Resection for Hepatocellular Carcinoma is a Good Option in Child-Turcotte-Pugh Class A Patients With Cirrhosis Who Are Eligible for Liver Transplantation

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The best treatment option for patients with single, early hepatocellular carcinoma (HCC) and cirrhosis, good liver function, and absence of portal hypertension remains to be established. The aim of this work was to compare the outcome of liver resection (LR) with that of liver transplantation (LT) for single, early HCC in Child-Turcotte-Pugh class A patients with cirrhosis younger than 70 years of age. Thirty-seven of 134 patients who underwent LR and 36 of 125 who underwent LT for HCC in our unit fulfilled the inclusion criteria. No differences were observed in mean tumor size (3 cm); HCC cirrhosis predominated in the LT group and older age in the LR group. Postoperative mortality was higher and hospital stay longer in the LT group. Patient survival was similar in both groups. Tumor recurrence was higher in the LR group (59% vs. 11%), extrahepatic recurrences predominated after LT and hepatic recurrences after LR. Disease-free survival was significantly better after LT. Eighteen patients presented hepatic recurrence after LR: 5 advanced and 13 early. Seventeen patients—13 with early HCC recurrence and 4 with liver failure—were potential candidates for salvage LT. However, 10 of 17 patients were older than 70 years at this time. Salvage LT could only be performed in 6 patients: 5 for HCC recurrence and 1 for liver failure. Results of salvage LT were similar to those of primary LT. In conclusion, only 27.6% of resected patients were eligible for LT. LR is a good option since it offers similar survival to LT. Salvage liver transplantation was performed in 16.2% of resected patients, with older age being the main contraindication. Outcome of salvage LT was similar to that of primary LT. (Liver Transpl 2005;11:1242-1251.)

Liver transplantation (LT) is the treatment of choice for early HCC in Child-Turcotte-Pugh class B or C cirrhosis or Child-Turcotte-Pugh class A patients with portal hypertension. However, the optimum treatment strategy for patients with early, single HCC and cirrhosis, good liver function, and absence of portal hypertension is far from being established. Liver resection (LR) in these cases is a very safe procedure that can be performed without delay. HCC recurrence will be the rule after a long period of follow-up; when it occurs, salvage LT can be offered if recurrence is diagnosed early. The question then arises as to whether LR is a good option "per se" in those patients eligible for transplantation or whether it is just a bridge to LT, which would be the best primary treatment if sufficient livers were available. No prospective, randomized studies have been reported comparing LR and salvage LT with primary LT for early HCC in cirrhotic patients who could be eligible for both treatments. The principal aim of our study was to compare the results of LR in this group of cirrhotic patients with HCC who would have been eligible for primary transplantation with a group of patients who underwent LT for known HCC with similar tumor stage at diagnosis and preserved liver function (Child-Turcotte-Pugh class A cirrhosis). The assumption was that results of primary transplantation in the resected group would have been similar to those of this transplant group since tumor stage and the operative risk of transplantation were similar.

Immediate salvage LT after LR has been proposed when microvascular tumor invasion or satellites are found on histopathologic study of the resected specimen since these features have been related to higher early tumor recurrence. Salvage LT is proposed when tumor recurrence or liver failure occur after LR. Previous reports have shown low applicability of salvage LT between 10% and 20%. Results of salvage LT are also controversial; recent articles concluded that they are clearly inferior to those of primary LT.

The aim of the present study was to answer these four questions: (1) What is the best option for patients...
with early single HCC eligible for resection and transplantation? (2) Is it a reasonable strategy to offer immediate LT after LR to patients with unfavorable histopathologic criteria? (3) What are the reasons for the low applicability of salvage LT? and (4) Does a previous LR jeopardize the result of salvage LT?

Patients and Methods

Study Design

This is a retrospective study of our data base of surgical treatment of HCC by LR and LT. The data were acquired prospectively.

