

Short-and-Long-Term Outcomes of Hepatic Resection for Hepatocellular Carcinoma in Cirrhotic and Non-Cirrhotic Liver Parenchyma

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Abstract

Background: Hepatocellular carcinoma (HCC) is the most frequent primary liver tumor, 90% of these setting in a cirrhotic liver. The aim of this study was to analyze the results of resected HCC in cirrhotic and non-cirrhotic patients in a 12 year period. Postoperative outcomes, overall survival (OS) and recurrence-free survival (RFS) were analyzed, as well factors involved.

Methods: The population consisted of patients with HCC who underwent surgical resection in our institution between January 2007 and December 2018. Data was retrospectively collected.

Results: 86 patients between 2007 and 2018 met inclusion criteria. 49 had a cirrhotic liver, while 37 patients had HCC in a non-cirrhotic liver. For cirrhotic patients, OS and RFS at 1, 3 and 5 years were 77%, 59%, 49% and 75.8%, 43.9%, 25%, respectively. Patients outside UCSF criteria ($p = 0.05$), several nodules ($p = 0.004$) and a larger tumor size ($p = 0.02$) were associated with poorer OS. Patients outside Milan ($p = 0.034$) and UCSF ($p = 0.012$), a greater amount of nodules ($p = 0.047$) and larger tumor burden ($p = 0.005$) had worse RFS. For non-cirrhotic patients, OS and RFS at 1, 3 and 5 years were 81%, 65%, 60% and 66%, 46%, 41% respectively. A greater number of nodules ($p = 0.025$) was associated with poorer OS.

Conclusions: Our study shows that liver resection is a safe procedure and can produce excellent results, both in cirrhotic and non-cirrhotic patients, independently to the size and number of tumors.

Keywords

Hepatocellular carcinoma, Liver cirrhosis, Hepatectomy, Hepatic resection

Introduction

Hepatocellular carcinoma (HCC) remains to date the most common primary tumor of the liver, and the sixth most frequent tumor worldwide [1]. 90% of all HCC thrive in the context of a pathological liver, usually due to hepatitis B virus (HBV), hepatitis C virus (HCV), or alcohol abuse. Universal vaccination against HBV, new effective antiretroviral therapies against HCV and lifestyle changes towards a sedentary, obese general

population with metabolic syndrome are soon to tip the scale towards other causes of cirrhosis, making non-alcoholic steatohepatitis (NASH) the leading cause of HCC in western countries [2,3].

HCC can, although rarely, present itself in a non-cirrhotic liver. In these patients, physiopathological and epidemiological factors (hereditary diseases, genomic mutations and exposure to external factors such as hormones and agrochemical products) greatly differ from

the ones associated to cirrhotic liver-HCC, and should therefore be considered a different clinical entity.

Therapeutic options in HCC differ according to the context upon which it settles. For healthy, non-cirrhotic livers, resective surgery remains the best alternative with very acceptable results, whereas HCC in a cirrhotic liver presents itself as a true challenge for physicians and surgeons alike. The Barcelona Clinic Liver Cancer (BCLC) [4] staging system is currently accepted worldwide as a guideline for decision taking in HCC, and is used in several society guidelines. BCLC staging stratifies patients according to Milan criteria [5], liver function (Child-Pugh-Turcotte score) and the patient's general clinical condition in five categories (very early-early-intermediate-advanced-terminal). This aids the physician in decision making for each individual patient. Liver resection is usually limited to small tumors with good liver function (BCLC 0-A), in patients without portal hypertension.

The aim of this study was to report and analyze the results of resected HCC in both cirrhotic and non-cirrhotic patients in our institution in a 12 year period. Short term postoperative outcomes as well as long term outcomes such as overall survival (OS) and recurrence-free survival (RFS) are analyzed and presented, as well as the possible factors that may influence survival.

Methods

Patients

The population of this study consisted of patients with HCC who underwent surgical resection as an intent-to-cure therapy by the hepato-pancreato-biliary section of our institution between January 2007 and december 2018. All data was retrospectively recollected using our institutional electronic medical records and stored in a remote database.

This study was approved by the institutional Ethics Committee (Protocol number 3474), and is in consonance with the Helsinki Declaration.

