

## Hepatocellular carcinoma in cirrhotic patients with portal hypertension: Is liver resection always contraindicated?

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### Abstract

**AIM:** To analyze the outcome of hepatocellular carcinoma (HCC) resection in cirrhosis patients, related to presence of portal hypertension (PH) and extent of hepatectomy.

**METHODS:** A retrospective analysis of 135 patients with HCC on a background of cirrhosis was submitted to curative liver resection.

**RESULTS:** PH was present in 44 (32.5%) patients. Overall mortality and morbidity were 2.2% and 33.7%, respectively. Median survival time in patients with or without PH was 31.6 and 65.1 mo, respectively ( $P = 0.047$ ); in the subgroup with Child-Pugh class A cirrhosis, median survival was 65.1 mo and 60.5 mo, respectively ( $P = 0.257$ ). Survival for patients submitted to limited liver resection was not significantly different in presence or absence of PH. Conversely, median survival for patients after resection of 2 or more segments with or without PH was 64.4 mo and 163.9 mo, respectively ( $P = 0.035$ ).

**CONCLUSION:** PH is not an absolute contraindication to liver resection in Child-Pugh class A cirrhotic patients, but resection of 2 or more segments should not be recommended in patients with PH.

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**Key words:** Liver surgery; Hepatic resection; Hepatocellular carcinoma; Portal hypertension

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### INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third leading cause of cancer death worldwide<sup>[1-3]</sup>. Surgical treatment is an effective treatment for HCC and the mortality after surgery has decreased in recent years in relation to improved surgical techniques and peri-operative management of patients<sup>[4-6]</sup>. The overall survival at 5 years after liver resection varies from 33% to 69% according to recent surgical series, although recurrence is still the major issue after surgery<sup>[7-13]</sup>.

The indications for surgical resection depend on the characteristics of the tumor (stage, number of nodules, size, presence of vascular invasion), on the general condition of patient, and on liver functional reserve<sup>[14]</sup>.

The presence of liver cirrhosis is the most important risk factor for the development of HCC, as 85%-95% of HCCs arise in cirrhotic livers<sup>[15-17]</sup>. HBV and HCV infections and alcohol abuse are the most frequent causes of cirrhosis: about 80%-85% of cases<sup>[7]</sup>. Portal hypertension (PH) is related to an increase in intrahepatic resistance due to the structural subversion of the liver and loss of vascular bed, and bleeding from gastroesophageal varices is one of the most important complications of cirrhosis<sup>[18]</sup>. On the basis of several studies<sup>[19,20]</sup>, the American Association for the Study of Liver Diseases (AASLD)<sup>[21]</sup> defined as clinical PH the presence of esophageal varices or thrombocytopenia (platelet count < 100 000/mm<sup>3</sup>) associated with splenomegaly. The European Association for the Study of the Liver (EASL)/AASLD guidelines consider PH as a relative contraindication to liver resection, because of the high risk of postoperative liver failure, as reported in some clinical series<sup>[21,22]</sup>. These results, however, have not been confirmed in more recent clinical studies<sup>[23-25]</sup>.

The aims of this study are to assess the results of liver resection in patients with HCC and cirrhosis with PH and the relationship in terms of survival between Child-Pugh stage, the extent of hepatic resection and the presence of clinical PH.

## MATERIALS AND METHODS

We retrospectively analyzed clinical data of 135 patients with cirrhosis undergoing liver resection with radical intent for HCC from 1995 to 2008 at the single Surgical Division of the Department of Surgery of the University of Verona. The patients' liver function was assessed by Child-Pugh classification. Clinical PH was defined according to AASLD guidelines as the presence of esophageal varices or thrombocytopenia (platelet count < 100 000/mm<sup>3</sup>) associated with splenomegaly<sup>[21]</sup>. The extent of resection was defined according to the classification of Brisbane<sup>[26]</sup>. After liver resection, patients underwent follow-up with serum  $\alpha$ -fetoprotein levels and abdominal ultrasound every 6 mo and computed tomography scan every 12 mo. The mean follow-up after surgery was 38.3 mo.

