**Title: Pilot study of living donor liver transplantation for patients with HCC exceeding Milan criteria (BCLC extended criteria).**

***Running Head:*** *LDLT for HCC exceeding Milan criteria.*

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**Abbreviations: AFP –** alpha fetoprotein; **GBWR –** graft to body weight ratio; **HCC –** hepatocellular carcinoma; **LDLT –** living donor liver transplantation; **OLT –** orthotopic liver transplantation; **OS –** overall survival; **PEI –** percutaneous ethanol injection; **RBC –** red blood cells; **TACE –** transarterial chemoembolization

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**Abstract:**

**Background & Aims**: A subset of patients with hepatocellular carcinoma (HCC) beyond Milan criteria might obtain acceptable survival outcomes after liver transplantation. Living donor liver transplantation (LDLT) has emerged as a feasible alternative to overcome the paucity of donors.

**Methods**: In 2001 we started a protocol for LDLT in Child A-B patients with HCC fulfilling a set of criteria – *the BCLC expanded criteria*- that expanded the conventional indications of transplantation: 1 tumor ≤ 7cm, 5 tumors ≤ 3cm, 3 tumors ≤ 5cm without macrovascular invasion or down-staging to Milan after loco-regional therapies.

**Results:** We present a prospective cohort of 22 patients with BCLC extended indications based on size/number (17) or down-staging (5) treated with LDLT between 2001 and 2014. Characteristics of the patients were as follows: median age: 57yr old; males/female: 20/2, Child-Pugh A/B: 16/6, AFP <100ng/mL: 21. Twelve patients received neo-adjuvant loco-regional therapies. At the time of transplantation, 12 patients had HCC staging beyond Milan criteria and 10 within. Pathological reports showed that 50% exceeded BCLC expanded criteria. Perioperative mortality was 0%. After a median follow up of 81 months, the 1-, 3-, 5- and 10-year survival was 95.5%, 86.4%, 80.2% and 66.8%, respectively. Overall, seven patients recurred (range 9-108 mo), and the 5-y and 10-yr actuarial recurrence rate was of 23.8% and 44,4%, respectively.

**Conclusion**: A proper selection of candidates for extended indications of living donor liver transplantation for HCC patients provide survival outcomes comparable to those obtained within the Milan criteria, but these results needs confirmation.

## INTRODUCTION

Liver cancer is the second leading cause of cancer-related death globally and has an incidence of 850,000 new cases per year. Hepatocellular carcinoma (HCC) represents approximately 90% of all cases of primary liver cancer(1,2). The prognosis of patients affected by HCC depends on the tumor stage and the degree of liver function impairment(2). Today, as a result of screening programs, about 30-40% of these patients can receive treatments with curative intent, including liver resection, liver transplantation and percutaneous ablation, with a 5-year survival between 50-75%(1–5).

Liver transplantation offers the possibility of removal of both HCC tumor and preneoplastic underlying disease and may be applied to patients with advanced liver failure. When strict criteria are applied (the so-called Milan criteria(6) – 1 tumor ≤ 5cm or 3 tumors ≤ 3 cm), the 5-year overall survival reaches 70%(7,8). Today, these criteria are included in the Barcelona Clinic Liver Cancer (BCLC) staging system for HCC(3–5).

Selected patients with HCC beyond the Milan criteria may still obtain acceptable rates of survival after liver transplantation, as pointed by several studies(9–13). These patients generally belong to an intermediate group between the ones with excellent prognosis after liver transplantation (Milan-in patients) and those with indicators of rapid disease progression (macroscopic vascular invasion, diffuse HCC or extrahepatic disease). Despite some efforts to expand indications of transplant for HCC patients beyond Milan criteria –based on tumor size and number of nodules or successful down-staging after preoperative therapies(9–13) - clinical practice guidelines have not adopted such extended criteria and the vast majority of transplant centers are still

excluding this type of patients from liver transplantation with cadaveric grafts(3,4,14).

The 2010 Consensus Conference on liver transplantation for HCC recommends living donor liver transplantation (LDLT) as an ethically acceptable alternative for patients with expected 5 year survival comparable to that of patients receiving a cadaveric graft, although the strength of recommendation is weak, because of the different approaches between transplant centers(14). From this point of view, LDLT represents an alternative option for patients with HCC beyond the Milan criteria, because it offers them a curative treatment without affecting the pool of donors for patients enlisted for deceased liver transplantation.

In 2000, our group began a local program of LDLT, and in March 2001 it was expanded following a specific protocol(15) allowing enlisting HCC patients beyond Milan criteria as per Table 1. The main objective of this pilot study was to assess the survival and recurrence rates after LDLT in this type of patients. We report herein the results of a pilot prospective study including 22 HCC patients with extended indications treated by LDLT and followed for a long- term period.

## PATIENTS AND METHODS

Between March 2000 and December 2014, 97 patients were effectively transplanted in the LDLT program of our Liver Transplantation Unit following a previously published protocol(16). Indication for transplantation was based upon HCC diagnosis in 39 (40.6%) of these patients, 22 of them being accepted according to expanded HCC criteria applied at our institution since March 2001 (Table 1)(15). These 22 patients represent our study population.

