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Living donor liver transplantation for hepatocellular carcinoma: a single center analysis of outcomes and impact of different selection criteria

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Summary

We examined the outcomes of patients who received living donor liver transplantation (LDLT) for HCC comparing the impact of up-to-seven criteria and Asan Criteria (AC) with Milan Criteria (MC). Between July 2004 and July 2009, of 175 consecutive LDLT, there were 45 consecutive patients with HCC. Forty patients who completed 12 months follow-up were enrolled. In search for the highest number of expansion, we selected AC as the extended criteria. Patients were divided into having tumors within MC, beyond MC within AC and Beyond Criteria (BC) groups. With a median follow-up of 46 months, overall 1, 3, and 5 years survival was −90%, −81%, and −70%, respectively. In patients within AC, estimated mean survival was 49.8 vs. 40.5 months for BC group ($P = 0.2$). Disease-free survival was significantly higher in patients within AC comparing with BC group; 48.0 vs. 38.6 months ($P = 0.04$). Preoperative AFP level >400 and poor tumor differentiation were factors adversely effecting recipient survival. On multivariate analysis, the presence of poor tumor differentiation ($P = 0.018$ RR: 2.48) was the only independent predictor of survival. Extension of tumor size and number to AC is feasible, without significantly compromising outcomes; however, the presence of poor tumor differentiation was associated with worse outcomes after LDLT.

Background

Living donor liver transplantation (LDLT) has emerged as the sole curative treatment alternative for patients with HCC, where cadaveric graft availability is limited [1,2]. The problem is particularly severe in Asia, where the deceased donor organ rates are fewer than 5 per million population, compared with 10–35 donors per million population in Western countries [3]. That is also the case for Turkey, located between Europe and Asia, which had a 3.1 per million population donation rate in 2007[4]. That was a figure comparable with Asia leaving LDLT as the sole curative option for patients with end-stage liver disease resulting with a significant contribution of LDLT data to European Liver Transplant Registry Database [5].

Living donor liver transplantation has the potential of providing increase in donor pool, eliminating the uncertainty of prolonged waiting times and the risk of dropout because of tumor progression [6]. However, LDLT has its own pitfalls with the emphasis on placing a healthy donor in a well-documented risk of morbidity and mortality [7]. The importance of balancing the benefits of the recipient to the risks of the donor reveals the importance of patient selection criteria for the operation.

Milan Criteria (MC) was consistently reported to be a good predicting tool with good outcomes [8]. However, recently there was a debate on MC being too strict and

that there were patients beyond criteria with potentially favorable prognosis after OLT [2,9]. As a consequence, many other groups have proposed alternative morphologic scores to select transplant candidates [10–15].

Lee *et al.*, recently published the outcome of one of the largest reported retrospective series of LDLT performed in patients with HCC at a single center [13]. They suggested a new criterion, namely Asan Criteria (AC) after multivariate analysis of risk factors for recurrence which rules in tumors with ≤6 nodules, the largest tumor size ≤5 cm, and the absence of gross vascular invasion with an actuarial 5-year survival of 76.3%. In contrast, those patients beyond the proposed criteria had only an 18.9% 5-year survival.

Mazzaferro *et al.* [15] reported a new proposal for HCC selection, namely up-to-seven criteria (USC). From a multicenter retrospective database of 1556 patients, they were able to identify a subgroup of 283 patients with the sum of tumor diameter and tumor number equaling seven, had an excellent 5-year survival estimate of 71.2%. They also confirmed that post-transplant outcome was not dependent on graft origin (i.e. deceased versus living donor grafts).

This study was undertaken to examine outcomes for a consecutive series of patients who received LDLT for HCC in a single institution over a 5-year period. The goal was to compare the outcomes of LDLT for HCC and the impact of two recently proposed criteria on patient selection.

