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Hepatectomy as Treatment of Choice for Hepatocellular Carcinoma in Elderly Cirrhotic Patients

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Abstract. In recent decades liver resection has become a safe procedure; however, the outcome of hepatectomies in aged cirrhotic patients is often uncertain. To elucidate early and long-term outcomes of hepatectomy for HCC in the elderly, we studied 241 cirrhotic patients who underwent liver resection for HCC between 1985 and 2003. According to their age at the time of surgery, patients were divided into two groups: aged > 70 years (64 patients) and aged ≤ 70 years (177 patients). Operative mortality was 3.1% in the elderly and 9.6% in the younger group ($p = 0.113$). Postoperative morbidity and liver failure rates were higher in the younger group (42.4% versus 23.4%, $p = 0.0073$; 12.9% versus 1.6%, $p = 0.0065$). Five-year survival rates are 48.6% in the elderly group and 32.3% in the younger group ($p = 0.081$). Considering only radical resections in Child-Pugh A patients, survival remains similar in the two groups ($p = 0.072$). Disease-free survival is not different in the two groups. A survival analysis performed according to the tumor diameter shows a better survival for elderly Child-Pugh A patients with HCC larger than 5 cm radically resected (50.8% versus 16.1% 5-year survival, $p = 0.034$). In univariate analysis, tumor size is not a prognostic factor in the elderly, whereas younger patients with large tumors have a worse outcome. Age by itself is not a contraindication for surgery, and selected cirrhotic patients with HCC who are 70 years of age or older could benefit from resection, even in the presence of large tumors. Long-term results of liver resections for HCC in the elderly may be even better than in younger patients.

The high prevalence of hepatocellular carcinoma (HCC) and prolonged life expectancy in the world population has led to increased numbers of elderly patients being considered for treatment. Liver transplantation is probably the treatment of choice for HCCs of less than 5 cm, but the lack of donors limits its application in elderly patients [1]. For this group of patients, liver resection remains the only potentially curative therapy for HCC [2, 3]. With improved surgical techniques, better perioperative assessments, and advances in anesthesia and medical care, liver resection has become a safe procedure even in aged patients [4, 5]. Improved results in recent years indicate that a high number of elderly patients could benefit from surgical management [6]. To elucidate surgical outcomes of hepatectomy for HCC in the elderly, we reviewed our experience of liver resections for HCC in cirrhotic patients.

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Methods

Between January 1985 and December 2003, 241 cirrhotic patients in our institutions underwent liver resection for HCC with curative intent. According to their age at the time of surgery, patients were divided into two groups: the first group included 64 patients aged > 70 years (20 patients aged > 75 years) and the second group included 177 patients aged ≤ 70 years. Distribution of patients per year is reported in Figure 1: 70.3% (45) of patients aged over 70 years underwent operation in the second half of our series 1995–2003.

Preoperative liver function was assessed according to the Child-Pugh classification [7]: during the last 10 years patients in class B and C were excluded from a surgical program. In the last four years an indocyanine green (ICG) retention test [8, 9] was performed in every patient considered for surgery. When liver function was not impaired, we always tried to perform an anatomical resection (one Couinaud's segment or more).

A major hepatectomy was defined as the resection of three or more Couinaud's segments. Resection was considered radical when all tumors were resected with a microscopic free surgical margin. Operative mortality was defined as death within 60 days after surgery or occurring before discharge from the hospital.

After liver resection, all patients entered a 3-month follow-up, consisting of serum alpha-fetoprotein detection and abdominal ultrasonography; a computed-tomography (CT) scan was performed every year.

Continuous variables were compared between groups by the umpaired *t*-test or the Mann-Whitney *U*-test; categorical variables were compared by the chi-squared test or by Fisher's exact test. Patient survival was calculated using the Kaplan-Meier method. The statistical analysis of differences between results was determined with the log-rank test. A p value < 0.05 was considered significant.