***Patients***

*Recipients and Donor Selection.* The complete preoperative study and the donation planning were done according to the *Spanish Law of Organ Donation*, as previously described(16). Detailed explanations related to the procedure, its complexity and possible complications is a critical part of the process for both the donor and the recipient(17). Inclusion criteria of the recipients were as follows: diagnosis of HCC according to EASL and AASLD guidelines(3,4,18), age between 18 and 70 years, BCLC expanded criteria for LDLT (see Table 1), ECOG performance status 0 and Child-Pugh A or B class. Preoperative HCC staging work–up included four-phase abdominal CT scan or MRI, thorax X ray and bone scintigraphy. Size of the main nodule was established according to either CT scan or MRI, whereas additional nodules would require 2 coincidental imaging techniques if size between 1-2 cm, and one imaging technique if size > 2cm, showing the radiological hallmark of HCC. AFP plasma levels > 1000 ng/mL required further work-up to discard advanced disease (laparoscopic ultrasound and body CT scan). Status of vascular invasion was defined by Doppler US and/or MRI. Doubts regarding the nature of a portal thrombosis were ruled out by biopsy studies. Recipient exclusion criteria were: patients older than 70 years, single tumor larger than 7 cm or smaller but with satellites (defined as any HCC $\leq$ 2m within a 2cm ring around the main nodule), multinodular tumor beyond inclusion criteria, diffuse HCC, neoplastic vascular invasion of any vessel, lymph node involvement or extrahepatic tumor disease, Child-Pugh C class or ECOG performance status > 0. In case of recipients aged between 66-70 yrs old, additional cardiovascular (normal cardiac stress test),

respiratory (low risk of complications by pulmonary function testing) and renal test (normal renal function) were conducted. Recipient evaluation includes the same parameters as in conventional liver transplantation. Donor selection criteria included age between 18 and 55 years, ABO group compatibility with the recipient, healthy individuals with graft to body weight ratio (GBWR) higher than 0.8 and normal psychological work-up. All donors signed informed consent in front of a judge according with the law. Work-up for donors has been reported in previous studies of our group(16,19). A key aspect of this work-up is the analysis of graft vascular and biliary distribution, and graft volume using CT scan and MRI-angiography, which can anticipate the complexity of the surgery and eventually even contraindicate the procedure(19,20). Donors with liver steatosis by imaging techniques and normal blood analysis, were only considered in case that liver biopsy demonstrates <20% of liver steatosis.

*Feasibility.* The protocol execution contained two parts: the feasibility part (9 cases) and the complete final pilot study (up to 22 cases). The feasibility run-in part involved the evaluation of the first 9 LDLT cases, and results have been previously communicated(21). In this part we assessed whether the protocol was feasible, the number of potential cases emerging out of the total HCC cases visited, the number of donors per candidate recipient, and the reasons for accepting/rejecting the candidate. The study team estimated that the results obtained at this cut-off point were adequate, and thus agreed proceeding to the completion the study with an initial target sample size of ~20 cases. For the purpose of the current report, the recruitment ends at December 2014, and the follow-up expands to February 2017.

*Patient characteristics.* Baseline characteristics of the patients before LDLT are depicted in Table 2. For every recipient, data regarding age, sex, etiology and preoperative stage of hepatic disease, treatment performed before LDLT (as neo-adjuvant or down-staging therapy), pre and post-transplantation liver function, alpha fetoprotein (AFP) levels before and after LDLT, preoperative radiological stage, explant histological result, number and type of intra and postoperative complications according to the Clavien-Dindo scale(22), intensive care unit (ICU) and hospital stay, type of immunosuppression, follow-up, recurrence and death were prospectively recorded in a database and analyzed.

***Methods***

*Loco-regional therapies previous to LDLT.* In 12 patients (54.5%) loco-regional therapies were performed (11 cases treated with TACE and one case with PEI) (Figure 2). In five of these cases, down-staging (i.e. remaining within Milan criteria in two consecutive radiological assessments) allowed inclusion in the expanded criteria used at our center. In all the remaining cases, patients were already meeting one of the "size and/or number" expanded criteria.

*Surgical intervention and postoperative period*. The LDLT procedure followed the protocol of our Liver Transplantation Unit, as previously described(16,19,20). All 22 transplants were performed using the right liver lobe. Surgical procedure details, intraoperative incidences, ICU and hospital stay, postoperative complications and immunosuppression therapy used were also recorded. Postoperative immunsupression regimens followed a standardized protocol. In principle, the immediate post-transplant immunosupression treatment includes methylprednisolone in descending dosage along with calcineurin inhibitors (tacrolimus, but cyclosporine in cases of

pre-transplant diabetes). Mycophenolate mofetil is generally used until reaching therapeutic levels of calcineurin inhibitors. mTOR treatments, such as everolimus, were used in 4 cases.

*Follow up and assessment of recurrence.* After being discharged, all patients were followed monthly in the outpatient clinic until 90 days from LDLT, every other month during the 1st year after LDLT, and every three months until two years from the transplantation. In addition to conventional clinical parameters (symptoms related to the tumor or hepatic decompensation), radiological explorations (US, CT or MRI) and liver function assessment were performed in each outpatient visit during the first two years. Follow-up beyond this time period with blood test and radiological imaging was based upon clinical criteria.