Patients and methods

Between July 2004 to July 2010, 175 consecutive LDLTs were performed at Department of Solid Organ Transplantation Florence Nightingale Hospital, Istanbul, Turkey. Using a prospectively collected transplant database, we performed a review of all patients who underwent LDLT for HCC. There were 45 consecutive LDLT recipients with pathologic diagnosis of HCC during the study period that completed 1 year postoperative follow-up. Two patients who had mixed cholangiocellular and HCC and a patient with fibrolamellar HCC were excluded from this analysis. One patient who did not complete a 12-month follow-up and another patient who died in the perioperative period were also excluded.

Study design

Overall, 40 patients included in the analysis were divided into criteria groups, namely MC, USC, AC, and Beyond Criteria (BC) groups (Fig. 1). Preliminary analysis showed that compared with MC, USC enrolled three more patients, a 7.5% expansion; however, AC provided nine

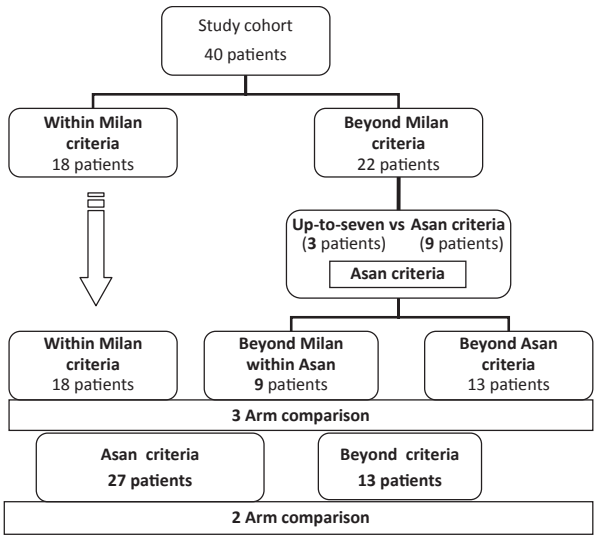

Figure 1 Study design.

(%22.5) more patients ($P = 0.03$). In search for the highest number of expansion with similar outcome, we selected AC as the extended criteria. Patients were divided into having tumors within MC, beyond MC within AC and BC (Asan) groups. For two arm comparison, patients were grouped into within AC and BC. Primary endpoints were both patient and recurrence-free survival.

Pretransplant evaluation

The indication for LDLT was HCC with neither extrahepatic metastasis nor macroscopic vascular invasion in conventional imaging studies. Tumor size and number was not regarded as limitations. Exclusion of patients with extrahepatic metastasis was made by chest, cranial-thoraco-abdominal CT scan, and bone scintigraphy. No preoperative tumor biopsy was performed.

Three patients had pretransplant tumor biopsies before they were referred to our center. Another three patients had tumor resections (one patient anatomical, two patients nonanatomical). One patient had TACE at another center and two patients had percutaneous RFA.

Patients with tumors beyond MC underwent exploratory laparotomy on the day of transplantation before anesthetization of the donor to determine extrahepatic spread and lymph node status with frozen section.

Operative management

Our standardized evaluation protocol for potential living liver donors and techniques of donor graft hepatectomy and recipient total hepatectomy in LDLT have been described previously [16]. In brief; the graft consisted of

the right lobe with or without the middle hepatic vein (HV). The recipient right HV opening was widened by trimming the vessel edges and the graft HV was anastomosed to the recipient right HV opening with the IVC cross-clamped. Multiple graft HV was reconstructed either via direct caval anastomosis, venoplasty, or by the use of cadaveric interposition grafts to the inferior vena cava (IVC). The graft was reperfused after portal vein anastomosis followed by hepatic artery reconstruction using microsurgical techniques in all cases. Intraoperative doppler evaluation of the anastomoses were performed at this stage. Biliary reconstructions were performed via duct-to-duct anatomosis with or without stent.

Histopathologic studies

All explants were examined by a single pathologist and categorized based on tumor number, size, distribution, differentiation, and lymphovascular invasion to determine tumor stage according to the TNM [17], Milan, USC, and AC. The presence and absence of micro or macrovascular invasion were also recorded. Patients with tumors that were not recognized before transplantation but identified on the explanted liver were regarded as having incidental tumors.