### Statistical analysis

Data were collected and analyzed with SPSS statistical software (SPSS version 16.0 Inc., Chicago III). The differences between categorical variables were analyzed with a  $\chi^2$  test. The differences between continuous variables were also analyzed with a  $\chi^2$  test.

Survival analysis was carried out with the Kaplan-Meier method. Univariate analysis for survival was performed with the Kaplan Meier method, with the Log Rank test to verify significance of differences. The statistical analysis included two different steps; in the first we analyzed the prognostic significance of the PH in all patients and in the second step we analyzed the prognostic significance of PH in different subgroups according to the Child-Pugh class and the extent of liver resection (wedge/

segmentectomy or  $\geq 2$  segments). Finally, multivariate analysis with Cox's regression model was performed with the following variables: Child-Pugh class, PH and type of hepatectomy. A *P* value lower than 0.05 was considered significant.

## RESULTS

The prevalence of PH in all patients was 32.5%. The analysis of our data showed that patients with PH who underwent surgery had worse liver function compared to those without PH (patients in Child-Pugh B class 33% *vs* 11% respectively, *P* < 0.01), with serum bilirubin level > 2 mg/dL in 29% *vs* 3% respectively, *P* < 0.01 and serum transaminases AST > 80 U/L in 52% *vs* 25%, *P* = 0.01 and ALT > 80 U/L in 48% *vs* 19% respectively, *P* = 0.01 (Table 1). The one and 3-mo mortality rates were 4.6% and 13.9% and 1.1% and 3.3% for patients with and without PH, respectively (*P* = 0.20 and *P* = 0.05). The morbidity rate reached no statistical significance for patients with and without PH respectively (37% *vs* 32%, *P* = 0.59). The liver-related morbidity (ascites, encephalopathy, jaundice) was significantly higher in patients with PH than in patients without PH, 32% *vs* 13% respectively (*P* = 0.03) (Table 2).

The 3-year and 5-year survival in patients without PH was higher than in patients with PH (68.4% and 61.2% *vs* 48.7% and 44.9% respectively, *P* = 0.047). These results are reported in Figure 1A.

Survival analysis in patients with Child-Pugh B cirrhosis did not demonstrate significant differences in patients with or without PH (3-year survival of 31.3% *vs* 11.9%, *P* = 0.465) (Table 3).

Also, in Child-Pugh class A patients the survival analysis did not show significant differences in patients with or without PH, with a 3-year and 5-year survival of 63.0% and 57.3% *vs* 72.0% and 63.2% respectively (*P* = 0.257). These results are summarized in Table 3.

Furthermore, we evaluated the relationship between survival, extent of liver resection and PH in Child-Pugh class A patients.

In limited resections (wedge or one segment) we found no statistical differences between patients with or without PH. In these patients the 5-year survival was 72.4% and 61.4% respectively (*P* = 0.458, Figure 1B, Table 3).

When resection of two or more segments was performed, survival was significantly longer in patients without PH with a 5-year survival of 64.5% compared to 25.0% in patients with PH respectively (*P* = 0.035, Figure 1C, Table 3).

Multivariate analysis with Cox's regression model confirmed that Child-Pugh class was related to survival with a HR of 2.57 (*P* < 0.01), whereas PH and type of hepatectomy were not related to survival (Table 4).