*Pre-LDLT radiological exam and histological explant analysis*. Median time between donor and recipient evaluation (including treatment/down-staging) and transplant was of 4,5 months. Assessment of pre-LDLT radiological exam included number, site and maximum diameter of tumor nodules, viable tumors after neo-adjuvant therapy, and satellites nodules. The pathological report of the explanted liver includes the following information: description of number, location and maximum diameter of all tumor nodules, differentiation degree, presence of micro or macrovascular invasion, and satellite nodules.

***Statistical Analysis***.

Epidemiological and analytical quantitative data are expressed as mean ± SD. Follow-up length, overall survival and time to recurrence are expressed as median (range). Probability curves of patient and graft survival were calculated according to the Kaplan-Meier method and compared by the Mantel-Cox test. Differences between qualitative variables were assessed by the Fischer exact

test; differences between quantitative variables were analyzed by t-test. All the calculations were performed by using the IBM© SPSS Statistics version 22 package.

## RESULTS

***Feasibility.*** The feasibility run-in part of the study was conducted between March 2001 and December 2002 (Figure 1), as previously reported(21). During this time period 381 patients with HCC were visited in our BCLC program, among which 142 (37%) received either resection (22 cases), orthotopic liver transplantation (36 cases) or percutaneous ablation (84 cases). A total of 34 patients (9%) were considered for the specific protocol for LDLT as per BCLC expanded criteria. Finally, 205 patients received loco-regional or symptomatic treatment according to guidelines(18). No systemic therapy with sorafenib was available at that time as standard of care, since benefits of this therapy were reported afterwards(23).

Among 34 patients evaluated for LDLT, 13 did not find/required any donor candidate (recipient refuse the procedure: 10; HCC progression while evaluation: 2; Recipient unable to identify a donor: 1), whereas 21 provided 57 potential donors. Among these cases, 12 recipients had an inadequate donor [20 donors evaluated: blood ABO incompatibility (5), liver steatosis (6) or medical contraindications (9)]. Finally, 9 patients received a LDLT during this run-in period, representing ~25% of the 34 receptors evaluated, and 2,6% of the total HCC patients visited during this time period. All these data were considered acceptable for the feasibility/run-in period, and thus the protocol was approved for completion, with a final recruitment number of 22 cases.

***Loco-regional treatment and tumor stage prior to LDLT.*** Out of the 22 final candidates with BCLC extended indications, 17 patients were included in the protocol due to extended "size & number" criteria, and 5 due to downstaging to Milan criteria from any previous size (Figure 2). All patients achieving downstaging to Milan criteria were treated with TACE (overall, median time on downstaging was 134 days). Among 17 additional patients meeting "size & number" criteria, 7 received treatment (6 with TACE and 1 with PEI) as a bridge therapy while waiting to complete pre-transplant evaluation in patients with long evaluation times.

Thus, overall 12 patients were ultimately treated with neo-adjuvant loco-regional treatment while waiting for LDLT or to achieve downstaging. Out of the 12 cases treated, 5 (22.7%) achieved complete response, six (27.3%) partial responses and one case showed stable disease. Four patients who responded to treatment presented hepatic recurrence before LDLT. Median time between last radiological exploration (MRI in 19 cases, and CT scan in 3) and LDLT was 59 days. At the last imaging technique prior LDLT, 10 out of 22 patients (45.5%) presented a tumor stage inside Milan criteria.

***Surgical data***. Mean GBWR estimated before surgery was of 1.26 ± 0.32, while the actual GBWR calculated with the graft lobe weight was of 1.09 ± 0.27. Total surgery time between donor and recipient intervention was of 417 ± 83 minutes. Mean final portal and arterial flow were of 1552 ± 520 ml and 189 ± 101 ml respectively. Eleven patients required red blood cells transfusion during surgery (mean of 3.9 ± 3.1 RBC concentrates / transfused patient), 14 plasma transfusion (mean of 1714 ± 738 ml / transfused patient) and 3 platelets

transfusion (mean of 6.4 ± 5.5 platelet units / transfused patient). No patient developed small-for-size syndrome.

***Explant histological results***. Explant histological characteristics are depicted in Table 3. Median size of the main nodule was 32,4 mm, 19 patients presented multinodular disease, 10 (45.5%) microvascular invasion and 9 (40%) satellites. In terms of pathological tumor staging, 4 patients (18.2%) were inside Milan criteria, 7 patients (32%) were beyond Milan criteria but inside our BCLC expanded criteria and 11 patients (50%) were beyond these criteria. Overall, the number of tumors in the histological exam was higher than in the last radiological imaging prior LDLT (5 cases in explant *vs* 3 in MRI/CT before LDLT).

***Postoperative period and follow-up***. Perioperative complications for donors and recipients are summarized in Table 4. Median intensive care unit stay and total hospital stay for receptors was 6±4 days (3-24) and 27±22 days (9-101), respectively. Medical complications for the recipient occurred in 12 cases (54%) and surgical complications in 16 cases (72%). Among the latter, biliary leak (13 cases) resulting in surgical treatment in 8 cases was the most notorious. Perioperative mortality was 0%. Regarding long-term complications, 9 patients presented HCV-induced cirrhosis and there was 1 case of chronic rejection. No indication for retransplantation was made.