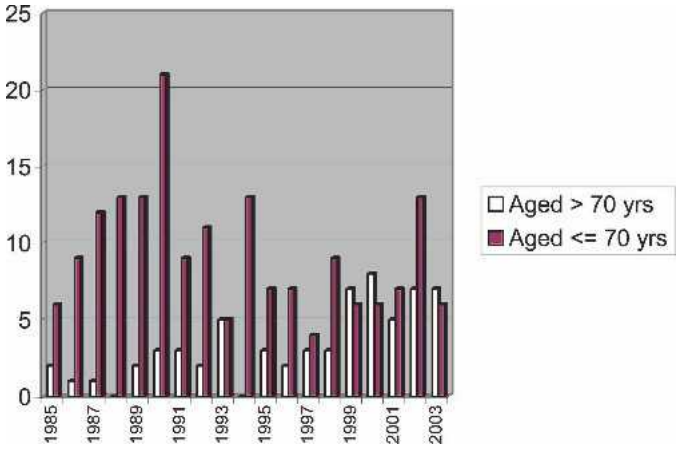

Fig. 1. Patient distribution per year, according to age.

Results

Preoperative conditions are shown in Table 1. Mean age was 74.4 years (range: 71–84 year) for the first group and 60.9 years (range: 26–70 year) for the second group. Hepatitis C virus was significantly more frequent in the elderly group (60.9% versus 38.9%, $p = 0.0025$). No other differences were found between the two groups.

Intraoperative data are reported in Table 2. Younger patients had higher rate of non-radical, resections (7.9% versus 0%, $p = 0.024$), and they received more intraoperative plasma transfusions (74.6% versus 59.4%, $p = 0.022$). Pathologic findings are reported in Table 3 and are similar in both groups. Liver cirrhosis was confirmed by a pathologist in every patient.

Operative mortality was 3.1% (12 patients) in the older group and 9.6% (17 patients) in the younger group ($p = 0.113$). Considering only Child-Pugh class A patients, operative mortality was 1.9% (1 patient) in the first group and 5.1% (7 patients) in the second group ($p = 0.445$). Causes of mortality were as follows: liver failure in 7 patients (1 patient over 70 years of age), esophageal bleeding in 4 patients, hemoperitoneum in 2 patients, cardiac failure, stroke, respiratory failure, portal vein thrombosis, sepsis, and a duodenal perforation in 1 patient each (the last one in a 74-year-old man).

Postoperative morbidity was higher in the younger group (42.4% versus 23.4%, $p = 0.0073$). Type and distribution of complications are reported in Table 4. Postoperative liver failure occurred in 23 young patients (12.9%) and in 1 elderly patient (1.6%) ($p = 0.0065$). Reintervention was necessary in 3.1% (2 patients) of the elderly group and 7.3% (13 patients) of the younger group. A higher complication rate is related to a longer hospital stay of younger patients (14.8 versus 11.2 days, $p = 0.021$).

Actuarial curves of overall survival are shown in Figure 2. The 1-, 3-, and 5-year survival rates are, respectively, 81.3%, 57.1%, and 48.6% in the older group and 74.1%, 49. 6%, and 32.3% in the younger group ($p = 0.081$). Considering only radical resections in Child-Pugh A patients, survival remains similar in the two groups: 87.9%, 68.4%, and 58.2% in the aged patients versus 83.8%, 60.1%, and 39.7% in the younger ones ($p = 0.072$) (Fig. 2). Disease-free survival did not differ in the two groups (Fig. 3): 1-, 3-, and 5-year disease-free survival rates are respectively 88.5%, 62.5%, and 30.6% in the older group and 77.5%, 52.2%, and 37.7% in the younger group ($p = 425$); the same results are obtained considering only Child-Pugh A patients who underwent a radical resection (Fig. 3): 5 year disease-free survival is 32.9% in elderly patients vs 39.9% in younger ones ($p = 0.50$).

A survival analysis was performed according to the diameter of the tumor; the results of that analysis show a better survival in the case of tumor larger than 5 cm in the elderly Child-Pugh A patients treated with radical resection: 1-, 3-, and 5-year survival rates are respectively 81.6%, 50.8%, and 50.8% in the older group and 67.5%, 35.3%, and 16.1% in the younger group ($p = 0.034$) (Fig. 4). Moreover, the prognostic role of tumor diameter was analyzed both for younger and older patients: in the elderly group tumor size is not a prognostic factor, whereas in the younger group the prognosis is significantly worsened by the increase in tumor the diameter (5 year survival in patients with tumor diameter ≤ 5 versus > 5 cm: 49.6% versus 16.1% in the younger group, $p = 0.0006$, 58.4% versus 50.8% in the elderly group $p = 0.78$) (Fig. 5).