Patient Population

From October 1988 to December 2002, 259 patients with HCC underwent surgery in our Hepatobiliary and Liver Transplantation Unit: 134 underwent LR with complete excision of the tumor, and 125 underwent LT. Distribution of patients according to Barcelona Liver Cancer (BCLC) staging classification is shown in Table 1. Inclusion criteria for this study were: age under 70 years (the age limit for LT in our unit), absence of comorbidity precluding LT, single tumor at diagnosis less than 5 cm in diameter and Child-Turcotte-Pugh class A cirrhosis and age < 70 yrs, n = 9; entering the study: cirrhosis and age < 70 yrs, n = 37). Transplantation BCLC: stage A, n = 76; Child-Turcotte-Pugh class A, n = 50; Child-Turcotte-Pugh class B, n = 48; Child-Turcotte-Pugh class C, n = 28 (patients entering the study: Child-Turcotte-Pugh class A single tumor at diagnosis, n = 36). Abbreviations: BCLC, Barcelona Liver Cancer Group; LR, liver resection; LT, liver transplantation; PH, portal hypertension.

Table 1. Tumor Stage and Liver Function According to BCLC Classification of Patients Resected and Undergoing Transplantation for HCC

| BCLC Stage10 | LR       | LT       |
|-------------|----------|----------|
| A (early HCC)* | 73       | 76       |
| A1†         | 40       |          |
| A2‡         | 16       |          |
| A3§         | 13       |          |
| A4¶         | 4        |          |
| B (advanced HCC)# | 44      | 40       |
| C (extrahepatic spread)** | 17      | 9        |
| Total       | 134      | 125      |

NOTE. Other patient populations are as follows: Resection A1 + A2, n = 56 (excluded from study: non-cirrhotic liver, n = 10; cirrhosis and age ≥ 70 yrs, n = 9; entering the study: cirrhosis and age < 70 yrs, n = 37). Transplantation BCLC: stage A, n = 76; Child-Turcotte-Pugh class A, n = 50; Child-Turcotte-Pugh class B, n = 48; Child-Turcotte-Pugh class C, n = 28 (patients entering the study: Child-Turcotte-Pugh class A single tumor at diagnosis, n = 36). Abbreviations: BCLC, Barcelona Liver Cancer Group; LR, liver resection; LT, liver transplantation; PH, portal hypertension.

Table 2. Inclusion Criteria for the Study

| Criteria                                                                 |
|--------------------------------------------------------------------------|
| Age under 70 years                                                       |
| No contraindication for major surgery                                   |
| Tumor stage at diagnosis: single, less than 5 cm in diameter             |
| Liver parenchyma: cirrhosis                                              |
| Liver function: Child-Turcotte-Pugh class A                              |
| Resection: normal bilirubin, no portal hypertension (A1), portal hypertension (A2); tumor location: peripheral |
| Transplantation: bilirubin > 1 mg/dl and portal hypertension (A3, A2); tumor location: central (A1) or peripheral |

Liver Resection

Surgical techniques and postoperative treatment have been reported previously. Intraoperative ultrasound examination was performed on all occasions to rule out other foci of HCC and to perform radical surgery with safe margins. The majority (95%) of LRs performed were minor resections, including bisegmentectomy, monosegmentectomy, and tumorectomy, whereas only 2 patients underwent major LR (Table 3). Hypertrophy of the contralateral lobe was present in these two cases. Intermittent clamping of the hepatic hilum—10 minutes of occlusion followed by 5 minutes reperfusion—was usually performed to avoid blood loss during parenchymal transaction. Blood transfusion was required in 35% of cases. Complete excision of the tumor was confirmed by pathologic examination: minimal margin from the tumor to cut surface was less than 1 cm in 61% of cases and more than 1 cm in 39% of cases.
Follow-Up
Abdominal ultrasonography, alphafetoprotein, and liver function tests were performed in all patients every 3 months, and abdominal CT scan was performed every 6 months to detect possible tumor recurrence or liver failure.

Treatment of HCC Recurrence
A new complete evaluation was made when hepatic HCC recurrence was diagnosed including a TACE as staging and treatment procedure. LT was proposed in cases of early HCC recurrence in patients eligible for the procedure, whereas repeat hepatic resection, an ablation technique, or TACE was indicated in early HCC recurrence in patients not eligible for LT. TACE was the only treatment performed in stage B recurrent HCC.

Liver Transplantation
Candidates for LT were included on the waiting list after signing their informed consent. Mean waiting time was 95 days, range 15 to 150 days. There were no exclusions from the waiting list for tumor growth.

Surgical Techniques
Recipient hepatectomy with inferior vena cava preservation was performed in all cases. In 80% of cases, a duct-to-duct anastomosis without T-tube was used for biliary reconstruction.