From the donor stand point, 5 patients (22%) presented perioperative complications, one of which was grade IIIb Clavien-Dindo scale(22) (bile leak which required surgical reintervention).

***Overall Survival***: After a median follow-up of 81 months (range 7-188), 8 patients died, four of which due to HCC recurrence (Table 5). Actuarial

provability of survival at 1, 3, 5 and 10 years was of 95.5%, 86.4%, 80.2% and 66.8%, respectively (Figure 3).

***Recurrence rates.*** At the end of follow-up 7 patients recurred, 2 only in the liver (91 and 62 months after LDLT), 1 in liver and bone (at 9 months), 1 in form of liver tumor and peritoneal carcinomatosis (at 58 months), 1 in the liver and mediastinal lymph nodes (at 57 months), 1 in the liver and adrenal gland (54 months), and 1 as bilateral adrenal gland (9 years after LDLT). Four patients died within the first year after presenting the recurrence, whereas three patients (liver recurrence with mediastinal lymph nodes at 57 months and with adrenal gland metastasis at 54 months respectively and adrenal gland metastases) are still alive. All seven patients were initially HCV positive and five of them had cirrhosis recurrence confirmed by histology. Explant histology showed that six of the patients were outside BCLC extended criteria, with microvascular invasion in 5 cases and satellites in 3. One of the patients was inside BCLC expanded criteria but presented microvascular invasion and satellites. No relationship was found between the recurrence and the type of immunosuppression. Overall, the actuarial probability of recurrence at 5 and 10 years was of 23.8 % and of 44.4% respectively (Figure 4). One of recurrences was detected 1 year after the patient had received HCV direct-acting antivirals. Two patients were treated with sorafenib, and four are currently dead due to tumor progression.

***Prognostic Factors.*** Better overall survival was observed for patients that were within the Milan criteria (n=10) in the last radiological exploration before LDLT when compared with patients that were beyond these criteria (n=12) at the same time period (5-y and 10-yr survival 90% and 90% vs. 70% and 52.1%, respectively; p=0.046) (Figure 5). Survival was not significantly influenced by

any other variable related with preoperative stage, histological explant analysis or intra and postoperative complications.

## DISCUSSION

The incidence of HCC is steadily growing globally, but just around 30-40% of those patients are amenable for potential curative therapies(1–5). Benefits from OLT are clearly achieved when applying the Milan criteria, which have been widely adopted by Clinical Practice guidelines of management of HCC(3,4), guidelines of liver transplantation(14) and by the US United Network of Organ Sharing. Recent meta-analysis of patients undergoing OLT for HCC within Milan criteria confirm that a 5-yr and 10-yr survival rates of 70% and 50%, respectively, are consistently reported(7). Nonetheless, the applicability of OLT in those patients is limited due to the shortage of donors, a problem that has not been solved during the past two decades. As a consequence, a proportion of patients dies on the waiting list or is not even considered for OLT. In parallel, different studies have shown 5-yr survival rates > 50% in selected patients with HCC beyond Milan criteria submitted to liver transplantation when compared to their counterparts within Milan criteria(9–13), posing the question of whether Milan criteria are too strict for nowadays radiological standards compared to those of 1996(6).

LDLT can be a thorough alternative to OLT in referral centers because it is not limited to the shortage of donors(14,24). This strategy appears appealing since there is no prejudice for other candidates to OLT in the waiting list, mostly cirrhotic patients with end-stage disease. Of note, guidelines have emphasized that from the ethical perspective the concept of double equipoise (meaning a balance between the risk of a healthy donor and the benefit for the HCC patient) should be considered(14). The risk of mortality for a donor of the right lobe is reported to be around 0.17%(25).

LDLT has been proposed in two areas: for patients on the waiting list of OLT and for those exceeding Milan criteria. A recent meta-analysis has pointed out that outcomes for LDLT and OLT are similar in terms of survival(26) when considering Milan–in only patients. The most burning question, however, and the one addressed in the current study, is whether LDLT is safe and efficacious in patients exceeding Milan criteria. Such patients are mostly categorized as BCLC stage A or B and are treated with chemoembolization in most instances, achieving median survival rates ranging from 30-45 months(3,4). In some series, however, median survival ~50 months has reported in outstanding candidates(27), which provide a framework for comparing the outcomes reported herein with LDLT. So far, expansion of criteria has been mostly based upon tumor size and number, in the case of USCF(12) and up-to seven criteria(9), tumor volume(28) or even molecular characteristics based upon gene expression(29). Finally, AFP has also been incorporated into the selection of candidates in France(30) and Canada (31), where patients with AFP > 1,000 ng/dL are excluded from transplant due to poor outcome.

We herein present the outcome data of a pilot prospective cohort study with pre-defined modest expansion criteria previously reported(15). These criteria are based upon size and number (single $\leq$ 7cm, 3 nodules $\leq$ 5 cm, 5 nodules $\leq$ 3 cm), or tumor behavior (down-staging to Milan after loco-regional therapies), absence of tumor-related symptoms (ECOG 0) and well-preserved liver function (Child A or B). Almost all patients were transplanted with AFP < 100 ng/mL, and there were no patients with AFP >1,000 ng/mL. Results of this pilot study reveal potential implications on the future management of HCC for a small population of patients with LDLT due to the survival outcome achieved.