Patients with a history of previous liver resection were excluded, so were patients who had received previous treatments with intent-to-cure such as radiofrequency ablation (RFA) or orthotopic liver transplantation (OLT). Patients with missing data in medical records were also excluded. Medical background and physical examination was initially performed. Afterwards, serological tests were performed, which included basic blood cell counts, renal and liver function tests, such as creatinine, bilirubin, prothrombin time, HBV and HCV antigen and antibody loads. Imaging studies included chest X-ray, abdominal ultrasound, CT scan and magnetic resonance. Cirrhotic patients were surveilled for varices with gastroscopy, and liver fibrosis was assessed by biopsy, fibroscan or evidence of portal hypertension as a surrogate.

Definitions

Preoperative diagnosis of HCC was based mainly on radiological findings, as well as anatomopathological assessment. LI-RADS system [6] was used to diagnose HCC in at least one high quality method (contrast-enhanced abdominal CT scan, or gadolinium-enhanced abdominal magnetic resonance). Those cases without radiological certainty were defined via percutaneous biopsy. Cirrhosis was diagnosed either by liver biopsy or fibroscan using METAVIR scale [7], or by evidence of extrahepatic manifestations such as esophageal varices. Postoperative complications were documented and analysed using the Dindo Clavien grading system [8], grouping grades I and II as minor complications and III-V major complications. Postoperative liver failure (the inability of the liver to correctly synthesize and excrete metabolites) was defined and graded using the ISGLS definition [9] of elevated INR and Bilirubin levels at day 5 or more. Overall survival was defined as the time lapse between the liver resection and patient death or loss of follow-up, whichever the cause. Recurrence free survival as the time lapse between surgical treatment and the apparition of radiological evidence suggestive of HCC.

Statistical analysis

Data was analysed using *STATA MP -13 (Statacorp LLC, Texas, EEUU)*. Numerical data is shown as a mean and standard deviation (SD), or median and range when appropriate. Categorical variables were compared using χ^2 or Fisher's exact test when appropriate, and continuous variables were compared using the independent sample t-test. A *p* value of ≤ 0.05 was considered statistically significant, with a 95% confidence interval. OS and RFS were obtained via Kaplan-Meier curves, compared with log-rank tests. Cox regression model was used for univariate and multivariate analysis.

Results

A total of 93 patients were submitted for surgical resection of HCC at our center between 2007 and 2018. Of these 93 patients, 86 met all of our inclusion and none of the exclusion criteria. Clinical features, radiological findings, preoperative data and specimen findings are shown in **Table 1**. Of all 86 patients, 49 presented in the setting of a cirrhotic liver, while 37 patients had HCC in a non-cirrhotic liver. Age was similar in both groups, with a mean of 64.02 years (SD 12.56) in the cirrhotic group, and 60.32 (SD 17.97) in the non-cirrhotic cohort.

Both groups had a male predominance, 71% in the cirrhotic group and 60% in the non-cirrhotic group. Results were analyzed for both cohorts separately.

Cirrhotic patients

The vast majority of HCC were diagnosed either by

Table 1: Baseline characteristics.

	Cirrhotic (n=49)	Non-cirrhotic (n=37)
Age¹	64.02(12.56)	60.32 (17.97)
Male gender² ☒	35(71.42%)	25 (68.62%)
Clinical features ☒²		
Ecografical surveillance	19(36.8%)	1 (2.70%)
Incidental finding☒	19(23%)	12(32.43%)
nonspecific symptoms☒	5(29.9%)	20(54.05%)
Others☒	6(6.9%)	4(10.81%)
Radiological findings		
Largest tumor size (mm) ³	68.26(41.41)	101(43.52)
Total tumor size (mm) ³	79.91(45.10)	116.05(65.37)
Number of nodules☒☒ ¹	1.95(1-10)	1.24 (0.49)
Macroscopical invasion ☒ ²	8(16.32%)	9(24.32%)
Preoperative AFP (ng/dl)☒ ¹	805.96(1,5-80.000)	3572.32
Preoperative portal embolization☒ ²	11(20,2%)	6(16,21%)
Neoadjuvant therapy☒ ²	12(24,48%)	2(5,40%)
Within Milán ☒ ²	19(38.78%)	5(13.51%)
Within UCSF☒ ²	23(46.94%)	8(21.62%)
Specimen findings		
Largest tumor size (mm) ³	59.38(35.23)	97.56(52.78)
Number of nodules ☒ ¹	1.69(1-10)	1.37(1-3)
Lymphovascular invasion ☒ ²	25(51.02 %)	19(51.35%)
Edmondson-Steiner☒ ²		
Grade II	6(12.24%)	3(8.11%)
Grade II	20(40.82%)	12(32.43%)
Grade III	14(28.57%)	18(48.65%)
Grade IV	9(18.37%)	4(10.81%)
surgical margins ¹	1 (2.04%)	3 (8.33%)