Posttransplantation Management and Follow-Up
Immunosuppressive therapy after LT consisted of a double-drug regimen of cyclosporine or tacrolimus in combination with corticosteroids. Azathioprine or, more recently, mycophenolate mofetil were used in cases of rejection or toxicity from calcineurin inhibitors. The dose of corticosteroids was gradually tapered to discontinuation at 3 to 6 months after LT. Patients were followed in the outpatient clinic once a week during the first month and as clinically indicated thereafter. Tumor recurrence was screened by ultrasound or CT and alpha-fetoprotein measurement every 3 months. No adjuvant chemotherapy was administered to any patient after LT. HCC recurrence in the liver or elsewhere was treated symptomatically.

Survival and Statistical Analysis
Follow-up was censored in November 2004. All data are expressed as mean (SD) and comparisons between means were made by Student $t$ test or Mann-Whitney $U$ test for parametric and nonparametric analyses. Survival estimates were determined using Kaplan-Meier analysis. All statistical analyses were performed using SPSS software (SPSS, Inc., Chicago, IL). A $P$ value less than 0.05 was considered significant.

Results

Patient Demographics and Tumor Characteristics
Thirty-seven patients in the LR group and 36 patients in the LT group fulfilled the inclusion criteria. There was male predominance and advanced age; almost half the patients were older than 65 years in the LR group. The predominant etiology of cirrhosis was hepatitis C virus (HCV), particularly in the LT group. More patients were treated preoperatively with TACE in the LT group. Mean tumor size was 3 cm. Another nodule was found on pathologic study of the specimen in two transplanted patients. Microscopic vascular invasion was greater, but not significant, in the LR group, whereas satellitosis predominated in the LT group. Median hospital stay was longer for LT and median follow-up was similar. Demographics and characteristics are presented in Table 4.

| Table 3. Type of Liver Resection |
|---------------------------------|
| Type of resection | Number of patients |
|-------------------|-------------------|
| Major hepatectomy | 2                 |
| Right hepatectomy (V-VI-VII-VIII) | 1              |
| Left hepatectomy (II-III-IV) | 1                 |
| Minor hepatectomy | 35                |
| Bisegmentectomy   | 12                |
| Left lateral segmentectomy (II-III) | 4              |
| Right lateral segmentectomy (VI-VII) | 3              |
| Others            | 5                 |
| Monosegmentectomy | 8                 |
| Atypical or tumorectomy | 15              |

| Table 4. Patient Demographics and Tumor Characteristics |
|--------------------------------------------------------|
| No. of patients | Liver transplant | $P$ value |
|-----------------|------------------|-----------|
| Resection       | LT               |           |
| Mean age, yrs   | 62±6             | 59.9±7.6  | 0.7       |
| Age > 65 yrs, n (%) | 18 (48)      | 5 (13.9)  | 0.001     |
| Sex M/F, n      | 29/8             | 22/14     | 0.1       |
| Etiology HCV, % | 61               | 83.3      | 0.035     |
| Preop. TACE, n (%) | 8 (21.6)     | 18 (50)   | 0.02      |
| Tumor size (cm) | 3.2±1            | 3.0±1     | 0.8       |
| No. of nodules  | 1                | 1.0±0.2   | 0.9       |
| Vascular invasion, n (%) | 6 (16.2) | 2 (5.6) | 0.4     |
| Satellites, n (%) | 3 (8.1)        | 10 (28)   | 0.02      |
| Postop. stay, days | 10.1±5        | 29±41     | 0.07      |
| Median follow-up | 50 mo           | 44 mo     |           |
Mortality and Survival after LR and LT

Seventeen LR patients (46%) and 13 LT patients (36%) died during follow-up. No significant differences were observed in overall mortality between the groups. In the LR group, postoperative mortality was nil; only 1 patient died before 3 months from pneumonia, 11 died from HCC recurrence, 3 from liver failure, and 3 from other causes. In the LT group, postoperative mortality was 5.6%. Two patients died from sepsis: one after urgent retransplantation for primary nonfunction (this patient had received a right lobe transplant from a split liver) and the other from necrotizing pancreatitis. Two patients died before 6 months from abdominal sepsis after reoperations due to biliary peritonitis and ischemic colitis, respectively. An additional four patients died before 1 year of follow-up: two from HCC recurrence and two from aggressive cholestatic HCV recurrence. After 1 year, five patients died: two from HCC recurrence, one from respiratory infection, and two from HCV recurrence. Overall actuarial survival was similar in both groups (Fig. 1). Median survival was 85 months in both groups, and 1-, 5-, and 10-year actuarial survival after LR and LT was 92% and 78%, 70% and 65%, and 50% and 60%, respectively (P = 0.8). Survival of HCV-infected patients after LR and LT was analyzed separately since this group was significantly larger in LT. No differences in survival were observed. One-, five-, and ten-year actuarial survival after LR and LT in HCV-positive patients was 91% and 77%, 71% and 66%, and 38% and 59%, respectively (P = 0.8). Mortality and survival data are presented in Table 5.