Survival data was remarkable. Overall survival at 5 and 10-yr was of 80% and 66.8%, after a median follow up of around 81 mo. These figures compare well with those reported for deceased liver donor transplantation(7), which is the master framework for any comparison(14). Even when further analyzing outcomes in patients maintaining beyond Milan criteria in the last radiological exam before LDLT –despite the small sample size (12 patients) - the 5 and 10-yr probability of survival is still around 70% and 50%, respectively. Of note, the current European report of liver transplantation for HCC including ~19,000 cases –within/beyond Milan criteria- reports a 10-yr survival rate of 50%(32). Survival also outperforms the outstanding median of ~50 months reported after TACE in selected patients(27). Thus, overall the survival figures fit well with the pre-planned expectations, and the accepted outcomes for proposing LDLT in HCC.

On the other hand, the actuarial probability of recurrence at 5 and 10 years was of 23.8 % and of 44.4%, respectively. As expected, the majority of the patients showed a pathological staging beyond BCLC extension criteria, mostly as a result of additional small nodules not detected in pre-operative imaging staging. In fact, 6 out of 7 cases recurrences occurred in patients with pathological staging beyond *BCLC extension criteria*. While 5-yr recurrence rates are slightly higher than the ones reported for patients within Milan (23.8%), 10-yr recurrent data requires some analysis. The latter figure is difficult to interpret since almost no data has been reported in terms of 10-yr recurrence rate after liver transplantation. Interestingly, one of the late recurrences was detected after 1 year of HCV treatment with direct antiviral agents, which adds further data in the controversy on the potential increase of HCC recurrence with these agents (33).

In terms of potential chemopreventive intervention, a recent randomized trial failed to demonstrated benefits in terms of recurrence-free survival for sirolimus-based immunosuppression treatment in preventing recurrence after HCC transplant(34). Thus, so far only candidate selection might diminish this figure(9).

Overall, the results are positive, but certainly need to be validated prior being considered for consensus criteria. In addition, they should be carefully interpreted. First, applicability of LDLT in our environment was low, since we were able to effectively operate only 22 patients within a 14-yr period. In fact, applicability of LDLT was explored in the first run-in part of the study(21). Out of a total of 381 patients with HCC visited during a twenty-two months period, only 34 were potential candidates for LDLT (9%), and among those only 9 were effectively transplanted, representing 25% of those evaluated and around 2,6% of the total HCC population of a center of reference. Second, considering the concept of double equipoise, we need to emphasize that 5 donors (22%) presented post-operative complications, one of which requiring surgical re-intervention. This complication rate is below the previously reported on a large series of cases(35). Recipient complications were within the expected range reported, with no perioperative mortality. Third, a proportion of patients with extended indications actually presented down-staging, meaning a pre-operative staging prior transplant of Milan-in after loco-regional therapy(14,34). This treatment was adopted in order to achieve down-staging to Milan (median of 134 days of down-staging before LDLT) as the primary inclusion criteria in five cases or because they were treated while waiting for completing the pre-operative evaluation, which as a whole lasted 4,5 months. These considerations

should be taken into account for tempering the potential excitement when analyzing the raw outcome obtained in the global context of LDLT(36,37). Of note, the recently reported AASLD guidelines suggest, based on low evidence, that patients beyond Milan criteria should be considered for transplantation after successful down-staging into the Milan criteria (38).

In conclusion, our study adds a valuable piece of information in the context of the effectiveness of LDLT for extended indications of HCC. This prospective study report acceptable survival outcomes comparable to those obtained within the Milan criteria, thus supporting a minor expansion in the selection criteria of HCC candidates for LDLT. Despite that the 10-yr recurrence is high, the outcome is counterbalanced by the long-term transplant benefit achieved (39). We propose, therefore, pursuing these extended criteria in other centers of excellence, since these results need further prospective confirmation before being adopted by clinical practice guidelines.

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## TABLES

| Table 1. BCLC Expanded Criteria Proposed for Living Donor Liver Transplantation. | |
|---|---|
| Size and number criteria | |
| | Single HCC 5-7 cm |
| | Multinodular HCC: up to 3 nodules ≤ 5 cm or 5 nodules ≤ 3 cm |
| Down-staging criteria | |
| | Downstaging: Partial response to any tumor stage by using loco-regional therapies that has been confirmed by 2 radiological techniques (CT scan or MRI) separated at least 1 month |

