz et al.[44] (2000)*	9	50	33	55	Tumor stage
Mergental et al.[39] (2007)					
Primary LT	62	49	49		Macrovascular invasion and lymph node invasion
Rescue LT	43	58	48		Macrovascular invasion and <12-month delay between resection and LT

NOTE: Only series with 5 or more patients are included.
*FL-HCC only.

the treatment of choice for all patients with NC-HCC. It is conceivable that LT as an initial option could offer better outcomes to some patients with NC-HCC in comparison with partial liver resection. The aforementioned risk factors that are associated with a high recurrence rate after liver resection could be very helpful in identifying subgroups of NC-HCC patients who would benefit from LT. The Milan criteria (1 lesion < 5 cm or 3 lesions < 3 cm), which have been validated in the therapeutic algorithm for HCC in patients with cirrhosis, are not applicable to patients with NC-HCC because virtually all these patients have tumor diameters and numbers exceeding these criteria. Lymph node invasion and vascular invasion are the main predictors of recurrence and DFS after LT. An in-depth analysis of 27 well-documented NC-HCC patients who underwent LT (including 21 FL-HCC patients) and 62 ELTR patients who underwent primary LT for unresectable NC-HCC (including 7 FL-HCC patients) supports this.[38,39] In the ELTR study, the actuarial 5-year OS and DFS rates were 49% and 49%, respectively. The median tumor diameter in this patient group was 11 cm; only 5% of the patients fulfilled the Milan criteria. In agreement with the data obtained after partial liver resection, the tumor diameter, more than 4 tumor nodules, and microvascular invasion were not identified as significant determinants of survival after LT, whereas macrovascular invasion and lymph node invasion were (the 5-year survival rate was 45% with invasion and 59% without invasion). Similar observations were made in the group of 43 ELTR patients (including 4 patients with FL-HCC) who underwent salvage LT for intrahepatic tumor recurrence after liver resection. The actuarial 5-year OS and DFS rates in this group were 58% and 48%, respectively. Despite a significantly lower median tumor diameter of 3 cm (in comparison with the primary LT patient group), only 25% of these patients fulfilled the Milan criteria. Macrovascular invasion and a time period of less than 12 months between the previous partial resection and tumor recurrence were significant risk factors for poor outcomes. This short time span probably reflects a more aggressive tumor biology. Concise pathological assessments of the resected tumor and the nontumor liver tissue could thus be very helpful in identifying those patients with a high risk of tumor recurrence after liver resection and LT.

In summary, because the incidence of tumor recurrence after (extended) liver resection is high and rescue LT for tumor recurrence can be curative, there is a possible role for LT in patients with NC-HCC. Macrovascular invasion, lymph node invasion, and an interval of less than 12 months between the previous partial resection and recurrence (in the case of tumor recurrence) are significant risk factors for poor outcomes. The tumor diameter and the Milan criteria do not significantly affect outcomes.

Separate Note on FL-HCC[43-50]

Because the analysis of the literature shows that NC-HCC and FL-HCC are still perceived differently on account of their different clinical presentations, courses, imaging results, and outcomes, some brief remarks about this tumor variant are made here.

FL-HCC is a very rare and well-differentiated HCC tumor variant that accounts for 0.8% to 1% of all HCCs. This tumor is slow-growing and occurs only in young patients with a normal liver. FL-HCC frequently expresses the marker des-gamma-carboxyprothrombin (DCP); AFP is expressed in less than 10% of these

patients. FL-HCC is said to be associated with a (more) favorable prognosis.[45-47] In fact, FL-HCC is an aggressive tumor associated with a less than 50% 5-year OS rate, even in resectable cases. There are several reasons for this discrepancy and the frequently optimistic results reported for FL-HCC: (1) the series are usually small and lack statistical power; (2) the diagnostic pathological triad necessary to unequivocally diagnose this subtype of HCC is frequently missing; (3) FL-HCC often occurs in cirrhotic or abnormal livers; (4) follow-up is frequently lacking; and (5) most importantly, the outcomes of FL-HCC are mostly compared to the outcomes of HCC in general.[46,47] A literature review by Kakar et al.[43] clearly showed that the outcomes of FL-HCC and NC-HCC are similar when same-stage diseases are considered; the outcomes of FL-HCC are much better than the outcomes of HCC with cirrhosis. The results of the ELTR study (unpublished data, 2011) confirm these findings. These observations, along with the fact that (1) FL-HCC did not differ from other HCCs arising in a normal liver with respect to any variable (except for the tumor size and the Milan inclusion criteria)[39] and (2) the proliferative activities of these tumor variants (eg, as determined by immunohistochemistry for Ki-67) were also similar,[35,43,44] explain why HCC in normal livers and FL-HCC were deliberately pooled together in the ELTR study. This allowed a valuable statistical evaluation of the place of LT in the treatment of NC-HCC to be made.