## DISCUSSION

Liver resection is currently the treatment of choice for

**Table 1** Patients characteristics according to the presence/absence of portal hypertension

Variable	Portal hypertension		P value
	Yes (%)	No (%)	
<i>n</i>	44	91	
Age (yr)			0.55
< 70	31 (70)	60 (66)	
> 70	13 (30)	31 (34)	
Etiology of liver disease			0.21
Alcohol	7 (16)	24 (26)	
Viral hepatitis	36 (82)	59 (65)	
Other	1 (2)	8 (9)	
Serum ALT level (U/L)			0.01
< 80	23 (52)	74 (81)	
> 80	21 (48)	17 (19)	
Serum AST level (U/L)			0.01
< 80	21 (48)	68 (75)	
> 80	23 (52)	23 (25)	
Child-Pugh class			0.01
Class A	29 (66)	81 (89)	
Class B	15 (33)	10 (11)	
Bilirubin level (mg/dL)			0.01
< 2	31 (71)	88 (97)	
2-3	8 (18)	3 (3)	
> 3	5 (11)	0 (0)	
Albumin level (g/L)			0.01
< 28	7 (16)	8 (9)	
28-35	18 (41)	14 (15)	
> 35	19 (43)	69 (76)	
Platelet count			0.01
≤ 100 000/mm <sup>3</sup>	31 (70)	0	
> 100 000/mm <sup>3</sup>	13 (30)	91 (100)	
Esophageal varices			0.01
Yes	17 (39)	0	
No	27 (61)	91 (100)	
α-fetoprotein level (ng/dL)			0.86
< 20	19 (43)	42 (46)	
> 20	25 (57)	49 (54)	
Size (cm)			0.03
< 3	14 (32)	30 (33)	
3-5	21 (48)	23 (25)	
> 5	9 (20)	38 (42)	
Number of nodules			0.51
Single	32 (73)	65 (72)	
2 HCC	8 (18)	12 (13)	
3 HCC or more	4 (9)	14 (15)	
Macrovascular Invasion			0.16
No	42 (95)	73 (80)	
Yes	2 (5)	18 (20)	
Microvascular invasion			0.24
No	29 (66)	43 (47)	
Yes	15 (34)	48 (53)	
Type of hepatectomy			0.58
Wedge resection	10 (23)	16 (18)	
Segmentectomy	26 (59)	52 (57)	
More than 1 segment	8 (18)	23 (25)	

ALT: Alanine transaminase; AST: Aspartate transaminase; HCC: Hepatocellular carcinoma.

single HCC and it is a safe treatment in terms of peri-operative complications, even in patients with liver cirrhosis<sup>[6,27]</sup>. The outcome of surgical resection is strongly related to hepatic functional reserve. For this reason, the majority of patients with liver cirrhosis cannot undergo surgery because of the high risk of postoperative liver failure.

**Table 2** Mortality and morbidity rates according to the presence/absence of portal hypertension

	Portal hypertension		P value
	Yes (%)	No (%)	
<i>n</i>	44	91	
1 mo mortality	2 (4.6)	1 (1.1)	0.20
3 mo mortality	6 (13.6)	3 (3.3)	0.05
Overall morbidity	16 (37)	29 (32)	0.59
Cardiac complications	0	3 (3.3)	0.20
Pulmonary complications	10 (23)	18 (20)	0.71
Hepatic complications	14 (32)	12 (13)	0.03

**Table 3** Survival analysis according to different groups of patient and presence/absence of portal hypertension

Variable	<i>n</i>	Median survival (mo, 95% CI)	Survival		P value
			3-yr	5-yr	
Overall					0.047
Without PH	91	65.1 (49.7-80.4)	68.4	61.2	
With PH	44	31.6 (3.4-59.9)	48.7	44.9	
Child-Pugh B					0.465
Without PH	10	27.7 (1.3-65.5)	31.3	31.3	
With PH	15	15.1 (11.7-18.5)	11.9	-	
Child-Pugh A					0.257
Without PH	81	65.1 (47.7-82.4)	72.0	63.2	
With PH	29	60.5 (6.4-114.6)	63.0	57.3	
CP A-limited Hx					0.458
Without PH	58	64.9 (62.9-67.0)	72.4	61.4	
With PH	21	94.0 (54.0-134.0)	72.7	72.7	
CP A-Hx ≥ 2 segments					0.035
Without PH	23	163.9 (-)	64.5	64.5	
With PH	8	64.4 (54.0-134.0)	50.0	25.0	