| Table 2. Baseline Characteristics of the 22 patients before LDLT | |
|---|---|
| **Epidemiological and clinical data** | |
| Mean age (years) | 57,3 ±6,0 |
| Sex (M/F) (%) | 20 (90.9%) / 2 (9.1%) |
| Etiology of hepatic cirrhosis | |
| Hepatitis C virus (%) | 14 (63.6%) |
| Hepatitis B virus (%) | 2 (9.1%) |
| Alcohol (%) | 4 (18.2%) |
| Hepatitis C virus + alcohol (%) | 2 (9.1%) |
| Expanded criteria used as indication for LDLT (%) | |
| 1 tumor 5-7 cm | 3 (13.6%) |
| 3 tumors < 5 cm | 7 (31.8%) |
| 5 tumors < 3 cm | 7 (31.8%) |
| Down-staging to Milan criteria | 5 (22.7%) |
| Previous descompensation | |
| Encephalopathy (%) | 0 (0%) |
| Variceal bleeding (%) | 0 (0%) |
| Ascites (%) | 7 (31.8%) |
| **Analytical data** | |
| Serum bilirubin (mg/dL) | 1,6 ± 0,9 |
| Prothrombin activity (%) | 72,0 ± 12,3 |
| Serum albumin (g/L) | 34,0 ± 4,8 |
| ALT (IU/L) | 81,5 ± 72,0 |
| AST (IU/L) | 84,4 ± 61,8 |
| Gamma-glutamyltranspeptidase (IU/L) | 108,2 ± 59,7 |
| Alkaline phosphatase (IU/L) | 299,0 ± 111 |
| Blood urea nitrogen (mg/dL) | 15 ± 3,7 |
| Creatinine (mg/dL) | 0,9 ± 0,2 |
| Alpha-fetoprotein (<10/10-100/>100 ng/mL) | 17,2 ± 247(13/8/1) |
| Child-Pugh score (A/B/C) | 6 ± 1,1(16/6/0) |

| **Table 3. Explant histological results after LDLT and imaging-pathological correlation** | | |
|---|---|---|
| **Explant histological results** | | |
| Size of main nodule (mm) | | 32,4±1,7 |
| Multinodular (%) | | 19 (86,4%) |
| | 2 nodules | 7 (36,8%) |
| | 3-4 nodules | 3 (15,8%) |
| | >4 nodules | 9 (56,3%) |
| Historical grade (complete necrosis*/I/II/III) | | 1/5/11/5 |
| Microvascular invasion (%) | | 10 (45,5%) |
| Satellite nodules (%) | | 9 (40,9%) |
| Pathological assessment of extension | | |
| | Beyond Milan (%) | 18 (81,8%) |
| | Beyond San Francisco (%) | 16 (72,7%) |
| | Beyond Up-to-7 (%) | 13 (59,1%) |
| **Imaging-pathological correlation**** | | |
| | Preoperative | Histological result |
| Number of tumors (median) | 3 | 5 |
| Size of largest tumor (mm) | 30,1±15,44 | 32,5±1,7 |
| Bilobular lesions | 12 (54,5%) | 15 (68,2%) |
| Beyond Milan | 12 (54,5%) | 18 (81,8%) |
| Beyond BCLC extended | 0 | 11 (50%) |

* Complete necrosis at explant: 1CR. ** Median time of last CT/MRI prior to LDLT: 59 days (5-151days);

**Table 4. Recipient and donor perioperative complications**

| | | |
|---|---|---|
| **Recipient preoperative complications** | | |
| ICU stay (days) | | 6,1±4,3 |
| Hospital stay (days) | | 27,7±22,6 |
| Perioperative mortality | | 0 |
| Medical complications | | 12 (54,5%) |
| Respiratory complications | | 1 |
| Renal failure | | 2 |
| Infections | | |
| | Bile/abcess/others | 6/1/4 |
| Ascites | | 1 |
| Acute rejection | | 3 |
| Surgical complications | | 16 (72%) |
| Biliary complications* | | 16 (72%) |
| | Biliary leak | 13 (31%) |
| | Treatment (medical/surgery) | 5/8 |
| | Biliary stenosis | 9 (40%) |
| | Treatment (surgery/I.R/ERCP) | 3/5/1 |
| **Donor characteristics and outcome** | | |
| Number of donors | | 22 |
| Mean age (years) | | 33,7 ±9,61 |
| Gender (M/F) (%) | | 15 (68%)/7 (31%) |
| Radiological overestimation of lobe weight | | 13 (59,1%) |
| Graft to body weight ratio (GBWR) (median, range) | | 0,86 (0,74-0,99) |
| Hospital stay (days, range) | | 10,3 (6-35) |
| Complications (%) | | 5 (22,7%) |
| | Clavien-Dindo Classification (I/II/III) | 2/2/1 |
| | Surgical reintervention | 1 |
| | Long-term complications | 0 |

* 5 cases with both biliary leak and stenosis

| Table 5. Deceased Patients: Median survival and Cause of Death | |
|---|---|
| **Overall survival (months)** | **Cause of death** |
| 7 | Hepatic artery thrombosis |
| 17 | HCC recurrence |
| 25 | Complications of HCV-cirrhosis |
| 60 | HCC recurrence |
| 71 | HCC recurrence |
| 94 | HCC recurrence |
| 138 | Complications of HCV-cirrhosis |
| 144 | Complications of HCV-cirrhosis |

## FIGURE LEGENDS

**Figure 1.** Feasibility study. Applicability of the LDLT for extended indications of HCC during the run-in period from March 2001 to December 2003