In patients with multiple lesions in the liver explant, the highest tumor histologic grade was recorded. Total tumor volume calculation was based on the maximum radius of each tumor than by the sum of the volume of each tumor using $[(4/3)\ \pi r^3]$ formula, as reported [14].

Postoperative follow-up and treatment

After transplantation, immunosuppression consisted of a triple regimen of mycophenolate mofetil with cyclosporin or tacrolimus and steroid taper which was tailed off at the end of 6 month. Then a target trough level of 3–6 ng/ml for tacrolimus was continued.

In patients with chronic hepatitis B, lamivudine monoprophylaxis with add-on adefovir dipivoxil for high viral DNA breakthrough was used. The patients were monitored regularly by measurement of serum α-fetoprotein level and doppler USG every 3 months in the first year then twice thereafter and thoracoabdominal CT scan when clinically indicated, otherwise yearly. MRI confirmation was done when necessary.

Follow-up protocol for HCC consisted of serum alpha-fetoprotein measurement every 3 months in the first 2 years and then twice a year thereafter. Abdominal ultrasonography (USG) was performed by a single experienced radiologist every 6 months in the first 2 years and yearly thereafter. Computerized tomography (CT) was performed annually or whenever clinically indicated. Magnetic resonance imaging (MRI) was performed for confirmation of suspicious lesions after USG or CT. The major endpoints studied were HCC recurrence and patient death. No patient was lost to follow-up.

None of the study cohort received pre- or postoperative systemic chemotherapy, including sorefenib, TACE, or radiotherapy. However, four patients (10%) had surgical resection, one patient (2.5%) had RFA, and another two patients (5%) had both treatments for control of their recurrent disease.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (range) and comparisons between subgroups were performed using the Mann–Whitney *U*-test and one-way ANOVA test. Categorical variables were compared using chi-squared test or Fisher's exact test. Deaths from all causes were included in the calculation of survival. Survival analysis was performed using Kaplan–Meier analysis, with the log-rank test. Variables related to the patient, liver graft and HCC were analyzed for prognostic significance. Univariate Cox-regression analysis was used to find variables that have significant impact on survival and recurrence. Variables with $P < 0.10$ were included in a multivariate backwards Cox-Regression analysis model. A *P*-value less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS 17.00 for Windows (SPSS, Chicago, IL, USA).

Results

The median follow-up of the 40 patients included in the study who underwent LDLT for HCC was 46 months (range: 18–72 months).

Demographic characteristics of patients with HCC

Table 1 demonstrates the preoperative demographics of the transplant recipients. There were 33 men (82.5%), seven women (17.5%), and ranged in age from 40 to 72 years (mean 55 years). There was no significant difference in age, gender, and body mass index (BMI) of the patients according to groups. Measures of disease severity such as the Child–Pugh score and Model for End-Stage Liver Disease (MELD) score, and the etiology of the underlying liver disease were also comparable. The causes of the underlying liver disease were hepatitis C virus-induced ($n = 9$, 22.5%) or hepatitis B virus-induced ($n = 25$, 62.5%) cirrhosis (six of them had HDV superinfection), alcohol abuse ($n = 5$, 12.5%), and cryptogenic cirrhosis ($n = 1$, 2.5%).

Table 1. Comparison of preoperative characteristics of 40 patients according to criteria groups.

(%)		Within MC *n* = 18 (%)	Beyond MC within AC *n* = 9 (%)	Beyond AC *n* = 13 (%)	*P*
Gender	Male	16 (40)	8 (20.0)	9 (22.5)	
Age	Mean ± SD	55.7 ± 8.5	56.1 ± 3.8	54.9 ± 6.7	0.9
MELD	–	16.28 ± 4.836	15.33 ± 5.220	13.77 ± 5.819	0.4
Child	A	3 (7.5)	2 (5)	4 (10)	0.8
	B	9 (17.5)	5 (12.5)	4 (10)	
	C	6 (15)	2 (5)	5 (12.5)	
Etiology	HBV	7 (17.5)	4 (10)	8 (20)	0.6
	HBV + HDV	5 (12.5)	1 (2.5)	0	
	HCV	4 (10.0)	2 (5.0)	3 (7.5)	
	Alcohol	2 (5.0)	2 (5.0)	1 (2.5)	
	Kryptogenic	0	0	1 (2.5)	
MELD score	MELD < 15	6 (15)	5 (12.5)	7 (17.5)	0.3
	15 < MELD < 20	7 (17.5)	2 (5)	4 (10)	
	20 < MELD < 25	4 (10)	1 (2.5)	2 (5)	
	MELD > 25	1 (2.5)	1 (2.5)	0	
Largest tumor diameter mm (CT scan)	Mean ± SD	24.50 ± 10.35	35.56 ± 9.82	74.08 ± 31.85	< 0.001