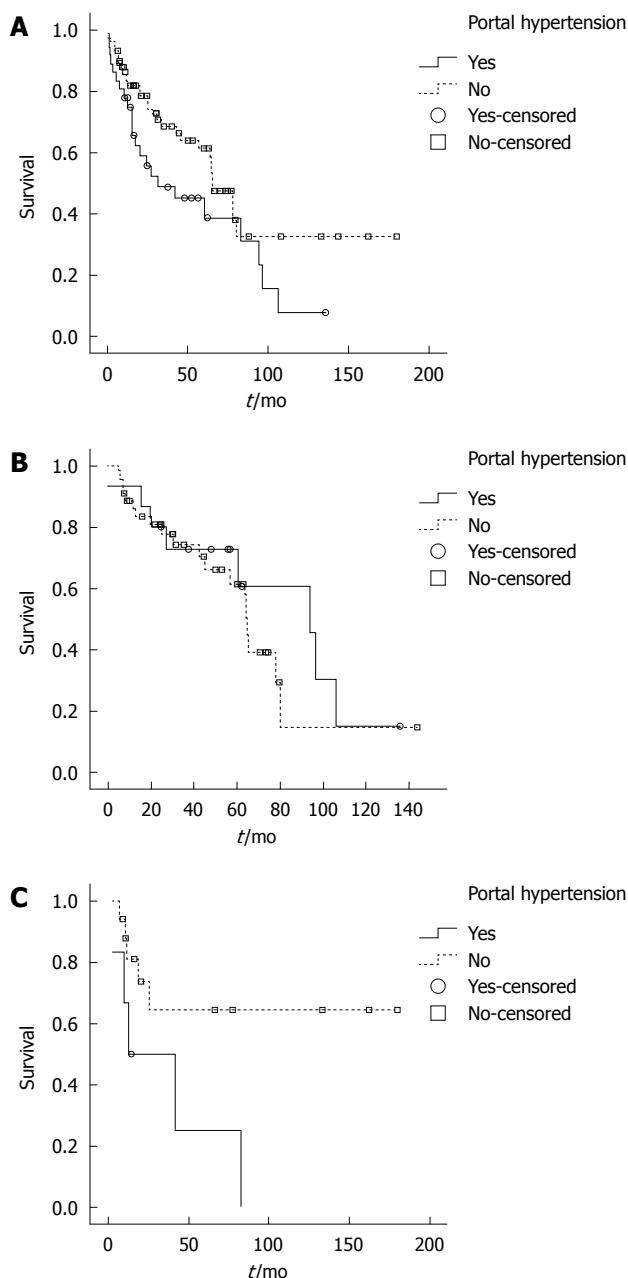
CI: Confidence interval; PH: Portal hypertension; CP: Child-Pugh score; Hx: Hepatic resection.

**Table 4** Multivariate Cox's regression model of variables related to survival

Variable	HR	95% CI	P value
Child-Pugh class (B vs A)	2.57	1.31-5.01	0.005
Type of hepatectomy (≥ 2 segments vs limited)	1.05	0.50-2.21	0.880
PH (presence vs absence)	1.51	0.84-2.68	0.160

CI: Confidence interval; PH: Portal hypertension.

