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ORIGINAL ARTICLE

DIFFICULTIES OF LIVING DONOR LIVER TRANSPLANTATION FOR HEPATOCELLULAR CARCINOMA PATIENTS: EXPERIENCE FROM FIRST 150 CASES

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Abstract

Introduction: Living donor liver transplantation (LDLT) can provide life-saving therapy for many patients with hepatocellular carcinoma (HCC), who otherwise would succumb due to tumor progression. Offering LDLT to patients with HCC, however, raises complex issues for the donor, the recipient, and the medical team.

Methods: The records of patients with HCC among the 150 recipients who underwent LDLT at National Liver Institute (NLI), Menoufiya University, Egypt, from April 2003 to October 2011, were retrospectively revised. The aim was to answer several questions: Should we expand the criteria for liver transplantation for HCC? What is the response to loco-regional therapy and role of tumor down-staging? What are the difficulties of evaluation? Is there especial technique considerations? What about the outcome and recurrence?

Results: HCC was the indication of LDLT in 35 (23.3%) of cases. Of these 35 HCC cases, 28 (80 %) cases were within Milan criteria, 4 (11.4%) cases had benign portal vein thrombosis (PVT). positron emission tomography (PET) was performed two weeks before LDLT to exclude distant HCC metastases. Exploration-first and Portahepatis-first were the used techniques. Three (8.5%) cases had recurrent HCC

Conclusion: Milan criteria remain a valid tool to select candidates for LDLT to achieve optimal results but expanding the criteria give chance to more patients with comparable outcome. Alfa-fetoprotein (AFP) of >1000 ng/mL should be considered an exclusion criterion for liver transplantation. PET scan might be of particular value in excluding extrahepatic HCC extension. Benign PVT does not contraindicate LT for HCC patients. Exploration-first and Portahepatis-first techniques are recommended in HCC cases.

Keywords: Hepatocellular carcinoma, Living donor liver transplantation, Milan criteria, recurrent HCC.

INTRODUCTION

Hepatocellular carcinoma is the most common primary hepatic malignancy, representing more than 90% of primary liver neoplasms.(1)

Transplantation is currently the only life-saving therapy for patients with unresectable HCC and cirrhosis. LDLT offered an acceptable chance and duration of survival for HCC patients. It was not only a relatively safe procedure provided that every effort was taken to minimize donor

morbidities, but also beneficial for HCC recipients, however, offering LDLT to patients with HCC, however, raises complex issues for the donor, the recipient, and the medical team.[2]

The Milan criteria have been widely regarded as the "gold standard" for DDLT in HCC recipients. However, the criteria for LDLT in HCC have not been established. The Milan criteria are derived from cadaveric organ allocation, but the situation is quite different in LDLT, in which the donor has a strong will for giving and dedication, and the liver graft is considered a private gift instead of a public resource.[2]

Tumor recurrence is the main concern during transplantation for HCC. Recurrence rates are approximately zero with solitary, well-differentiated tumors less than 2cm, but it is approximately 10% with Milan criteria and it goes up to 50% in patients who have tumors greater than 5 cm with portal vein invasion.[1]

The aim of this work is to stroke the difficult controversies related to liver transplantation for recipient with HCC attempting to answer several questions: Should we expand the criteria for liver transplantation for HCC? What is the response to loco-regional therapy and role of tumor down-staging? What are the difficulties of evaluation? Is there especial technique considerations? What about the outcome and recurrence?

MATERIAL AND METHODS

This is a retrospective analysis of liver transplanted patients in the National Liver Institute, Menoufiya University, Egypt, in the period from April 2003 to October 2011. During this period, 150 patients underwent LDLT and HCC was the indication of LDLT in 35 (23.3%) of recipients. Their records were analyzed for the following data:

I. Preoperative data: Demographic data of the donor and recipient, preoperative evaluation of the recipient, diagnosis and evaluation of primary tumor, evaluation of metastasis, management of HCC pretransplant, and pretransplant selection criteria for HCC patients:
   - Milan criteria (single tumor ≤ 5 cm; or ≤ 3 tumors each ≤ 3cm; no vascular invasion and no distant metastases).[3]
   - University of California San Francisco criteria (single tumor ≤ 6.5 cm; or ≤ 3 tumors, none >4.5 cm and total diameter ≤ 8 cm, no vascular invasion).[4]

II. Operative data: Operative details especially; findings of exploration, operative techniques and the presence of any intra-operative difficulties were recorded.