Tumor Recurrence

HCC recurrence was significantly higher after LR (59%) than LT (11%). Tumor recurrence after LT was mainly extrahepatic or systemic (75%) and appeared between 5 and 40 months (mean, 16 months) after LT. Lungs, adrenal glands, and bone were the most frequent sites of recurrence. Only symptomatic treatment was

| Table 5. Mortality and Survival After LR and LT |
|-----------------------------------------------|
|                                      | Resection (n = 37) | LT (n = 36) | P value |
|-----------------------------------------------|
| Mortality, n (%)                             | 17 (46)           | 13 (36)    | 0.3     |
| Early mortality (< 3 mo), n (%)              | 1 (2.7)           | 2 (5.6)    | 0.4     |
| Sepsis, n (time)                             | 0                 | 2 (5 mo, 6 mo) | 4       |
| HCC recurrence, n (time)                     | 11                | (6, 8, 19, and 46 mo) | 3       |
| Liver failure                                | 3                 | 4          |         |
| HCV recurrence                               | —                 | (4, 9, 32, and 69 mo) | 2       |
| Others                                       | 2                 | 1          |         |
| Tumor Recurrence                             | Overall HCC recurrence, n (%) | 22 (59) | 4 (11) | 0.001 |
|                                              | Hepatic recurrence, n (%) | 18 (48.6) | 1 (2.7) | 0.001 |
|                                              | Time of diagnosis, mo | 40 ± 25 (2 = 74) | 5 |         |
|                                              | Survival after diagnosis, mo | 55 ± 29 | 1 |         |
|                                              | Extrahepatic recurrence, n (%) | 4 (10.8) | 3 (8.3) | 0.2     |
|                                              | Time of diagnosis, mo | 15.3     | 16.5    |         |
|                                              | Survival after diagnosis, mo | 1, 5, 4, 10 | 3, 2, 6 |         |
|                                              | Mean disease-free survival | 52 ± 7 | 86 ± 13 | 0.01    |
given and all patients died soon after the recurrence was diagnosed. Tumor recurrence data are presented in Table 5.

Tumor recurrence after LR predominated in the liver (83%) and appeared at a mean of 40 months after LR. Some recurrences presented early, probably as intrahepatic metastases of the resected tumor or synchronous foci of HCC, but most cases were metachronous, new foci of HCC in the cirrhotic liver that appear long after LR. Extrahepatic recurrences after LR appeared early, around 1 year after LR, and were not treated.

A significant difference was found in disease-free survival after LR and LT. Mean disease-free survival times were 52 and 86 months, and 1-, 5-, and 10-year actuarial disease-free survival for the two groups was 84% and 77%, 39% and 64%, and 18% and 56%, respectively ($P < 0.04$) (Fig. 2).

**Treatment of Hepatic Recurrence after LR**

Eighteen patients presented HCC recurrence located only in the liver. Five recurrences were classified as advanced since they were multinodular, larger than 5 cm, or diffuse; three were treated with TACE. The majority of patients (13) presented an early BCLC stage A HCC recurrence and LT could be proposed. However, 7 of the 13 patients were older than 70 years at the time of evaluation and LT was not considered owing to the age limit. Five patients were treated by TACE and one by re-resection; this patient died from sepsis after LR. Six patients younger than 70 years were evaluated for LT and five actually underwent transplantation. One patient dropped out of the waiting list soon after inclusion owing to bone metastases. Mean survival after TACE and LT performed for recurrence was 22.8 and 36.6 months, respectively. Survival after different treatments for HCC recurrence is shown in Figure 3, and treatment of hepatic recurrence after LR data are shown in Table 6.