PH in cirrhotic patients is considered a relative contraindication for surgery in EASL/AASLD guidelines. Bruix *et al*<sup>[12]</sup> analyzed the outcome of 29 Child-Pugh class A patients with PH [defined as porto-hepatic gradient (HVP) greater than 10 mm Hg] and observed a higher likelihood of postoperative liver failure in these patients compared to those without PH. The authors justified these results because liver resection in patients with PH can reduce the portal vascular bed without a reduction of portal flow and this condition can lead to a further increase of portal pressure. These hypotheses were not confirmed by a study by Fujisaki *et al*<sup>[28]</sup> that reported



**Figure 1 Overall survival analysis in patients.** A: Overall survival analysis in patients with or without portal hypertension (PH); the difference between the two groups was statistically significant ( $P = 0.04$ ); B: Overall survival analysis in Child-Pugh score (CP) A patients with or without PH, in the subgroup of patients submitted to limited resection ( $P = 0.45$ ); C: Overall survival analysis in CP A patients with or without PH, in the subgroup of patients submitted to resection of 2 or more segments ( $P = 0.03$ ).

on a group of 54 patients, in whom severity of PH was not worsened by liver resection. Llovet *et al*<sup>[29]</sup> in another study showed that clinical PH (assessed by the simultaneous presence of gastric-esophageal varices, thrombocytopenia lower than  $100\,000/\text{mm}^3$  and splenomegaly, or on a portal-hepatic venous pressure gradient greater than 10 mm Hg) is a predictor of postoperative liver failure and that it is related to long term survival. These authors studied 77 patients divided into 3 groups based on the presence or absence of PH and bilirubin level. The 5-year

survival of patients without PH was 74%, while the patients with PH and bilirubin lower than 1 mg/dL had a 5-year survival of 50%, and the patients with PH and bilirubin greater than 1 mg/dL had a 5-year survival of 25%. Other studies confirmed a correlation between PH and increased mortality and complications. Poon *et al*<sup>[30]</sup>, in a study of 1222 patients undergoing liver resection for hepato-biliary cancers, showed that the presence of thrombocytopenia at the time of surgery is a risk factor in multivariate analysis for surgical complications. Similarly, Jarnagin *et al*<sup>[31]</sup> in a study of 1803 patients showed that preoperative thrombocytopenia is associated with a postoperative increased risk of mortality.

On the contrary, other authors did not detect a significant correlation between PH and liver failure after surgery<sup>[32,33]</sup>. Ishizawa *et al*<sup>[23]</sup> analyzed 322 Child-Pugh class A patients and found good long term results in patients with or without PH, (3- and 5-year survival of 71% and 56% *vs* 81% and 71% respectively,  $P = 0.008$ ). Capussotti *et al*<sup>[24]</sup>, in a study of 217 patients including 99 with PH at the time of surgery, showed that the 3- and 5-year survival rates are greater in patients without the presence of PH (62% and 40% *vs* 45% and 29% respectively,  $P = 0.020$ ). However, resection in patients with PH and good hepatic function (Child-Pugh A) had similar results in terms of 3- and 5-year survival (65% and 41% *vs* 60% and 41%,  $P = 0.503$ ). This study also shows that patients with PH have a higher incidence of postoperative complications, particularly those related to the deterioration of liver function (27% *vs* 15%,  $P = 0.030$ ). Kawano *et al*<sup>[25]</sup> evaluated the results of liver resection in patients with esophageal varices. This study found that patients with esophageal varices had a better 5-year survival (70% *vs* 47%,  $P = 0.045$ ); the authors underlined that patients with PH had a more frequent early diagnosis of HCC due to more careful follow up. More recently, Choi *et al*<sup>[34]</sup> reported that the 5-year survival rate of patients with clinical PH affected by single nodular HCC without macrovascular invasion was 78.4%, even if in Child-Pugh A cirrhotic patients, the presence of clinically significant PH was significantly associated with postoperative hepatic failure and poor prognosis after resection of HCC.

The data from our study confirm the recent experiences in the literature. Patients with PH at the time of surgery showed worse liver function and this justifies the increased number of complications related to the deterioration of liver function and the increased postoperative 3-mo mortality. Long term survival was significantly related to PH with significantly shorter survival ( $P < 0.04$ ).