III. Postoperative data: results of pathological study of explanted liver, postoperative complications, diagnosis and treatment of HCC recurrence, and analysis of survival (total survival and tumor free survival), perioperative mortality and cause of death.

Statistical Analysis: Data were collected and SPSS (Statistical Package for Social Science) program were used for statistical analysis. Descriptive statistics: Quantitative data were shown as mean, SD, and range. Qualitative data were expressed as frequency and percent. Analytical statistics: Chi- square test, Student t-test and Mann Whitney test were used. Logistic regression model was used to give adjusted odds ratio and 95% confidence interval of the effect of the different factors on the recurrence of the malignancy. Sensitivity, specificity, positive and negative predictive values, and diagnostic accuracy of the pre-operative tests were calculated. Kaplan-Meier was plotted for analysis of survival. P-value was considered statistically significant when it was less than 0.05.

RESULTS

One hundred and fifty LDLT were performed at NLI from April 2003 to October 2011, 35 (23.3%) of them had HCC, They were 33 (94.3%) males and 2 (5.7%) females. Their mean age was 47.8±5.2 years, 34 (97.1%) patients had positive HCV and only one (2.8%) patient had positive HCV+HBV.

Mean preoperative AFP was 320.4±917.2 ng/ml. Nineteen (54.3%) patients had normal AFP, 9 (25.7%) patients had AFP ranging (20–400 ng/ml), 3 (8.6%) patients had AFP ranging (400–1000 ng/ml), and 4 (11.4%) patients had high level of AFP > 1000 ng/ml.

The protocol for radiological diagnosis of HCC at NLI depends mainly on multislice triphasic computerized tomography (CT) scan, which showed sensitivity in detecting HCC in the studied cases of 100%.

According to our protocol of diagnosis, preoperative true cut needle biopsy of hepatic focal lesions (FL) is indicated only when the diagnosis is uncertain (FL does not have the typical character of HCC in CT scan or in the context of non-cirrhotic liver, especially with normal AFP). Preoperative biopsy was taken from 2 patients. One patient had 2 cm left (Lt) lobe FL and the biopsy revealed no malignancy, however, pathological study of the explanted liver in this patient revealed HCC grade II. In the second case biopsy verified HCC grade I. Neither of them had biopsy-related complications nor post transplantation HCC recurrence.

As regard the selection criteria, 28 (80%) patients were within Milan criteria, and 7 (20%) patients were beyond Milan. However, 33 (94.3%) patients were within UCSF criteria, and 2 (5.7%) patients were beyond UCSF criteria.

The total survival in patients within Milan at 6 m was (74.3%), and at 1y, 3y, and 5y was as follow, (71.4%), (62.9%), and (31.4%) respectively, however, the total survival in patients within UCSF criteria at 6 m was (64.5%), and at 1y, 3y, and 5y was as follow, (71.4%), (62.5%), and (33.3%) respectively.

Metastatic work up including CT chest, CT brain and bone scan were performed routinely for all patients. In early cases PET scan was performed for HCC patients with unclear findings; (presence of suspicious portahepatis lymph node (LN), associated PVT, or suspicious extrahepatic lesion). Depending on its supposed usefulness; dating from June 2010 (including the last 12 HCC cases) PET scan became routinely performed for all HCC cases.

PET scan was done in 18 (51.4%) out of the 35 patients with HCC, 9 (50%) patients had active metabolic intake of 2-[18F] fluoro-2-deoxy-D-glucose (FDG) in the liver. The accuracy of PET scan in detecting HCC was 60.9%, with sensitivity 52.2%, and specificity 66.7%.

Four (11.4%) patients had preoperative PVT. The challenge was to confirm its benign nature in context of presence of HCC. This was achieved by four steps: first; the revision of any previous radiological studies for the possible presence of old PVT, second; The thrombus character in CT scan and duplex US as being chronic reanalyzed, adherent to the wall, non-vascular and being extrahepatic in main portal vein (PV), Third; the presence of multiple large collaterals were usually in favor of benign thrombus. Finally, PET scan was performed to all cases to rule out malignant thrombus. In these 4 patients with PVT, endothrombectomy of the PVT was performed during transplantation surgery. Pathological studies of the thrombus confirmed its benign nature in all cases. Two patients with preoperative PVT developed posttransplant PVT.