Discussion

Liver transplantation, surgical resection, and local ablation techniques represent the standard therapeutic options in the treatment of HCC in cirrhotic patients [10]. Transplantation has the advantage of removing the cirrhotic liver together with the tumor itself and gives the best results [11]. Nevertheless, because of the shortage of donors, patients older than 70 years are excluded from transplantation programs [1]. So far no randomized trial has been conducted to compare results of local ablative therapies and hepatic resection in the treatment of HCC in cirrhotic patients. Because of the unclear data on long-term survival after local ablation of HCC, especially for large tumors, liver resection remains the preferred treatment, with 5-year survival rates ranging from 40% to 50% [12–14].

The role of surgery for HCC in elderly cirrhotic patients is still undefined because of the high level of operative risk and the high tumor recurrence rate. Human organ functions usually deteriorate with age, and elderly patients have a high incidence of comorbid illness. In addition, HCC is frequently associated with cirrhosis, which is itself a cause of high mortality and morbidity rates after hepatectomy [15]; therefore this group of patients has been considered to have a high risk for liver resections [16, 17]. Nevertheless, results of liver resection are continuously improving [18] and two studies without mortality after liver resections for HCC have been recently published [19, 20]. Our group recently reported a low mortality rate for major liver resections in cirrhotic patients [21]. Thus, even if increased operative mortality rates after hepatic resection in elderly patients have been previously reported [4, 22, 23] improved liver surgery experience and better perioperative care have led to early surgical outcomes in the elderly similar to those of younger patients: [2, 5, 24, 25] operative mortality associated with liver resections in aged patients improved in the last decade from 10%–20% [16] to about 5% [26]. In our series mortality is low, and the incidence is similar in older and younger patients (1.9% and 5.1%, respectively, in Child-Pugh A patients).

Similarly, recent series reported decreased morbidity rates in aged patients [27]. In our experience elderly patients presented significantly fewer postoperative complications and lower liver

Table 1. Preoperative characteristic of patients undergoing liver resection for hepatocellular carcinoma HCC.

Characteristics	Age > 70 (n = 64)	Age > 70 (n = 177)	p Value
Age	74.4 (71–84)	60.9 (26–70)	
Sex			
Male	47 (73.4%)	145 (81.9%)	
Female	17 (26.6%)	32 (18.1%)	0.148
Cirrhosis ethiology			
B viras	7 (10.9%)	38 (21.4%)	0.064
C virus	39 (60.9%)	69 (38.9%)	**0.0025**
B + C virus	2 (3.1%)	4 (2.3%)	0.930
Hemochromatosis	(0%)	2 (1.1%)	0.960
Alcoholic	13 (20.3%)	55 (31.1%)	0.101
Child-Pugh classification			
Class A	54 (84.4%)	138 (77.9%)	A vs B/C
Class B	8 (12.5%)	37 (20.9%)	
Class C	2 (3.1%)	2 (1.1%)	0.238
AFP (ng/ml)	807.21 (3.7–30760)	868.57 (1–53800)	0.628
AFP > 20 ng/ml	30 (46.9%)	89 (50.3%)	0.640
AFP > 200 ng/ml	13 (20.3%)	38 (21.4%)	0.846
ASAT (U/I)	58.29 (7–218)	59.98 (11–424)	0.812
ALAT (U/l)	55.69 (7–199)	64.05 (6–293)	0.261
Albumin (g/dl)	35.91 (22.9–48)	36.63 (20.9–48.9)	0.515
ICG-15(%)	9.25 (0.34–23.2)	7.19 (0.12–19.9)	0.285

AFP: alphafetoprotein; ASAT: aspartate aminotransferase; ALAT: alanine aminotransferase; ICG-15: indocyanine green clearance test
Bold types are significant p values