1= [mean (standard deviation)], 2= n (%)

[n (%)]

3= [mean (range)],

Table 2: Surgical procedures.

Procedure	Cirrhotic (n = 49)	Non-cirrhotic (n = 37)
Right hepatectomy	10 (20.41%)	12 (32.43%)
Left hepatectomy	2 (4.08%)	2 (5.41%)
Atypical hepatectomy	20 (40.82%)	7 (18.92%)
Left lateral sectionectomy	6 (12.24%)	3 (8.11%)
Right trisectionectomy	5 (10.20%)	5 (13.51%)
Left trisectionectomy	0	3 (8.11%)
Central hepatectomy	3 (6.12%)	1 (2.70%)
Extended right hepatectomy	2 (4.08%)	1 (2.70%)
Extended left hepatectomy	0	2 (5.41%)
Posterior lateral sectionectomy	1 (2.04%)	1 (2.70%)

sonographical surveillance (36%), or presented with nonspecific symptoms (30%). At diagnosis, the largest tumor size on average was 68.26 mm, with an average of 1.95 nodules per patient. Eight patients (16.32%) had macrovascular invasion at diagnosis. Interestingly, only 38% of patients underwent surgery within Milan Criteria (19 patients), and 46.94% within UCSF criteria (23 patients). Specimen data are also included in Table 1.

The most frequent procedures were atypical hepatectomies accounting for 40.82% of all procedures (20 patients). Right hepatectomy was second in frequency, performed in 10 patients. A total of 30 patients received a minor hepatectomy (3 sections or less), with the remaining 19 patients being submitted to major hepatectomy. Preoperative portal embolization was necessary in 11 patients (20%) (Table 2).

Postoperative complications are summarized in Table 3. A total of 25 complications were recorded in these 49 patients. Most of them consisted of minor complications (18 complications). Five major complications were recorded for this cohort. Two patients required postoperative pleural drainage, one due to pneumothorax,

the other to pleural effusion. A third patient required CT-guided percutaneous drainage of a postoperative biloma. One patient was reoperated due to evisceration. Two of the 49 patients (4%) died in the early postoperative period. The first one had to be intervened immediately after original surgery due to hypovolemic shock secondary to hemorrhage, and evolved torpidly afterwards. The second patient developed postoperative liver failure followed by multiorgan failure. The subject had undergone a right hepatectomy without prior portal embolization.

The mean follow-up time was 31.50 months (0.5 months-102 months). OS for the cirrhotic patients at 1, 3 and 5 years was 77%, 59%, 49% respectively. RFS at 1, 3 and 5 years for this group was 75.8%, 43.9%, 25%. RFS and OS Kaplan-Meier curves are shown in Figure 1 and Figure 2. Table 4 shows univariate analysis of different clinical, radiological and specimen factors regarding OS and RFS. Patients outside UCSF criteria ($p = 0.05$), several nodules in the specimen ($p = 0.004$) and a larger total tumor size (sum of the largest diameter of each nodule) with a ($p = 0.02$) were all associated with poorer overall survival. Regarding RFS, patients outside Milan ($p = 0.034$) and UCSF ($p = 0.012$) criteria, a greater amount of nodules ($p = 0.047$) and a larger tumor burden ($p = 0.005$) were all associated with worse outcomes. Multivariate analysis for these variables can be seen in Table 5. A greater tumor number ($p = 0.025$) was the only independent factor associated with poorer OS, while there was no independent factor linked to RFS in the multivariate analysis.

Table 3: Postoperative complications using Dindo-Clavien grading system.