**Patients with Unfavorable Histopathologic Criteria**

Overall and disease-free survival of patients with vascular invasion and satellites found on histopathologic study of the specimen obtained after LR and LT were analyzed. Patient survival was lower and tumor recurrence higher in these patients after LR or LT, although these differences were not significant. When a comparison was made between LR and LT in the group of patients with unfavorable histopathologic criteria, no significant differences were observed in actuarial patient survival (Fig. 4). One-, 5-, and 10-year actuarial survival rates after LR and LT were 89%, 67%, 56% and 49%, and 56% and 49%, respectively ($P = NS$). Moreover, extrahepatic HCC recurrences were significantly more frequent in patients with these criteria; 6 (28.5%) of 21 patients with unfavorable criteria vs.
only 1 (1.9%) of 52 patients without these criteria presented extrahepatic HCC recurrence ($P < 0.002$).

**Applicability of LT After LR**

Early hepatic recurrence and liver failure are indications for LT after LR; thus, 17 patients were potential candidates for LT: 4 for liver failure and 13 for early HCC recurrence. The rest were excluded owing to extrahepatic recurrence (4), advanced hepatic recurrence (5), and death from other causes (3). Eight patients (21.6%) are alive and free of recurrence after a mean follow-up of 68 ± 50 months (range, 19-55). Therefore, after a median follow-up of 50.8 months, salvage LT was performed in 16.2% (6 of 37) of all resected patients and 35.3% (6 of 17) of potential candidates. Ten (59%) of the potential candidates were excluded for age over 70 years, the limit for LT in our program. These 10 patients were between 62 and 68 years old at the time of LR. Survival of these 10 patients from the time of LR was compared with that of an age-matched group of 25 patients treated with primary LT; no differences were observed in patient survival between groups (Figure 5). Median interval between LR and salvage LT was 31.9 months, ranging from 6 to 62 months. Indications for salvage LT were HCC recurrence in five cases and liver failure in one. Data regarding the applicability of LT after LR are presented in Table 7.

**LT After LR vs. Primary LT**

When results of LT regarding operative variables such as operative time, blood transfusion, postoperative complications, technical failures, reoperations, etc. were compared, no differences were observed between primary LT and

| Treatment | N | Age > 70 yrs, n | Advanced HCC | Mean Survival (mo) | Survival (mo) |
|-----------|---|----------------|--------------|--------------------|---------------|
| No        | 3 | 1              | 2            | 15 ± 1             | 9*, 6, 13*    |
| Rehepatectomy | 1 | 1              | 0            | 21* (post-op)      |               |
| TACE      | 9 | 5              | 3            | 22.8 ± 8           | 12*, 17*, 18, 19, 20*, 23, 24, 29, 32 |
| LT        | 5 | 0              | 0            | 36.6 ± 27          | 8*, 14, 37, 48, 76 |

*Deceased.

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**Table 6. Treatment of Hepatic HCC Recurrence After Liver Resection**

**Figure 4.** Actuarial patient survival after LR and LT of patients with unfavorable histopathologic criteria. The number of patients remaining in the analysis at each time point is indicated.

**Figure 5.** Actuarial patient survival after LR in 10 patients over 70 when salvage LT was indicated and a group of age-matched patients treated with primary liver transplantation.
salvage LT after LR. Tumor recurrence and patient survival were similar. Only one patient had HCC recurrence after salvage LT. Lymph node tumoral invasion was found at diaphragmatic crura after the recipient liver had been devascularized and LT could not be canceled. Although an extensive lymphadenectomy was performed, the patient suffered mediastinal and periaortic lymph node recurrence and died 6 months after LT. Patient survival after LT was even better, although not significant, in patients with previous LR. Data regarding the outcomes of patients after LT with and without previous LR are presented in Table 8.

**Discussion**

The therapeutic dilemma between LR and LT applies only to patients with a single, less than 5-cm tumor and cirrhosis with preserved liver function, normal bilirubin, and without portal hypertension. These patients are good candidates for LR but at the same time are eligible for transplantation provided they have no contraindications to LT such as age over 70 years or significant comorbidity. Results of LR in this group are excellent with almost no operative mortality, low morbidity, and good short-mid-term survival. However, the underlying cirrhosis is responsible for a high tumor recurrence rate and liver failure after LR. 