Table 2. Intraoperative data of patients undergoing liver resection for heptacellular carcinoma

Intraoperative data	Age > 70 (n = 64)	Age > 70 (n = 177)	p Value
Radical resection	64 (100%)	163 (92.1%)	**0.024**
Major hepatectomy	20 (31.3%)	37 (20.9%)	0.095
Anatomical resection	46 (71.9%)	140 (79.1%)	0.238
Pringle maneuver	51 (79.7%)	139 (78.5%)	0.846
Blood transfusion	21 (32.8%)	83 (46.9%)	0.051
Plasma transfusion	38 (59.4%)	132 (74.6%)	**0.022**

Bold types are significant p values

Table 3. Pathological data of patients undergone liver resection for hepatocellular carcinoma

Pathological data	Age > 70 (n = 64)	Age > 70 (n = 177)	p Value
Tumor diameter (mm)	52.19(8–150)	49.85 (9–260)	0.588
≤ 3	15(23.4%)	43 (24.3%)	0.891
> 3– < 5	27 (42.2%)	79 (44.6%)	0.736
> 5	22 (34.4%)	55(31.1%)	0.627
Number of tumors			
1	52(81.2%)	136(76.8%)	
2	9(14.1%)	34(19.2%)	
3	1 (1.6%)	3(1.7%)	1 vs > 1
4	(0%)	2(1.1%)	0.465
5or >	2(3.1%)	2(1.1%)	
Edmonson classification			
Gl	3 (4.7%)	6 (3.4%)	
G2	28 (43.7%)	80 (45.2%)	G1-2 vs G3-4
G3	31 (48.4%)	80 (45.2%)	0.986
G4	2(3.1%)	11(6.2%)	
Nakashima Type			
Expansive	51 (79.7%)	133 (75.1%)	
Infiltrative	13 (20.3%)	44 (24.9%)	0.463
Vascular invasion	33 (51.6%)	79 (44.6%)	0.341
Portal invasion	6 (9.4%)	13 (7.3%)	0.606
Satellite nodules	26 (40.6%)	80 (45.2%)	0.528
Resection margin > 1 cm	28 (43.7%)	70 (39.5%)	0.558

Table 4. Early results of liver resections for hepatocellular carcinoma on cirrhosis.

	Age > 70 (n = 64)	Age > 70 (n = 177)	p Value
Complications	15 (23.4%)	75 (42.4%)	**0.0073**
Hemoperitoneum	2 (3.1%)	9 (5.1%)	0.732
Bile leak	1 (1.6%)	3 (1.7%)	0.617
Abscess	–(0%)	6 (3.4%)	0.346
Liver failure	1 (1.6%)	23 (12.9%)	**0.0065**
Sepsis	1 (1.6%)	1 (0.6%)	0.461
Ascites	7 (10.9%)	28 (15.8%)	0.342
Reintervention	2 (3.1%)	13 (7.3%)	0.366
Operative mortality	2 (3.1%)	17 (9.6%)	0.113
Operative mortality (only Child-Pugh A patients)	1/54 (1.9%)	7/138 (5.1%)	0.445
Hospital stay (days)	11.2 (5–38)	14.8 (5–67)	**0.021**

Bold types are significant p values

failure rates. Although our study was retrospective, we analyzed two groups of patients that were similar in terms of preoperative characteristics (cirrhosis ethiology, liver function), surgical procedures, and pathological features. In addition, better early results in elderly patients can be explained by more meticulous patient selection in the aged, based on the absence of comorbidity and good performance status. Therefore, younger patients usually undergo more aggressive procedures in hope of cure, with the risk of lower rates of radical resections and higher rates of complications, as in our experience. Aggressive surgery may lead to the risk of postoperative liver failure, which was more frequent in the younger group and required more plasma transfusions. Our results confirm that age by itself should no longer be considered a risk factor for liver surgery.