Complications	Cirrhotic	Non-Cirrhotic
Minor complications (D-C I/II)	18	9
Mayor complications (D-C III/V)		
D-C IIIa/IIIb	3	3
D-C IVa/IVb	2	1
D-C V	2	1
Total complications 39	25	14

Non-Cirrhotic patients

54% of patients presented with nonspecific symp-

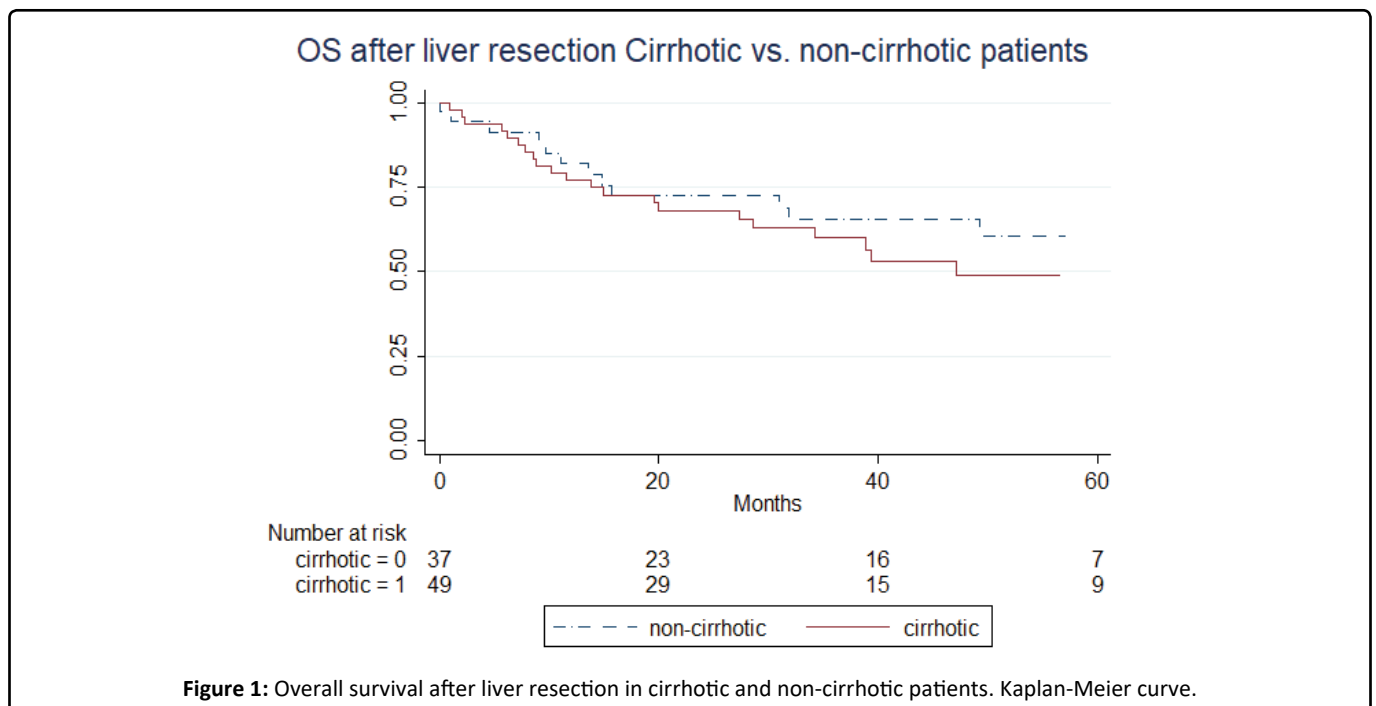


Figure 1: Overall survival after liver resection in cirrhotic and non-cirrhotic patients. Kaplan-Meier curve.