MC, Milan Criteria; AC, Asan Criteria; CT, computerised tomography.

Operative characteristics of recipients

All patients received right lobe grafts. The median operation time was 490 min (range: 300–765 min) and the median units of packed red blood cells transfused was five (range: 0–33 units). The median graft to recipient weight ratio was 1.22 (range: 0.85–1.94) and hospital stay was 17 days (range: 10–42 days).

Operative characteristics and outcome of living donors

The median operation time was 272 min (range: 221–348 min), operative blood loss was 315 ml (range: 210–716 ml) and radiologically estimated remnant liver/total liver ratio was 34 (range: 28–42). Middle HV was harvested with 14 (35%) of grafts. The median graft weight was 877 ml (range: 543–1468 ml), parenchymal transection time was 65 min (23–150 min) and postoperative hospital stay was 9 days (range: 5–20 days).

There were no donor deaths. Eleven donors (27.5%) developed postoperative complications. One donor developed a bile duct stricture that was treated with endoscopic balloon dilatation. Another developed prolonged hyperbilirubinemia that resolved spontaneously. Other complications included atelectasis (9), pleural effusion (3), and wound infection (1).

Gross and microscopic characteristics of HCC

No tumor was found in the extrahepatic nodes on the frozen section evaluations and on explanted specimens. A single tumor was present in 18 cases, six cases had two nodules, four cases had three nodules, and more than three tumor nodules were detected in 12 cases (Table 2). Patients beyond AC had significantly more multinodular and bilobar tumors ($P = 0.001$ and $P = 0.01$, respectively). of six patients with microvascular invasion, only one patient (2.5%) was within AC group and five patients (15%) were in BC group ($P = 0.001$).

The median AFP level was 40.5 ng/ml prior to transplantation with a range of 2 to 2217 ng/ml (Table 2). Patients in BC group had higher AFP levels which did not reach statistical significance ($P = 0.07$). Poor tumor differentiation was seen in two (5%) patients within AC and in six (15%) patients in BC groups.

HCC recurrences and risk factors

All HCC recurrences occurred within the first 36 months and HCC recurred in nine (22.5%) of the 40 recipients during follow-up period. There were two (5%) recurrences in patients within MC, two (5%) in beyond MC within AC and five (12.5%) recurrences were in patients beyond AC (Table 2).

Stepwise Cox regression analysis was performed using following parameters: tumor size, MC, USC, AC, AFP level > 400, lobar distribution of tumors, total tumor volume, maximum tumor size, tumor differentiation, and microvascular invasion. Poor tumor differentiation and preoperative AFP level > 400 were significant predictors of tumor recurrence, ($P = 0.02$ RR: 4.74 95% CI: 1.18–18), ($P = 0.003$ RR: 12.43 95% CI: 2.31–66.79), respectively.

Table 2. Comparison of different selection criteria by histopathologic features of hepatocellular carcinoma.