Among different Child-Pugh class patients we did not observe statistically significant differences in 3- and 5-year survival between patients with or without PH. In Child-Pugh class A patients submitted to minor resection, survival was not significantly affected by PH. Our study is the first in the literature to demonstrate the relationship between survival, PH and extent of hepatectomy. Surgery can produce good long term survival in patients with PH submitted to limited resection; conversely, PH had strong

adverse prognostic significance in patients who underwent resection of two or more segments. This data can help in the selection of patients and improve safety and long term results of surgery, as well as identify a group of patients who require resection of 2 or more segments, in whom resection is contraindicated and other non-surgical therapies should be applied.

This is a retrospective analysis from a single center. This allowed homogeneous data; however, multi-center studies are needed to confirm these results to reduce technical bias.

Our study confirms that the presence of PH at the time of surgery is not an absolute contraindication to resection in patients with liver cirrhosis. Although the rate of postoperative complications in patients with PH is greater, the results in terms of survival in the group of Child-Pugh class A patients is similar in patients without PH. Also, in patients with PH, limited liver resection can be performed with results comparable to those in patients without PH. Conversely, surgical resection of 2 or more segments in patients with PH results in significantly shorter survival and should not be recommended.

## COMMENTS

### Background

The presence of liver cirrhosis is the most important risk factor for the development of hepatocellular carcinoma (HCC): 85%-95% of HCCs arise in cirrhotic livers. Portal hypertension (PH) is related to increase in intrahepatic resistance due to the structural subversion of the cirrhotic liver and loss of vascular bed, and bleeding from gastro-esophageal varices is one of the most important complications of cirrhosis. The European Association for the Study of the Liver/American Association for the Study of Liver Diseases (AASLD) guidelines consider PH as a relative contraindication to liver resection, because of the high risk of postoperative liver failure, as reported in some clinical series. On the contrary, other authors have not detected a significant correlation between PH and liver failure after surgery.

### Research frontiers

Surgical treatment is the most effective treatment for HCC and the mortality after surgery has decreased in recent years in relation to improved surgical techniques and peri-operative management of patients. Moreover, only about 30% of patients affected by HCC can be submitted to surgery, because of the characteristics of the tumor (stage, number of nodules, size, presence of vascular invasion), the general condition of the patient, or liver functional impairment, such as PH.

### Innovations and breakthroughs

Recently, authors have not detected a significant correlation between PH and liver failure after surgery. The data from this study confirm the recent experiences in the literature. Survival analysis in patients with Child-Pugh A and B cirrhosis did not demonstrate significant differences in patients with or without PH. Moreover, limited resections (wedge or one segment) showed no statistical differences between patients with or without PH. When resection of two or more segments was performed, survival was significantly longer in patients without PH. Multivariate analysis with Cox's regression model confirmed that Child-Pugh, but not PH and type of hepatectomy class, was related to survival. This study is the first in the literature to demonstrate the relationship between survival, PH and extent of hepatectomy. Surgery can result in good long term survival in patients with PH submitted to limited resection; conversely, PH had strong adverse prognostic significance in patients who underwent resection of two or more segments.

### Applications

This study confirms that the presence of PH at the time of surgery is not an absolute contraindication to resection in patients with liver cirrhosis. Results in terms of survival in the group of Child-Pugh class A patients are similar to

patients without PH. Furthermore, in patients with PH, limited liver resection can be performed with results comparable to those in patients without PH. Conversely, surgical resection of 2 or more segments in patients with PH resulted in significantly shorter survival and is not to be recommended.

### Terminology

Clinical PH is defined according to AASLD guidelines as the presence of esophageal varices or thrombocytopenia (platelet count < 100 000/mm<sup>3</sup>), associated with splenomegaly.

### Peer review

In this retrospective study, the authors compare the results of liver resection for HCC in patients with and without PH. The authors show that resection is safe in CTP. A patients regardless of PH, in patients undergoing limited resection. The authors show no difference in survival between those with and without PH in CTP/A/B patients.

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