RFS after liver resection Cirrhotic vs- Non-cirrhotic patients

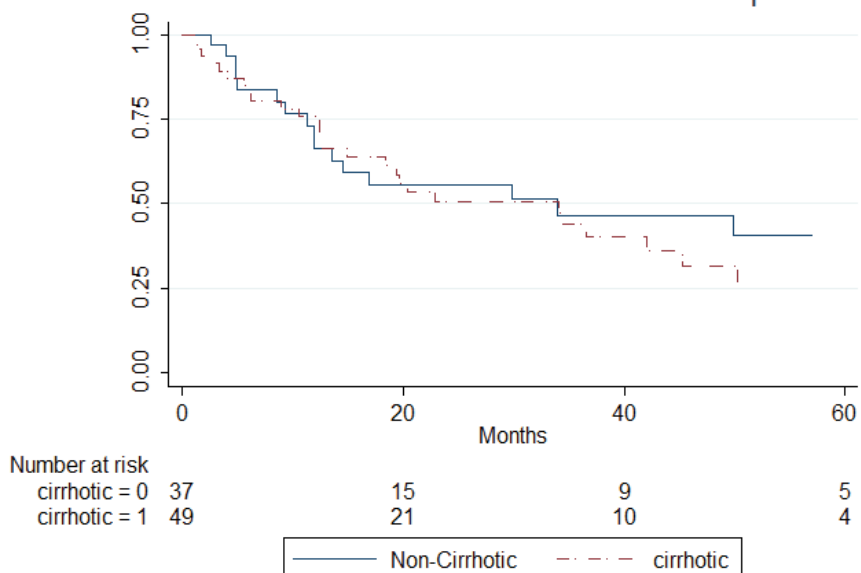


Figure 2: Recurrence-free survival after liver resection in cirrhotic and non-cirrhotic patients. Kaplan-Meier curve.

Table 4: Univariate analyses for OS and RFS for Liver resection.

	Overall Survival			
	Cirrhotic liver		Non-Cirrhotic liver	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age	0.99 (0.96-1.03)	0.867	1.00 (0.96-1.03)	0.999
Male gender	0.94 (0.40-2.02)	0.888	1.73 (0.56-5.38)	0.338
Milan	0.53 (0.22-1.28)	0.163	0.69 (0.19-2.51)	0.578
UCSF	0.42 (0.18-1.00)	0.050	0.45 (0.12-1.60)	0.219
Child-Pugh score	1.67 (0.72-3.87)	0.225		
BCLC	1.40 (0.61-3.23)	0.420		
AFP- serum levels*	1.79 (0.61-5.18)	0.282	2.28 (0.58-8.87)	0.234
Edmondson-Steiner	1.25 (0.55-2.80)	0.582	1.20 (0.42-3.43)	0.725
Tumor number	1.30 (1.08- 1.57)	0.004	2.14 (1.10-4.17)	0.025
Largest tumor	1.00 (0.99-1.01)	0.489	1.00 (0.99-1.01)	0.225
Total tumor size**	2.59 (1.16- 5.80)	0.020	1.60 (0.57-4.48)	0.363
Lymphovascular invasion	1.74 (0.78-3.90)	0.17		
Delta/tendencia NLR (late - baseline NLR)				
Delta/tendencia PLR				
	Recurrence-free Survival			
	Cirrhotic liver		Non-Cirrhotic liver	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Age	1.00 (0.97-1.03)	0.925	0.99 (0.97-1.02)	0.713
Male gender	0.80 (0.35-1.79)	0.593	0.77 (0.28-2.09)	0.622
Milan	0.39 (0.16-0.93)	0.034	0.86 (0.27-2.65)	0.795
UCSF	0.355 (0.15-0.79)	0.012	0.59 (0.20-1.71)	0.340
Child-Pugh Score	1.76 (0.78-3.94)	0.170		

BCLC	1.65 (0.74-3.67)	0.213		
AFP- serum levels*	1.64 (0.57-4.67)	0.354	1.02 (0.22-4-71)	0.972
Edmondson-Steiner	1.46 (0.96-2.21)	0.073	1.56 (0.85-2.87)	0.147
Tumor number	1.22 (1.00-1.50)	0.047	0.85 (0.34-2.11)	0.739
Largest tumor	1.00 (0.99-1.01)	0.205	1.00 (0.99-1.01)	0.948
Total tumor size**	3.01 (1.39-6.52)	0.005	1.06 (0.41-2.72)	0.888
Lymphovascular invasion	1.86 (0.86-4.03)	0.114	2.22 (0.77-6.42)	0.138

Table 5: Multivariate analysis for OS and RFS in Cirrhotic patients.