Salvage LT is the procedure of choice in these circumstances. This group of patients accounts for only a quarter of all resected patients for HCC in our experience. There are no prospective randomized studies in the literature comparing LR and salvage LT with primary LT for early HCC in patients with cirrhosis who could be eligible for both treatments. Many publications have compared the results of LR with LT for HCC; in general, patient survival is similar with both treatments whereas disease-free survival is better with LT. However, most studies include all patients resected or transplanted for HCC; therefore, a completely different set of patients is compared, since the majority are not eligible for both treatments. Some studies investigated the implication of such a strategy with a Markov-based decision analytic model and concluded that this strategy is adequate if good results of LR are obtained, HCC recurrence is diagnosed early and salvage LT can be proposed and above all, when waiting lists for LT are long. Two recent publications from Adam et al. and Bigourdan et al. concluded that LT provided better results compared with LR, whereas another from New York analyzed their experience with resection in patients eligible for transplantation and concluded that resection is a good alternative with results similar to reports from

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**Table 7. Applicability of Salvage LT After LR**

| Classification | No. patients |
|----------------|-------------|
| LR             | 37          |
| No candidates for salvage LT | 20 |
| Alive without tumor recurrence | 8 |
| Death from other causes | 3 |
| Extrahepatic HCC recurrence | 4 |
| Advanced hepatic HCC recurrence | 5 |
| Potential candidates for salvage LT | 17 |
| Early hepatic HCC recurrence | 13 |
| < 70 yrs | 6 (5 LT) |
| > 70 yrs | 7 |
| Liver failure | 4 |
| > 70 yrs | 3 (3 deceased) |
| < 70 yrs | 1 alive after LT |

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**Table 8. Outcome of Patients After LT With and Without Previous LR**

|                    | With previous LR | Without LR | P value |
|--------------------|------------------|------------|---------|
| No. of patients    | 6                | 36         |         |
| Operation time (min) | 339 ± 66     | 357 ± 79   | 0.5     |
| RPC transfusion (units) | 3.6 ± 5     | 4.3 ± 4    | 0.1     |
| Technical complications, n (%) | 0     | 6 (16)    | 0.4     |
| Reoperations, n (%) | 0                | 5 (14)    | 0.5     |
| Post-op stay (days) | 18.8 ± 10     | 29 ± 41    | 0.4     |
| Mortality < 3 mo, n (%) | 0             | 2 (5.6)   | 0.8     |
| Vascular invasion or satellites, n (%) | 2 (40) | 12 (33) | 0.5 |
| HCC recurrence, n (%) | 1 (20)       | 5 (14)    | 0.5     |
| Mortality, n (%) | 1/6 (16.6)     | 13/36 (36.1)| 0.4   |
| 1-5 yr act patient surv, % | 80-80         | 78-63      | 0.6     |
the United Network for Organ Sharing for LT in HCC.

Our study showed that no differences existed in patient survival between LR and LT. We confirmed the excellent results of LR obtained in this selected group of patients, with no operative mortality and very good short-term survival, which were better than those with LT. Tumor recurrence and liver failure were the main causes of mortality. Early mortality after LT in these Child-Turcotte-Pugh class A patients was also low; however, eight patients died during the first year after transplantation: four from complications of the transplantation procedure and four secondary to tumor recurrence and aggressive hepatitis C recurrence. The causes of mortality differed. In the LR group, only three patients died from causes unrelated to HCC recurrence or liver failure secondary to evolution of cirrhosis, whereas in the LT group more patients died from causes secondary to the more complex operative procedure and from consequences of immunosuppression, particularly aggressive recurrence of HCV infection.

LR can be performed without delay, whereas the applicability of LT depends on graft availability and waiting list priority. In programs where waiting times exceed 9 months, 15% to 20% of patients drop off the list owing to tumor progression.22 Therefore, results of LT for HCC on an intention-to-treat basis are worse. Treatment of the tumor with percutaneous ablation techniques or TACE is indicated when waiting times are longer than 3 months. In our program, mean waiting time was 90 days; therefore, no patient was removed from the list for tumor progression. Comparison of LR with LT in programs with significant dropouts from the list would have been even more favorable to resection.

Recurrence of HCC after LT is around 10% to 20% in most series and vascular invasion by the tumor is the most important predictor of recurrence.23,24 The percentage of patients presenting extrahepatic tumor spread after LR is also around 10% to 15%. They probably correspond to the same population; i.e., those with extrahepatic tumor spread prior to the surgical procedure. If this were known in advance LR or LT would be contraindicated. However, if LR is performed instead of LT, a graft salvage rate of 15% is achieved.