**Figure 2.** Flow-chart of BCLC extended criteria indications and neo-adjuvant treatments applied prior LDLT

**Figure 3.** Overall probability of survival of the 22 cirrhotic patients with BCLC extended indications for LDLT

**Figure 4.** Actuarial probability of recurrence of the 22 cirrhotic patients with BCLC extended indications for LDLT

**Figure 5.** Overall probability of survival according to last preoperative radiological exploration before LDLT

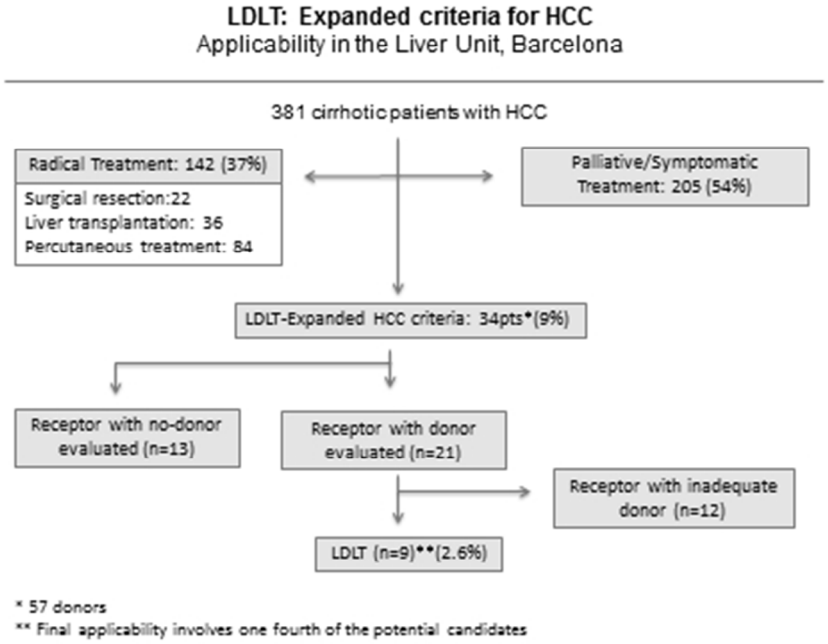


Figure 1. Feasibility study. Applicability of the LDLT for extended indications of HCC during the run-in period from March 2001 to December 2003

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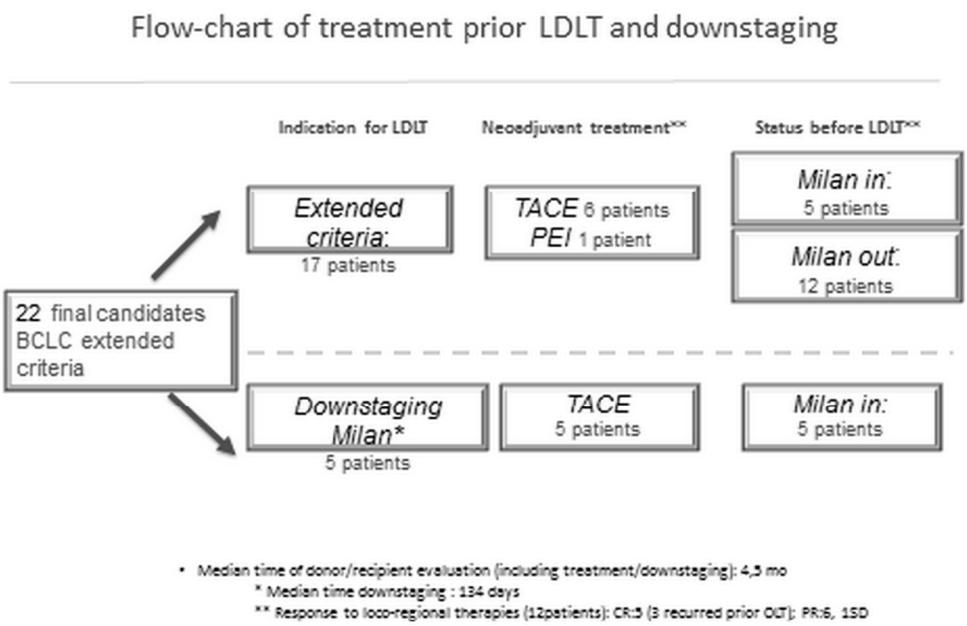


Figure 2. Flow-chart of BCLC extended criteria indications and neo-adjuvant treatments applied prior LDLT

128x96mm (300 x 300 DPI)