Four (11.4%) patients had preoperative portahepatis LN in CT scan. PET scan performed for all these cases and showed no malignant activity. These patients scheduled for what is called "exploration-first" i.e. exploration with excisional biopsy of the suspected lesions prior to dividing vital structures. Pathological examination of the excised LNs rolled out malignancy, and revealed reactive follicular hyperplasia in all cases.

There were 12 (34.3%) patients who underwent kind of locoregional ablative therapy for HCC previous to transplantation. Surprisingly, the decisions to do these ablative therapies for the HCC patients had been taken for therapeutic purpose and not for bridging or down staging, i.e. "before take the decision for liver transplantation" and without co-ordination with the transplantation team. Subsequently, multi-disciplinary HCC clinic had been established at NLI to achieve this co-ordination.

The 12 previous ablative therapy shown in table (1), the most common were trans-arterial chemo-embolization (TACE) in 5 patients and radiofrequency ablation (RFA) in 4 patients. The pathology of explanted liver showed no residual active tumors (well ablated) in two (16.7%) of these patients, and showed presence of active part of the tumor (not well ablated) in the other 10 (83.8%) patients.

Among this group of patient, 4 patients had complete ablation of HCC in contrast CT before transplant, posttransplantation pathological study of explanted liver showed active tumor tissue in two of them.

Table 1.Types of Pretransplantation locoregional therapy for HCC.

Ablative therapy	No (% of total 35 patients)	No of sessions	Time before transplant (m)
TACE	5 (14.3 %)	Mean = 2	Mean = 4 Range = (3 - 6)
RFA	4 (11.4 %)	Mean =1	Mean = 8 Range = (5 – 13)
TACE + RFA	2 (5.7%)	Mean = 2	Mean = 9 Range = (4 – 14)
Alcohol injection	1 (3.9%)	3	6
Pathological result: ➢ Well ablated ➢ Not well ablated	 2 (16.7%) 10 (83.3%)		

The survival of patients treated by preoperative ablative therapy was similar to patients without ablation.

The special operative procedures for all patients with HCC were "exploration first, and portahepatis dissection first". The aim was to verify the preoperative data, exclude abdominal metastasis, and to reduce the possibility of tumor seedling during liver manipulation.

As regards the finding of exploration-first; 4 patients had

portahepatis LN, one patient had suspicious omentum nodule and another one patient had dense adhesions with diaphragm (figure1). Biopsies obtained from these lesions were sent for pathological examination (frozen section), and were negative for malignancy.

LDLT had been discontinued in two patients dependent on this exploration; first one had 8 cm, bulging Rt lobe FL that was found to be encroaching IVC wall, the second one discovered to had Lt Portal division thrombosis with intraoperative US.

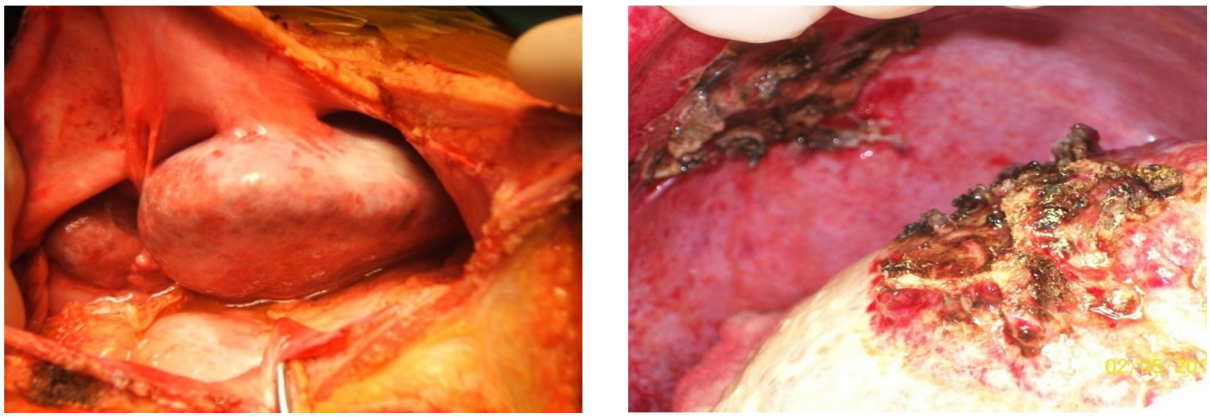


Fig 1. A case with excessive adhesions between liver and abdominal wall.