Early diagnosis and treatment of hepatic recurrence after LR are key to obtaining adequate post-LR survival. Salvage LT, which offers the best results, is the first choice, followed by resection, percutaneous ablation therapies, and TACE in the treatment of tumor recurrence. We showed that with aggressive follow-up, 72% of hepatic recurrences were diagnosed early and LT would have been indicated, whereas advanced HCC was found in 28% and alternative therapies were applied. These five patients represent 13.5% of all resected patients and, in fact, form the only group that could have benefited from a primary LT.

The Barcelona Liver Cancer (BCLC) group proposed immediate LT after LR in patients with unfavorable histopathologic signs such as vascular invasion or satellitosis. This approach was based on analysis of their experience with LR for HCC.3 A significantly higher early tumor recurrence rate and lower patient survival and disease-free survival were found in the group with unfavorable features. The initial experience with 16 resected patients has recently been presented: 86% of the unfavorable group had HCC recurrence, whereas only 2 patients (22%) presented HCC recurrence in the favorable group.6 Vascular invasion has been found by many authors to be a poor prognostic factor after both resection and transplantation owing to tumor extension to other parts of the liver via the vascular system; however, what is more important is that spread to other organs is more probable.23-26 This hypothesis has been confirmed in our experience since extrahepatic recurrence was found almost exclusively in patients with these unfavorable histologic features. The diagnosis of microvascular tumor invasion can only be made after study of the resected liver, if known in advance, it could be a contraindication for LT since tumor recurrence is higher and patient survival lower. Consequently, it does not seem reasonable to indicate immediate LT in patients with these unfavorable features, as the probability of extrahepatic tumor extension is greater. It seems more reasonable to follow these patients very closely and wait for tumor recurrence to occur. Patients with extrahepatic recurrence will be excluded from LT and grafts will be saved for other patients, whereas patients with early hepatic recurrence will undergo transplantation.

The applicability of salvage LT is low—33% of potential candidates in our experience. Older age is the main cause of exclusion since the mean age of the population with HCC and cirrhosis in Spain is around 60 years. When HCC recurrence or liver failure occurs in this population, many are older than 70 years. This could be an argument in favor of primary LT in HCC patients older than 65 years since salvage LT is not possible; however, older recipient age is a well known independent risk factor for decreased survival after LT.27 Comparison of survival of patients older than 70 years at the time of indication for salvage LT with a pair-age-matched group treated with primary LT confirmed that no benefit in survival would have been achieved with primary LT in this group of older recip-
In fact, the only group that could have benefited from primary LT would have been the five patients (5 of 37, 13.5%) who presented advanced hepatic recurrence despite strict follow-up and in whom salvage LT could not therefore be proposed. On the other hand, the 11% extrahepatic recurrence rate is similar to that of HCC recurrence after LT; therefore, primary LT would not have been a good alternative in these patients.

Results of LT in patients with previous LR was similar to primary LT. No penalty was paid in terms of postoperative complications, morbidity, or mortality. Patient survival and tumor recurrence were similar. The same results were obtained when our whole experience with 16 cases of LT after LR was compared with the whole group of primary LT for HCC. These results concur with the experience of most groups; only the Paul Brousse group reported worse results in cases of LT after LR.

In conclusion:

1. LR is a good option in this selected group of patients with early HCC in well-compensated cirrhosis eligible also for LT since patient survival is similar to that of primary LT. Tumor recurrence in the liver is more frequent but can be treated with salvage LT or other treatments. Moreover, LR has better applicability, lower cost, fewer postoperative complications, and simpler follow-up.

2. It is not recommended to offer immediate LT after LR in patients with unfavorable histopathologic criteria since patient survival after LR and LT is similar and extrahepatic tumor spread is greater. It is more reasonable to wait for HCC recurrence in a strict follow-up, offer LT to patients with early HCC recurrence in the liver and exclude those with extrahepatic recurrence.

3. Only a third of LR patients, potential candidates for salvage LT, are actually transplanted. Although 72% of hepatic HCC recurrences are transplantable, the age limit is the major contraindication for LT.

4. A previous LR does not jeopardize the result of LT.

Acknowledgment

The authors thank Christine O’Hara for help with the English version of the manuscript.

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