% of all patients	Within MC *n* = 18	Beyond MC within AC *n* = 9	Beyond AC *n* = 13	*P* asan	*P* criteria
Number of tumor(s)					
1	14 (35)	0	3 (7.5)	0.007	<0.001
1–3	4 (10)	2 (5)	6 (15)		
>3	0	7 (20)	4 (10)		
Multifocality	3 (7.5)	8 (20)	10 (25)	0.09	<0.001
Microvascular invasion	1 (2.5)	0	5 (12.5)	0.002	0.001
Bilobar tumor	1 (2.5)	5 (12.5)	7 (17.5)	0.01	0.08
Tumor differentiation					
Well	5 (12.5)	1 (2.5)	2 (5)	0.04	0.05
Moderate	11 (27.5)	8 (20)	5 (12.5)		
Poor	2 (5)	0	6 (15)		
pTNM AJCC					
1	5 (12.5)	0	0	0.02	<0.001
2	12 (27.5)	1 (2.5)	0		
3	1 (2.5)	8 (20)	13 (32.5)		
Total tumor volume	12.7 ± 13.5	33.1 ± 17.3	333.2 ± 425.4	0.01	0.03
Alpha-fetoprotein	95.4 ± 141.5	187.2 ± 339.4	390.1 ± 657.9	0.07	0.17

P asan: two arm comparison of tumors within and beyond Asan Criteria (AC).
P criteria: three arm comparison between within MC, beyond MC within AC and beyond AC groups.

Patient survival

In the study group; there were 10 (25%) deaths, three patients (7.5%) were within MC, two patients (5%) were beyond MC within AC and five (12.5%) were BC. Six (60%) deaths were because of tumor recurrence. Two of the five deaths from AC group and four of the five from BC group were resulting from tumor recurrence.

Kaplan–Meier analysis showed that estimated mean survival of the whole series was 56.6 months (95% CI 48.9–64.2 months) (Fig. 2a). Overall 1, 3, and 5 years survival was −90%, −81%, and −70%, respectively. In patients within AC overall estimated mean survival was 55.9 (95% CI 49.4–62.4) vs. 51 months (95% CI 36.1–65.8) for BC group (log-rank, $P = 0.2$). Overall 1, 3, and 5 years survival for patients within AC was −96%, −83%, and −78% and for patients BC were −76%, −67%, and −57%, respectively. Survival of patients within MC, beyond MC within AC and BC groups was not significantly different ($P = 0.3$) (Fig. 3a).

The presence of microvascular invasion and poor tumor differentiation in the explant resulted with significantly lower survival; 61 (95% CI 53.7–68.3 months) vs. 39.7 months (95% CI 17.7–61.7) ($P = 0.02$) and 63.6 months (95% CI 56.9–70.3 months) vs. 36.6 months (95% CI 19.8–53.5) ($P = 0.004$), respectively (Fig. 4a–b).

Univariate analysis showed that preoperative AFP > 400 and poor tumor differentiation were factors adversely effecting recipient survival. In multivariate analysis, the presence of poor tumor differentiation ($P = 0.01$, RR: 2.48, %95 CI = 1.07–6.98) was the only independent predictor of survival.

Disease-free survival

Kaplan–Meier analysis showed that overall 1, 3, and 5 years estimated disease-free survival of this cohort was −89%, −77%, and −74%, respectively (Fig. 2b).

Disease-free survival for patients with tumors within MC was not different than patients beyond MC 60 (95% CI 53,4–66.2) vs. 51.3 months (95% 38.4–63.2 months) (log rank, $P = 0.07$) (Fig. 3b). However, in patients within AC group disease-free survival was significantly higher compared with patients beyond AC group; 48.0 (95% CI 41.2–54.1 months) vs. 38.6 months (95% CI 27.6–53.8 months) (log rank, $P = 0.04$) (Fig. 3b). Overall 1, 3, and 5 years disease-free survival for patients within AC was −92%, −76%, and −76% for patients BC were −75%, −51%, and −51% respectively.

The presence of poor tumor differentiation resulted with significantly lower disease-free survival; 64.5 (95% CI 57.7–71.2 months) vs. 31.0 months (95% CI 13.1–48.9) ($P = 0.001$).