Six (17.1%) recipients needed venous grafts for hepatic veins (HVs) anastomosis, from the native liver PV in 5 (14.3%) recipients and from para-umbilical vein in the remaining recipient.

Four (11.4%) recipients had RT lobe grafts with 2 portal vein branches (donors with trifurcated PV type 2 and 3); therefore, PV had been reconstructed using Y-shaped graft obtained from explanted liver PV.

Microvascular invasion was found in 8 (22.9%) patients in pathological study of explanted liver (Table 2), and macrovascular invasion was not found in any patients.

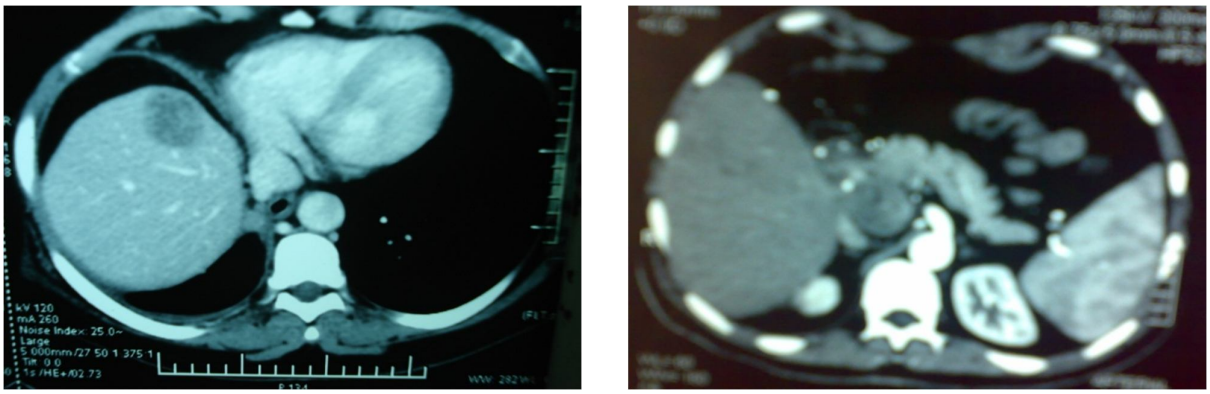
Table 2. Pathological study of explanted liver.

Pathological findings	NO (%)
Differentiation	
• Well differentiated	11 (31.4 %)
• Moderate differentiated	23 (65.7 %)
• Undifferentiated	1 (2.9 %)
Microvascular invasion	
• Yes	8 (22.9 %)
• No	27 (77.1 %)
Macrovascular invasion	
• Yes	0
• No	35 (100 %)

HCC recurred in 3 (8.6%) out of the 35 patients; all were in the first 2 years posttransplant. Their pretransplant data are shown in (Table 3), and operative and postoperative data are shown in (Table 4). Two patients had single Rt lobe FL, and one patient had multiple, bilobar FLs. Also, two patients were within Milan but one patient was beyond Milan and UCSF criteria. Two patients had previous ablative therapy for HCC. One patient had portal vein reconstruction using venous graft from his explanted liver PV.

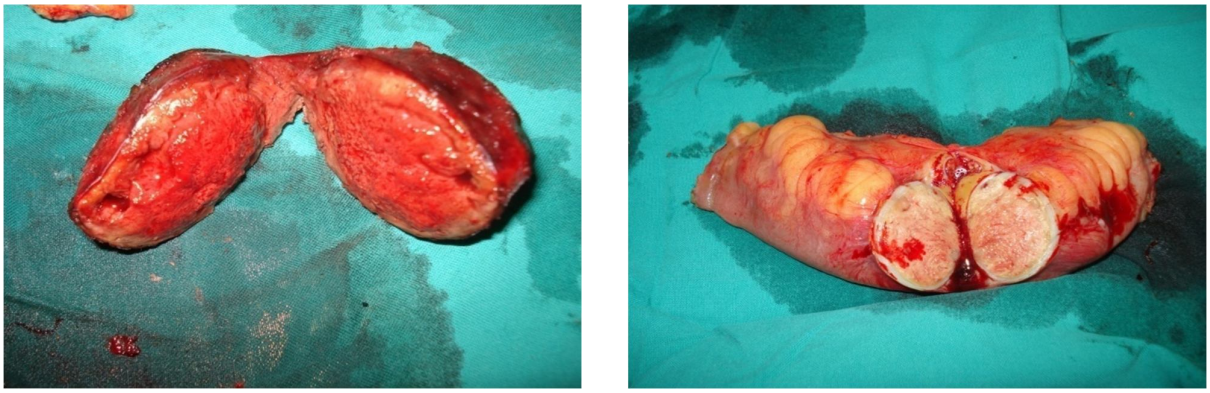
The pattern of recurrence was extrahepatic (in lung, bones, omentum and small intestine) as well as intrahepatic (figure 2). There was significant statistical relation between recurrence of HCC and AFP > 1000 u/ml.