Long-term results should always be considered when an elderly patient with HCC is scheduled for surgery. Results of elective liver resections in many series suggest that older cirrhotic patients have a worse outcome than younger patients, even if the differ-

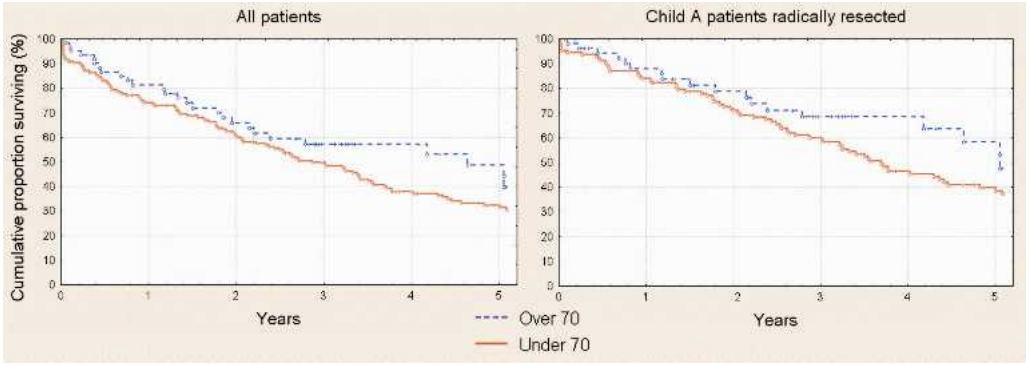

Fig. 2. Left: Overall survival actuarial curves of all patients undergoing liver resection for hepatocellular carcinoma (HCC) (> 70 vs ≤ 70 years $p = 0.081$). Right: Overall survival actuarial curves of Child-Pugh A patients undergoing radical liver resection for HCC (> 70 vs ≤ 70 years $p = 0.072$).

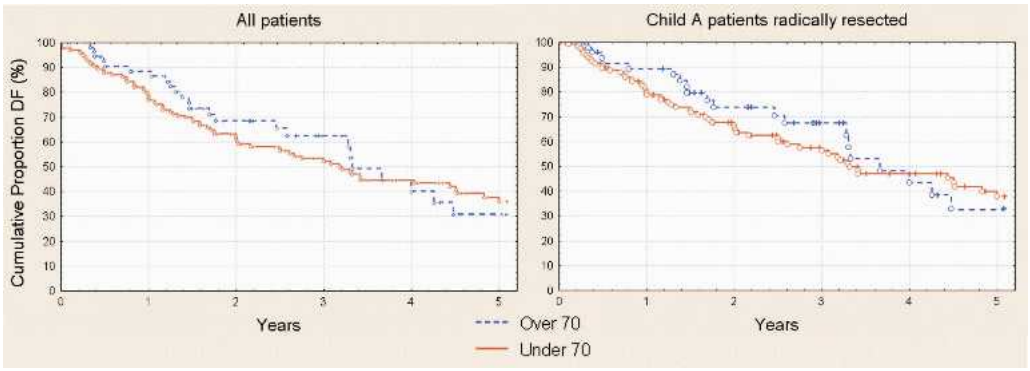

Fig. 3. Left: Disease-free (DF) survival actuarial curves of patients undergoing liver resection for HCC (> 70 vs ≤ 70 years $p = 0.425$). Right: DF survival actuarial curves of Child-Pugh A patients undergoing radical liver resection for HCC (> 70 vs ≤ 70 years, $p = 0.50$).

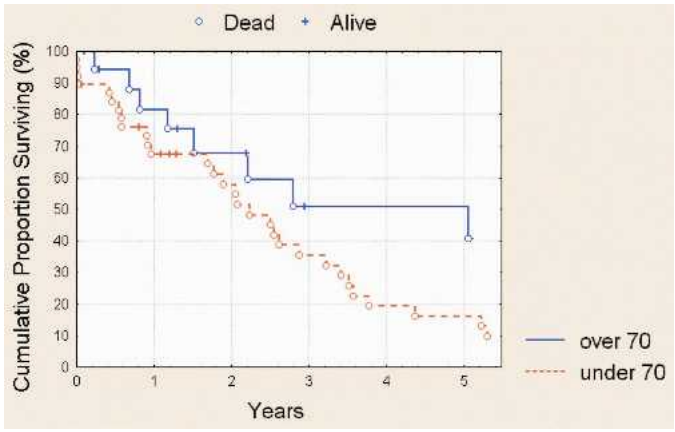

Fig. 4. Overall survival actuarial curves of Child-Pugh A patients undergoing radical liver resection for HCC larger than 5 cm (> 70 vs ≤ 70 years, $p = 0.034$).