Discussion

Our analysis revealed an overall estimated 5-year survival rate of 70% with a liberal selection policy in the current era of LDLT. During the study period, we have not changed our policy of transplanting patients with tumors

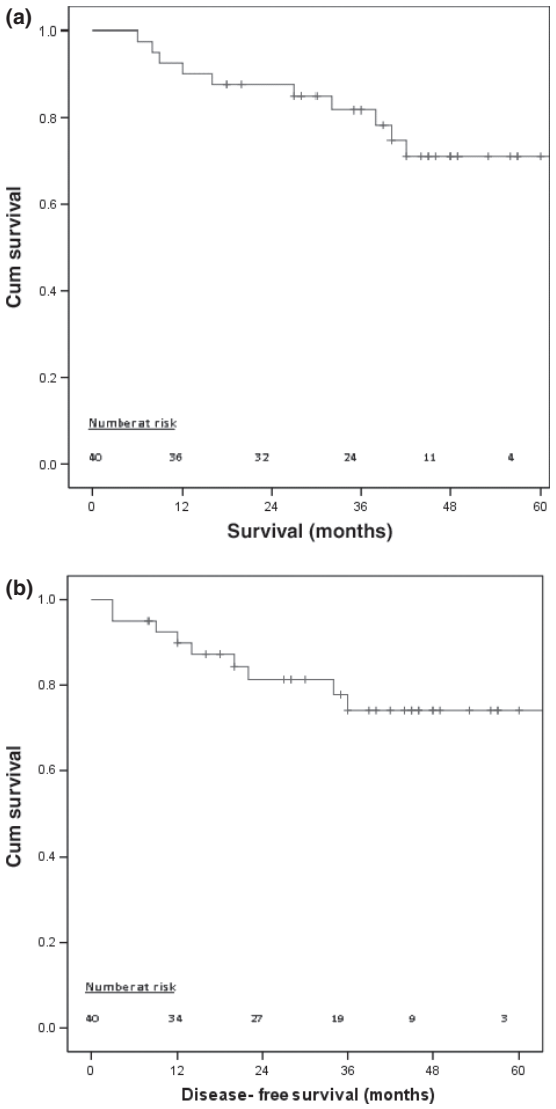

Figure 2 (a–b) Overall A-patient and B-disease-free survival of 40 patients after living donor liver transplantation for hepatocellular carcinoma.

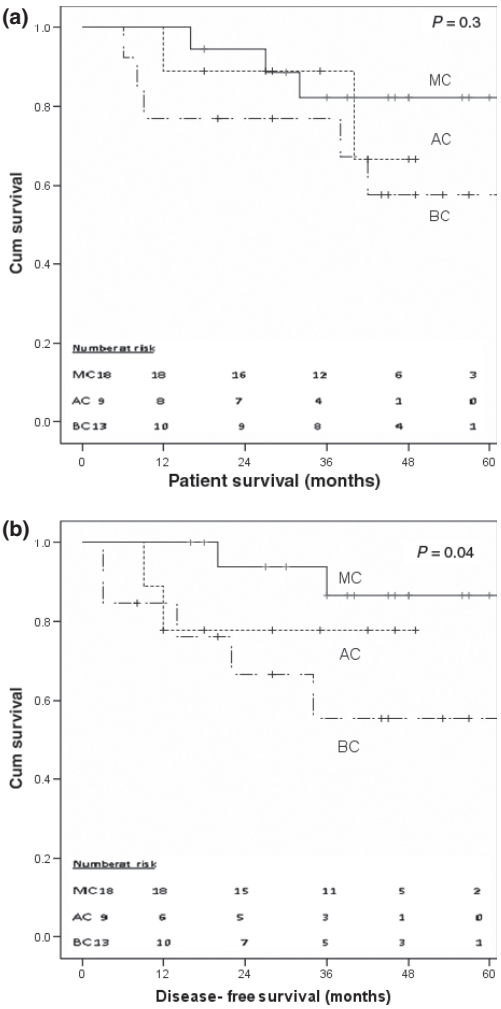

Figure 3 (a–b) Comparison of (a) patient and (b) disease-free survival according to different criteria groups of 40 patients after living donor liver transplantation for hepatocellular carcinoma. MC, Milan Criteria; AC, Asan Criteria; BC, Beyond Criteria.