Resection with extensive lymphadenectomy represents the only curative option for FL-HCC; without surgery, the survival time ranges from only 9 to 14 months. Lymphadenectomy is necessary because lymph node involvement is more frequent in comparison with HCC in patients with cirrhosis. This can be explained by the fact that the tumor burden is usually larger, and the hepatic lymph outflow remains present in a normal liver parenchyma. The 5-year OS rate after surgery reaches 50% (range = 32%-66%). Tumor recurrence can occur late, even after 5 or 10 years, and repeat hepatectomy (reported in 20%-60% of patients) can significantly prolong survival.[45,48] Vascular involvement and lymph node involvement are significant prognostic factors, but the tumor number, the tumor size, and the use of chemotherapy are not.[48] The somewhat better results reported after hepatectomy versus LT can be explained by the more advanced tumor stages and immunosuppression in liver recipients, as shown in the transplant series from Hannover (8 patients),[48] Birmingham, UK (9 patients),[44] and Pittsburgh (13 patients).[43] For example, 90% of the Pittsburgh patients were determined to be stage IVA or IVB. The 5-year OS rates for 28 resection patients and 13 transplant patients were 88% and 36.3%, respectively; the 5- and 10-year DFS rates were 33% and 30.8%, respectively. The 5-year survival rate after recurrence was 28%.[43] The 5-year OS rate of the partial hepatectomy series from the Memorial Sloan-Kettering Cancer Center (New York, NY), which included 28 patients, reached 56%.[48] There is some indication that adjuvant chemotherapy (a combination of 5-fluorouracil and interferon) may be useful and more applicable in these patients because they present with normal residual liver tissue.[49,50]

In conclusion, at the request of the consensus conference committee, we have examined the reported results of partial liver resection and transplantation in NC-HCC patients. Although the reported experience, especially in the field of LT, is small, the (surprisingly) high tumor recurrence rate after liver resection and the few reports of successful outcomes after LT for intrahepatic recurrence after partial resection in these patients may indicate that NC-HCC is an underused indication for LT. There is also growing evidence that FL-HCC and (well-differentiated) NC-HCC should be seen as a global entity and not as 2 very different tumor variants for which LT is exceptionally indicated. By enlarging the studied patient cohorts, this approach would allow better predictions to be made about the value of LT in patients with NC-HCC. The analysis of the larger ELTR series with 105 patients, which will be submitted in the very near future for publication, will be a major step forward and will allow transplant physicians to obtain better insight into this particular indication for LT. Appropriate patient selection and perioperative care should provide these mostly young patients access to potentially curative LT. Living donor LT will undoubtedly play a more important role in LT access for NC-HCC patients, who are at a clear disadvantage in the Model for End-Stage Liver Disease–based allocation system. In contrast to patients with HCC and cirrhosis, the Milan criteria and especially the tumor diameter do not seem to play preponderant roles in the outcomes of these patients. The most important factors for increased recurrence in the studied patient cohorts are multiple tumors, R0 resection, macrovascular invasion, and lymph node invasion. These risk factors for tumor recurrence must, therefore, be taken into consideration in order to adequately select candidates for LT. The ideal NC-HCC transplant candidate is that patient for whom, in the absence of macrovascular and/or lymph node invasion, secure R0 liver resection of a large tumor cannot be guaranteed and in whom 2 or more tumors have been diagnosed. In the case of recurrent intrahepatic HCC after resection, the time delay and the tumor biology of the (available) resected specimen should be taken into account in order to justify the indication for LT. In this context, it cannot be stressed enough that transplantation as a treatment for any kind of HCC includes both major surgery and immunosuppressive medications. Adjuvant chemotherapy and optimized immunosuppression (probably including rapamycin) should be further explored in order to improve the outcomes of LT in these particular recipients.[49-51] We hope that the results of the ongoing SILVER study[52] will confirm the experimentally proven antitumor properties of mammalian target of

rapamycin inhibitors in the clinical transplant setting.

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