ence is not statistically significant reports in all [16, 22, 23, 28]. Three recent series had similar results in old and young patients [24, 26, 27]. Takenaka et al. reported in 1994 a better 5-year survival rate in elderly patients, although the difference was not statistically significant; disease-free survival rates were similar in the two groups [2]. Results of our study are also encouraging: elderly patients have a better overall survival rate, although not statistically significant; nevertheless disease-free survival rates are similar in the two groups. Better outcomes in the elderly can be difficulty–justified. Lower HBsAg carrier rate and serum alpha-fetoprotein level have been reported in elderly patients, leading to the conclusion that hepatocarcinogenesis is different in the elderly [29–30]. A previous study comparing pathological findings in resected HCCs described a higher incidence of encapsulated tumors and a lower presence of satellite nodules in the older patients: both findings are positive prognostic factors for long-term survival of patients with HCC [31]. Nevertheless none of these differences were present in our patients, justifying a better survival in the elderly.

Roayaie et al. recently reported a lower disease-free survival after hepatic resection in patients with HCC on HCV-related cirrhosis compared to those with HBV hepatitis [32]. In our study, the elderly group, even with a significantly higher rate of HCV-positive patients, has a good recurrence-free survival, similar to that of the younger one. In aged patients, results of the hepatic resection in HCV-related cirrhosis are not different from those of HBV-related ones.

Many series report diameter as a prognostic factor after hepatectomy for HCC, with poor outcome for tumors larger than 5 cm [6, 33, 34]. Our data suggest that this is true only for young patients. In the elderly, diameter should not be considered a prognostic factor. To our knowledge this significant difference has not been previously reported. Patients over 70 years of age with large tumors should be scheduled for surgery with expected favorable results.

In conclusion, this study suggests that the therapeutic strategy for elderly patients with HCC should be as aggressive as for younger patients. Older age, by itself, is not a contraindication for surgery, and selected elderly patients with HCC may benefit from resection, even in presence of large tumors or HCV-related cir-

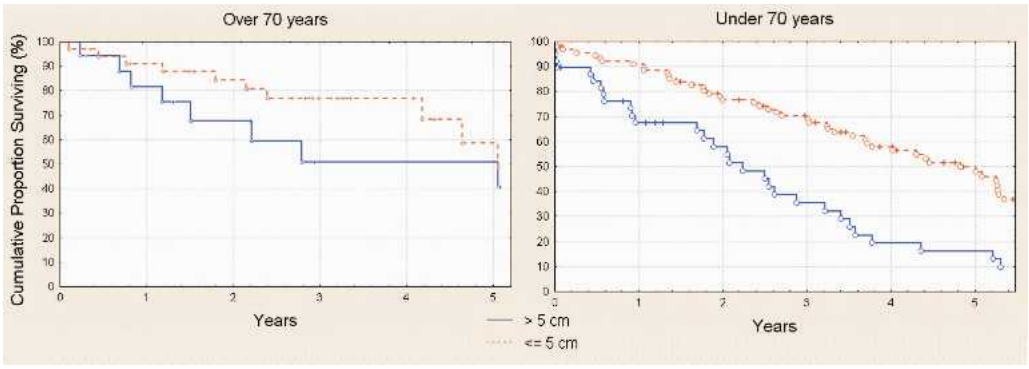

Fig. 5. Left: Overall survival actuarial curves of Child-Pugh A patients over 70 years of age undergoing radical liver resection for HCC (> 5cm vs ≤ 5 cm, $p = 0.78$). Right: Overall survival actuarial curves of Child-Pugh A patients under 70 years of age undergoing radical liver resection for HCC (>5cm vs ≤ 5 cm, $p = 0.0006$).

rhosis. Long-term results of liver resection for HCC in the elderly may even be better than in younger patients.

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