Median total survival was 2.5 years with less than 1 year survival from the time of diagnosis.



A B

Fig 2. A) Triphasic CT abdomen with hepatic recurrence of HCC. B) CT abdomen with hepatic and LN recurrence of HCC.



A B

Fig 3. Recurrent HCC (A, part of omentum and B, part of ileum with HCC metastasis).

Table3. Pre-transplantation data of cases with recurrent HCC.

	Case 1	Case 2	Case 3
Age (y)	47	49	56
Sex	Male	Male	Male
Child score	C	A	A
MELD score	29	19	18
AFP (ng /ml)	2230	124	1127
No of FLs	1	3	4
Total Size (cm)	5	6	9
Site	Rt. Lobe	Bilobar	Bilobar
Milan criteria	Within	Within	Beyond
UCSF criteria	Within	Within	Beyond
Preoperative ablative therapy	Alcohol injection	No	No

Table 4. Operative and postoperative data of cases with recurrent HCC.

	Case 1	Case 2	Case 3
Type of graft	Rt lobe	Rtlobe+MHV	Rt lobe
Use of native liver venous graft for HV	yes	No	no
Use of native liver venous graft for PV	no	Yes	no
PVT	No	No	No
CIT (min)	90	100	40
WIT (min)	60	90	50
Blood transfusion (units)	4	0	0
Differentiation	Moderate	Moderate	Moderate
Grade	III	III	II,III
Capsule	No	No	No
Micrvascular invasion	Yes	No	Yes
Macrovascular invasion	No	No	No
Immunosuppressant	Tacrolimus	Tacrolimus	Sirolimus
Site of recurrence	Lung, liver, omentum	Liver, LN	Bone
Time of recurrence (M)	29	17	20
Management	Operative (lung lobectomy, liver resection)	Operative	Internal fixation of
AFP post recurrence (ng/ml)	11352	700	900
Tumor free survival (y)	2.1	1.4	1.7
Total survival (y)	4	1.6	2.5

At the end of our study 20/35 (57.1%) patients were alive and 15/35 (42.9%) patients died. Peri-operative mortality at first month post-transplantation was 6/35 (17.1%).

DISCUSSION

HCC was one of the first indications for liver transplantation, because it was postulated that this approach would eliminate the tumor and cure the underlying liver disease. However, it soon became apparent that the success of liver transplantation depends on the tumor load; patients with extensive disease had very poor outcomes, whereas most patients with small tumors could be cured.[1] This led to many controversies around the use of liver transplantation in patients with HCC.[5]

Wolfort et al., 2010,[6] reported low sensitivity of PET scan for detection of HCC and that PET misses 30–50% of HCC lesions. In our pre-transplantation evaluation protocol special attention is given to detection of extrahepatic tumor spread, despite its low sensitivity (52.2%) in detecting HCC, in our current results PET scan demonstrated obvious value in exclusion of malignant nature of doubtful extrahepatic lesions and it recently become routinely performed in all HCC cases. Data need more future study.