Overall Survival				
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
UCSF	0.42 (0.18-1.00)	0.050	0.69 (0.23-2.01)	0.500
Tumor number	1.30 (1.08- 1.57)	0.004	1.31 (1.11-1.56)	0.002
Total tumor size**	2.59 (1.16- 5.80)	0.020	1.42 (0.53-3-75)	0.476

Recurrence-free Survival				
	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Milan	0.39 (0.16-0.93)	0.034	0.82 (0.17-4.02)	0.817
UCSF	0.355 (0.15-0.79)	0.012	0.73 (0.12-4.45)	0.740
Tumor number	1.22 (1.00-1.50)	0.047	1.13 (0.91-1.40)	0.259
Total tumor size**	3.01 (1.39-6.52)	0.005	1.94 (0.55-6-83)	0.299

toms which led to the diagnosis, and 32.43% of all 37 HCC presented as incidentalomas. Largest tumor at diagnosis had a mean value of 110 mm, with an average of 1.24 nodules per patient. 24% (9 patients) presented macrovascular invasion as a radiological finding. 8 patients were operated within UCSF criteria, and only 5 (13.5%) within Milan. Baseline characteristics can be seen in [Table 1](#).

Only 32.4% (12 patients) underwent minor liver resections (3 or less sections). The rest underwent proper right hepatectomy (12 patients), or greater (extended hepatectomy or Trisectionectomy). 6 patients underwent portal embolization prior to a greater hepatectomy. Surgical procedures are shown in [Table 2](#).

[Table 3](#) shows complications graded by Dindo-Claivien. A total of 14 complications were observed, of which 9 (64.2%) were minor complications. 3 patients required image-guided percutaneous drainage of intraabdominal abscesses. 1 patient required reintervention due to wound disruption. 1 patient evolved with clinically significant biliary leak secondary to anastomotic disruption early on after the initial surgery. The subject was intervened on and the disruption repaired, but died due to organ failure and sepsis.

Median follow up time was 32.13 months (range 0.3-105 months). OS and RFS at 1, 3 and 5 years for

the non-cirrhotic cohort were 81%, 65%, 60% and 66%, 46%, 41% respectively. Kaplan Meier curves for this group are also shown in [Figure 1](#) and [Figure 2](#). Univariate analysis for several variables is also shown in [Table 4](#). A greater number of nodules ($p = 0.025$) proved itself to be a factor associated with poorer OS. Univariate analysis for RFS could not demonstrate any risk factors for our non-cirrhotic cohort.

Discussion

HCC is an extremely complex entity, from its presentation in patients with a crippling disease such as cirrhosis to its oligosymptomatic presentation in non-cirrhotic population. Only 30% of HCC patients are suitable candidates for curative treatment on diagnosis, usually due to multicentricity [10]. Considering these numbers, early detection by effective screening programs is a crucial element in management of HCC. BCLC staging system is accepted worldwide as the benchmark for HCC staging in cirrhotic patients. Inside BCLC, curative resection is considered for patients within Milan criteria, with incipient liver disease (Child-Pugh A/super A), without portal hypertension or significant liver impairment (Bilirubin levels), and has a OS and RFS comparable to OLT [11].

This study analyses 86 patients who underwent surgical resection, divided according to the presence of cirrhosis, in a time lapse of 12 years in our institution.

On average, the largest tumor size for the cirrhotic cohort on the specimen 59.38 mm, and 97.56 mm for the non-cirrhotic cohort. This reflects the asymptomatic presentation in the non-cirrhotic population, as well as screening techniques in cirrhotic population. Long term outcomes regarding OS and RFS for our center are comparable to other current series [12-16]. Grigoire, et al. [16] published a series of 844 patients with HCC, divided into three groups with an intent-to-cure treatment: OLT, Liver resection and RFA. 518 of these patients were surgically resected, with OS at 1, 3 and 5 years of 82, 55 and 37%. These results are quite similar to our cohort, which presents a better 5 year OS (49%). It should be noted that most patients presented by Grigoire, et al. had single nodules (86%), and 55% of them were resected within Milan criteria, whereas only 38% of our patients were intervened on within Milan. Menahen, et al. [17] performed a meta-analysis of nine studies involving a total of 570 and 861 patients who underwent liver resection and OLT respectively. The OS for the liver resection group at 1 and 5 years respectively were 84.5% and 47.9%. RFS at 1, 3 and 5 years was available for 419 of liver resection patients, and were as follows: 83%, 54.4% and 35.6%. The study found no difference in OS at 1, 3 or 5 years, but did find a significant improvement at 10 years. RFS was significantly better at 3 and 5 years for the OLT group. It is to be duly noted once again that these survival rates (very similar to the ones in our series), are restricted to patients within Milan criteria, whereas our cohort counts with an important number of resected patients outside Milan criteria. Eligibility for liver resection has been one of the main debates regarding BCLC classification, being criticized by many for being too strict. In the last years several surgical groups aim to prove the validity of surgical resection beyond BCLC [18,19]. There are several studies that aim to validate liver resection for patients outside Milan/BCLC criteria. Last year, Tsilimigras, et al. [15] published a multicenter study of liver resections for HCC within and without BCLC. Although OS and RFS at 1, 3 and 5 years were significantly worse in the BCLC-B/C group, results were acceptable, but further prospective studies matching liver resection with adequate therapies (TACE or systemic therapies) are needed. Mortality for our cirrhotic cohort was 4%, in consonance with EASL-EORTC international guidelines [20].