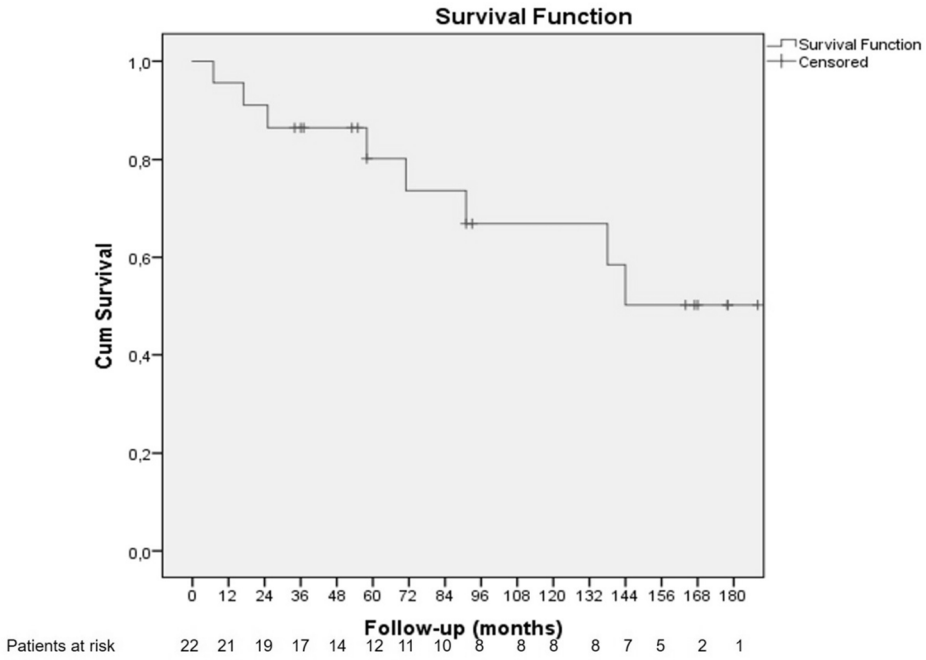


Figure 3. Overall probability of survival of the 22 cirrhotic patients with BCLC extended indications for LDLT

109x74mm (300 x 300 DPI)

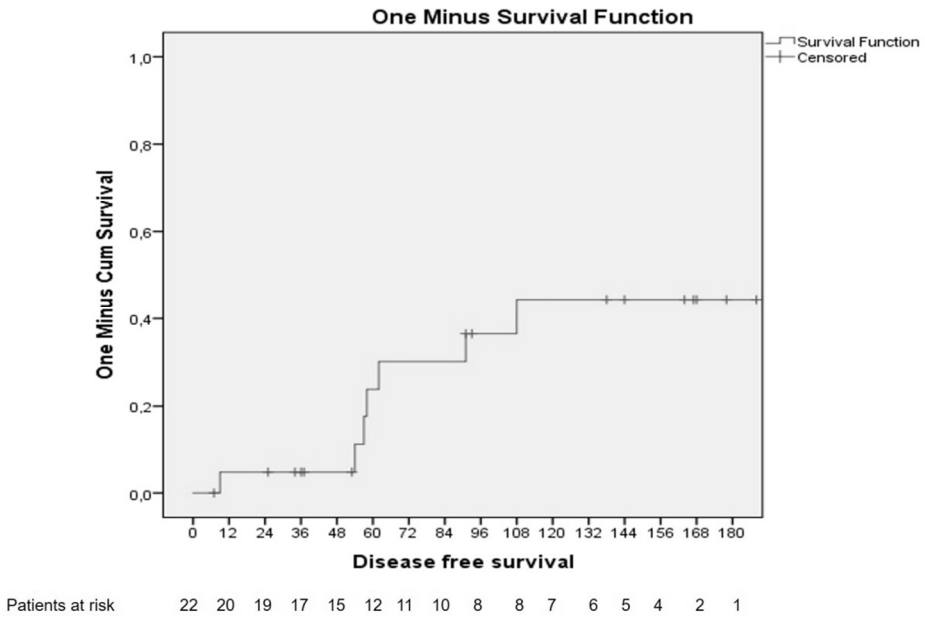


Figure 4. Actuarial probability of recurrence of the 22 cirrhotic patients with BCLC extended indications for LDLT

109x70mm (300 x 300 DPI)

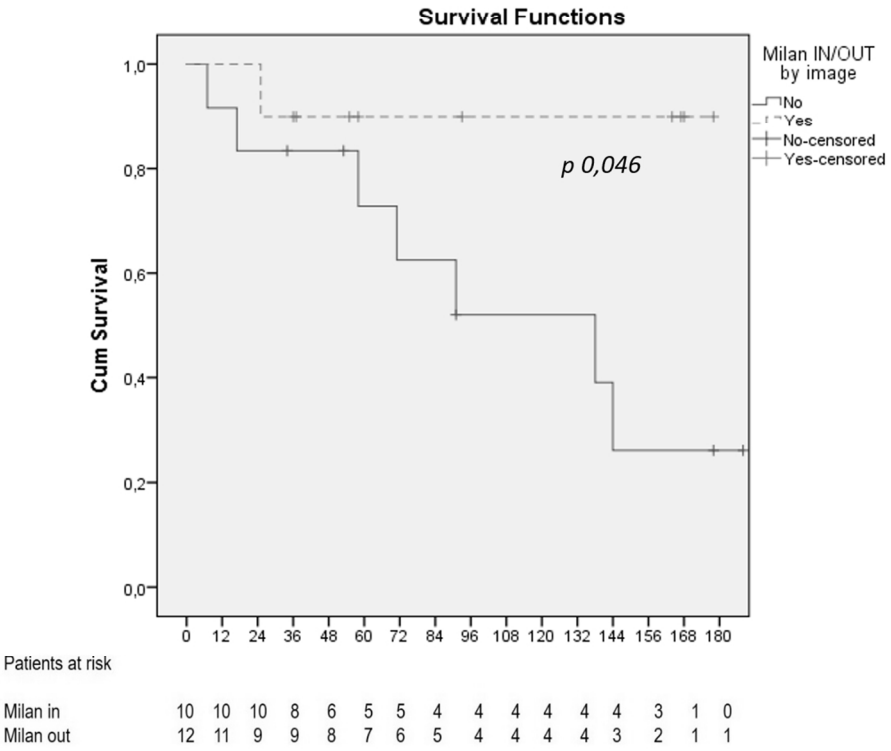


Figure 5. Overall probability of survival according to last preoperative radiological exploration before LDLT.

106x90mm (300 x 300 DPI)