With the improvements in the accuracy of noninvasive imaging, tumor biopsy is not required in cirrhotic patients with HCC being considered for liver transplantation; whose have high-quality dynamic CT or MRI findings typical for HCC.[5,7] According to our results, preoperative true-cut needle biopsies of FLs were obtained in only 2 (5.7%) patients with uncertain diagnosis, without seedling or complication. Other investigators reported that the risk of tumor seeding after liver tumor biopsy has been 2.7 %.[8]

Yang et al., 2007,[9] stated that, serum AFP level is accepted as a valid pretransplant estimative parameter, moreover, they are accepted predictor of tumor recurrence, later on, Vibert et al., 2010,[10] showed that there is no agreement on the cutoff values to consider, and concentration lower than 400 ng/ml has been used in selecting patients for liver transplantation after down staging protocols. Furthermore, persistently high AFP >1000 ng/mL despite locoregional therapy predicts a high risk for tumor recurrence and should be considered an exclusion criterion for liver transplantation.[11] Concerning preoperative AFP, in our study 4 (8.3%) patients had high level of AFP > 1000 ng/ml, two of them (50%) had recurrent HCC, moreover, there was statistical significant correlation between recurrence of HCC and pre-transplantation high AFP level of > 1000 ng/ml, accordingly, AFP level of > 1000 ng/ml was considered as threatening finding that portends a poor prognosis and regarded as exclusion criterion for LT in the subsequent cases.

Lasheen et al, 2010,[12] reported that PVT is not an absolute contraindication to LT in HCC patients if it is

proved to be a benign thrombus preoperative, it adds only some operative difficulty, also, they stated that tumor thrombus is a contraindication for transplantation. This was in agreement with our results that included 8 (16.7%) patients who had preoperative chronic PVT with multiple large collaterals, all were benign thrombus. All patients underwent thrombectomy during transplantation. The challenge was to confirm its benign nature and this was achieved using the mention four steps in our results including PET scan, which proved reliability in that cohort of patients.

The Milan criteria for HCC have been widely used for the selection of candidates for liver transplantation, and have limited the risk of tumor recurrence to an acceptable level.[3,13] Large single center studies on modest expansion beyond the Milan criteria based on preoperative imaging could achieve posttransplant survival comparable to that with the Milan criteria.[4,14]

More recent, Guiteau et al., 2010,[15] reported that the results of a well-designed, prospective, multi-center study from UNOS supported the belief that liver transplantation could benefit patients whose hepatocellular carcinoma exceeded Milan criteria. Also Silva & Sherman, 2011,[16] said that despite the Milan criteria being validated by many studies, this criteria are too restrictive and exclude a subset of patients with larger or more numerous tumors that could have excellent outcomes if were transplanted.

The issue of expanded criteria in LDLT is more complicated, that, the primary objective is to justify the risk to the donor based upon the probability of favorable outcome for the recipient; in addition, it is more difficult to define the minimal acceptable outcome. In the LDLT cases performed in our centre, 7 (20%) patients had HCC beyond Milan criteria, and even 2 (5.7%) patients were expanded beyond UCSF criteria, with comparable results. Only one case of recurrent HCC was recorded among these patients. This go with Yao et al, 2001;[4] who reported that by expanding the Milan criteria for transplanting patients with HCC, an additional 23% of patients were transplanted with excellent outcome.

Recently data have emerged suggesting that response to loco-regional therapy and downstaging for HCC exceeding the Milan criteria could serve as a prognostic marker for improved post-transplantation outcome and for the selection of candidates for liver transplantation.[17,18] A report involving 168 patients from two centers suggests that pretransplantation loco-regional treatment has no prognostic impact in patients with small HCC; however, it achieves improved survival in tumors at intermediate risk for progression.[19]

In relation to locoregional therapy in the current study, 12 (34.3%) patients exposed to these modalities prior to LDLT for therapeutic objective and not for bridging or down staging target. Furthermore, the adoption of a policy for expanding HCC criteria of acceptance, altogether with, establishing of multidisciplinary HCC clinic in corporation with the LDLT team, made a more prospect for future application and studying of these modalities in context of LDLT for HCC patients.

Concerning TACE in transplantation candidates, controversial data have been reported. While favorable results in terms of local tumor necrosis and improved recurrence-free survival were observed in some centers, others made the experience that apart from poor efficacy of TACE as 'bridging' treatment to transplantation, amelioration of liver function and increased rates of posttransplant septic complications can occur.[19] Martin et al., 2006,[20] showed that although the most popular bridging strategy is TACE, pathological studies showed a marginal advantage for RFA in terms of tumor necrosis. In our study, TACE and RFA were the most popular ablative therapy to be used.