beyond MC. Both donors and recipients were well informed about the increased risk of recurrence for patients beyond MC. Similar policies with extension of MC was also adopted by many transplant centers, paralleling the technical developments making LDLT a feasible option [18–20]. Kyoto group used a similar extended criterion that included any size or number of tumors in which there was no gross vascular involvement or distant metastasis at preoperative radiology. They reported a 4-year overall patient survival of 64% in all HCC patients and 59% in patients whose tumors were beyond the MC [21]. In accordance with our preliminary analysis of this cohort [22], patients within and beyond MC did not have a significant overall survival difference (52.1 months within MC group versus 41.2 months beyond MC group ($P = 0.16$), suggesting that there are patients outside MC that might have comparable survival.

In LDLT setting, a living donor graft is readily available enabling an elective operation. However, there are well-documented pitfalls, most importantly putting the healthy donor at risk of morbidity and mortality which underlines the importance of patient selection [23,24]. Recently, there has been a significant debate suggesting that the MC are too restrictive [25]. Two recent reports, a multi-institutional largely European and a study from a Korean group, suggested expansion of MC, providing the rationale for this analysis [13,15]. They were both derived from multivariate analysis of factors from explant pathology that have an impact on survival. Mazzaferro *et al.*, with contribution of 36 centers, gathered a database

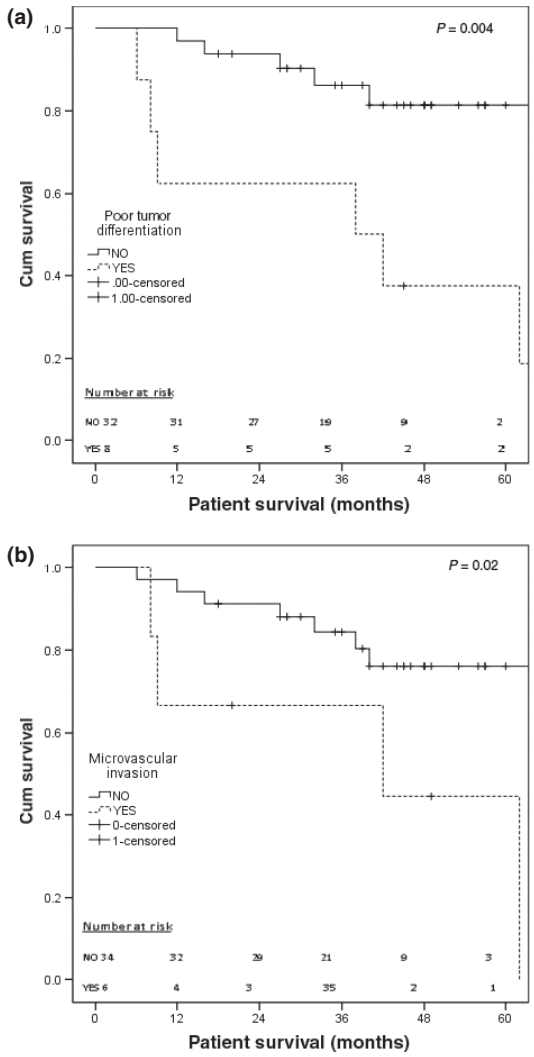

Figure 4 (a–b) Comparison of outcome of 40 patients with different tumor characteristics (a) presence of poor tumor differentiation (b) presence of microvascular invasion in the explant after living donor liver transplantation for hepatocellular carcinoma.

including 1556 patients. They reported a 5-year overall survival of 53.6% (95% CI 50.1–57.0) in patients with HCC exceeding the MC versus 73.3% in those with HCC within the MC ($P < 0.0001$). Their search for extended tumor characteristics with an estimated 5-year overall survival of at least 70%, generated a subgroup, the so-called USC. The 5-year overall survival estimate for this subgroup of 283 patients was 71.2%, which was not significantly different from the 444 patients who were within MC. However, Lee *et al.*, based on 221 LDLT recipients with HCC, retrospectively analyzed the outcome of patients beyond MC. They suggested that selection criteria for OLT can be expanded to the so called AC (≤6 nodules with the largest tumor size ≤5 cm and absence of gross vascular invasion). This cohort had an actuarial 76.3% 5-year survival.