Our non-cirrhotic group presented slightly better results in terms of OS and RFS when compared to the cirrhotic group. This is not a new finding, as it has been described by numerous other studies, including a 51 patient cohort from our own experience in 2010 [21]. This cohort of patients selected from 1990 to 2006 had a short term follow up of 1 2 and 3 years with a 3 years OS of 67% and a RFS of 37%, quite similar to our current study (65% OS and 46% RFS). Likewise, the mean tumor-

al burden for Ardiles, et al. study was of 80 mm, larger than the usual HCC in cirrhotic patients, but smaller than our current tumor size (110 mm). This most probably reflects the effects of experience and new techniques (portal ligation, ALLPS) on patient eligibility for major hepatic procedures.

There are but a few latin american studies regarding resected HCC. In 2007, Ruiz, et al. [22] published a series of 232 liver resections in HCC patients. Of the 190 R0 resections, only 31 were set in cirrhotic livers, and average tumor size was 15 mm, with AFP levels of 5467 ng/dl, for an average age of merely 36 years. These findings are in consonance with the high number of HCC in non-cirrhotic patients in this study. Despite the relatively high number of subjects included in the study (in a time lapse of over 25 years), lack of information regarding Milan, UCSF and BCLC stages for cirrhotic patients make it difficult to compare results to this series, and may possibly account for the lower OS and RFS in this study compared to the authors'. In 2010, Yañes, et al. [23] presented a series of 38 patients who underwent surgical treatment. This included OLT, RFA and LR. Only 8 patients underwent LR, with a 3 year OS of 85.7% and no recurrence. No additional demographic data or information regarding size, staging and cirrhosis are shown. The small number of patients and the lack of data greatly hinders any attempt at comparison. Martinez-Mier, et al. [24] recently published their findings regarding preoperative AFP levels and surgical outcomes in HCC. 19 BCLC A patients were included in this study, with a AFP average level of 463 ng/dl. Although no RFS data is presented, OS at 5 years was 55.9%. The authors of this study concluded that AFP levels over 15 ng/dl proved to be an independent factor for poorer OS in surgically resected patients.

The authors believe our series, although not quite as large in numbers as other studies worldwide, is one of the most complete and well designed studies for LR in HCC in Latin America, and compares very well to several series in other centers worldwide, showing that surgical resection is a valid alternative in developing countries as well.

Our study has its limitations. As a retrospective study, we encountered information bias when attempting to retrieve information from the medical records. This is specially the case for earlier patients (2007-2010). Another limitation to our study is follow-up drop out. Being a referral center for our country, it is not rare to find that many patients come to our institution for the surgical intervention, and continue their follow up in their hometown. We attempted to minimize the follow up loss by contacting lost patients to their last registered contact. Those patients who had recurrence and then lost follow up were assumed deceased, in order to reduce follow up bias.

Conclusions

Numerous studies prove liver resection to be a valid alternative to OLT in selected patients in terms of OS and RFS. This being said, OLT still presents superior results in the long term [17]. This is due to the fact OLT treats not only HCC, but the underlying liver disease, reducing the risk of multicentricity. Nonetheless, liver resection becomes a useful tool in the surgeon's arsenal in donor-scarce regions such as our country. For non-cirrhotic HCC, liver resection remains the standard of care as a curable treatment, with excellent results. Our study shows that liver resection is a safe procedure and can produce excellent results, both in cirrhotic and non-cirrhotic patients, independently to the size and number of tumors.

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