There is debate about how best to assess successful down staging, however, European Association for the Study of the Liver (EASL) guidelines suggest that such assessment should be exclusively based on the amount of viable tumor, as differentiated from necrosis by contrast CT or MRI.[21] In our study, of the 4 patients, whose their triphasic CT showed complete ablation of HCC, two (50%) of them had active tumor tissue in pathological study of explanted liver; indicating ineffective assessment of ablation and demonstrating the need to more studies in this issue. In our study the 3 year survival of patients treated by preoperative ablative therapy was similar to patients without ablation, also this is similar to what was reported by Lewandowski et al., 2009.[22]

In relation to our operative procedure all patients with HCC underwent "exploration-first"; a meticulous evaluation of the abdomen and hilum were performed prior to dividing vital structures, during which lymph node biopsies were obtained in 4 patients to rule out the possibility of metastatic disease, and they were negative for malignancy. In addition, portahepatis dissection was done as a first step before liver mobilization or isolation of IVC, aiming to prevent the release of malignant cells as a mean to prevent early recurrence of HCC. This procedure was also adopted by Mejia et al., 2012.[1]

Shirabe et al., 2007[23] stated that, microvascular invasion, which is identified only by microscopic observation, is associated with poorer outcome or increased recurrence rates after liver transplantation. On the other hand, Kornberg et al., 2009[24] showed that microvascular invasion cannot be reliably detected prior to transplantation as conventional imaging modalities are ineffective for preoperative detection of microvascular invasion and that only PET CT scan has a value in predicting microvascular invasion. In our study 8 (22.8%) patients had microvascular invasion only one of them had recurrent HCC posttransplantation. Another 3

patients of them had early hospital mortalities, therefore could not be assessed for recurrence.

The main concern after liver transplantation for HCC is the risk of tumor recurrence; in our study we had 3 (8.6%) patients with HCC recurrence. The time of diagnosis of HCC recurrence was 17, 20 and 29 postoperative month. These patients had a median total survival of 2.5 years, and less than 1 year survival from the time of diagnosis.

These results matched with Hollebecque et al., 2009[25] who stated that HCC recurrence occurred in 8 % of recipients within the first 2 years after liver transplantation, and was associated with a median survival of less than 1 year (7–18 months) from the time of diagnosis. On the other hand they also reported that, around 20% of cases with recurrence were first presented beyond 3 years post transplantation, indicating the need for prolonged surveillance.

Schlitt et al., 1999;[26] reported that, the majority of recurrences are extra hepatic; 53% of patients present with extra hepatic sites only, 31% with both extra and intra hepatic tumor, and only 16% with the liver as the sole site. Similar results were reported by Regalia et al., 1998[27] in which approximately 40% of patients had multiple organ involvement.

Concerning site of recurrence; in our study, extra hepatic recurrence was recorded in all cases (100%) mainly in the lungs and bones. However, hepatic recurrence was in two cases. AS well, Taketomi et al., 2010[28] stated that, most recurrences are associated with systemic tumor dissemination, thus retransplantation is not indicated, and moreover, in that minority of cases where localized recurrence is detected, however, direct treatment by surgery or ablation warrants consideration.

Roayaie et al., 2004,[29] reported the series from Mount Sinai Medical Center that documented 57 patients with recurrent HCC in 311 patients who had transplantations for HCC, 18 (32%) patients underwent potentially curative treatment, including resection of the transplanted liver (n=5), lung resection (n=7), radiofrequency ablation of hepatic lesions (n=3), adrenalectomy (n=2), and resection of a chest wall recurrence at a pretransplant tumor biopsy site (n=1), furthermore, other authors[26,27] reported surgical resection of isolated metastases recurrence in the liver, lungs, bone, and skin in 11 and 14 patients. According to our management of recurrent HCC, operative management was performed in all 3 patients with recurrence; multiple resections in the first one, exploration with intraoperative RFA in the second and palliative orthopedical operation in the third. Unfortunately, surgery was not curative in one of them, and even was dreadful in the other case.

In conclusion milan criteria remain a valid tool to select candidates for LDLT to achieve optimal results but expanding the criteria give chance to more patients with comparable outcome. Alfa-fetoprotein (AFP) of >1000 ng/mL should be considered an exclusion criterion for liver transplantation. PET scan might be of particular value in excluding extrahepatic HCC extension. Benign PVT does not contraindicate LDLT for HCC patients. Exploration-first and Portahepatis-first techniques are recommended in HCC cases.

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