Application of USC to our series provided a significantly lower rate of expansion in the number of patients enrolled comparing with AC. The USC increases the maximal tumor size; however, the size of the dominant nodule determines the allowed total number of other tumors to be ruled in. However, in AC, dominant nodule has no effect on the number of concomitant tumors with ruling in patients up to six nodules largest smaller than 5 cm. It was previously suggested that this restriction was a critical issue limiting widespread acceptance of University of California San Francisco criteria [26]. As our analysis was limited to a small number of patients, validity of this assumption would require report of the results of larger series. Our analysis revealed that poor tumor differentiation and microvascular invasion were existing at a significantly higher rate in patients beyond AC. These factors might be related to higher recurrence and lower survival in patients beyond AC group potentially enabling better patient selection with AC. Further confirmation of these factors might suggest the effectiveness and validity of AC determining the patients with tumors beyond MC but still have similar outcome with patients within MC.

Factors that predicted lower survival in our series included preoperative AFP > 400 and poor tumor differentiation. These determinants have been associated with poor outcome in prior series [13,14,27]. In our analysis, we used a cut-off level of 400 ng/ml to determine the impact of higher AFP levels on tumor recurrence [18]. Univariate analysis showed that a preoperative AFP level higher than 400 ng/ml and presence of poor tumor differentiation were also associated with a significant risk of tumor recurrence after LDLT. A high AFP may be related to the fact that these patients have particularly aggressive tumors that are rapidly progressive and likely to recur after LDLT. Our results confirm others that AFP levels may be a valuable preoperative predictor of tumor biology [28]. Several groups also reported the use of des gamma-carboxy prothrombin (DCP) and prothrombin induced by vitamin K antagonist II (PIVKA-II) as potential predictors of tumor behavior; however, they were both not used in our center [29]. Poor tumor differentiation was associated with both significantly lower disease-free survival and overall survival in our series. A recent series [30], reported that all patients with poorly differentiated tumors developed recurrence and died from their recurrence after LDLT. Furthermore, it was suggested that HCC larger than 5 cm with poor differentiation may predict the presence of microvascular invasion [31]. This study is in accordance with the previous results: more than half of our patients with poor differentiated tumors had recurrence and most deaths were resulting from

tumor recurrence in this subgroup. The preoperative detection of these two factors might be helpful to exclude patients with high recurrence risk avoiding a potentially harmful operation for the donors. However, this valuable information may only be obtained after pathologic examination of the specimen. Recently, there are reports suggesting the role of preoperative tumor biopsy to guide patient selection for transplantation demonstrating the safety and accuracy of the procedure [32]. In a recent multicenter study, Decaens *et al.* reported on the impact of tumor differentiation in predicting 5 year disease-free survival after deceased donor liver transplantation [33]. Moreover, Toronto group reported excellent outcomes for patients with tumors beyond MC with introduction of preoperative biopsy and excluding patients with poorly differentiated tumors [34]. Our results may also support the role of preoperative biopsy to detect patients with expectantly poor outcomes precluding futile LDLT. However, during the study period, we preferred to avoid preoperative biopsy in fear of tumor dissemination and its other reported limitations [35,36].

This study was limited by its retrospective design with relatively small sample size of 40 patients who underwent LDLT. Our follow-up period was relatively short; however, our analysis revealed that recurrence rates in patients within MC and AC groups were limited and all recurrences were in the first 3 years, both within our mean and median follow-up range. These results may justify our analysis and might provide further evidence for validation of AC as an extended criterion.

In conclusion, our study suggests that the extension of tumor size and number to so-called AC is feasible, without significantly compromising survival and recurrence rates in LDLT setting. In addition to a high preoperative AFP level, the presence of certain pathologic factors such as microvascular invasion and poor tumor differentiation might help predicting better outcomes.

Authorship

DB: designed the study, collected the data, wrote the paper. MD: collected the data, revised manuscript. OY, BA, CD and RK: collected the data. YY: designed the study. YT: designed the study, revised the manuscript.

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