ORIGINAL ARTICLE

Impact and outcomes of liver resection for hepatocellular carcinoma in patients with clinically significant portal hypertension

Impacto y resultados de la resección hepática por carcinoma hepatocelular en los pacientes con hipertensión portal clínicamente significativa

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Abstract

Purpose: *Clinically significant portal hypertension (CSPH), although not a contraindication for liver resection in cirrhosis, is considered a determinant prognostic factor for post-surgical outcomes. This study aims to investigate the effects of CSPH on short and long-term results after hepatic resection for hepatocellular carcinoma (HCC).* **Methods:** *Single-center retrospective analysis of 126 consecutive hepatic resections for HCC in Child-Pugh A patients, performed between 2008 and 2018. Patients were divided according to the presence of CSPH, defined as a hepatic venous pressure gradient ≥ 10 mmHg. To overcome selection bias, 42 patients with CSPH were matched through propensity score with 42 patients without CSPH. Intraoperative and post-operative outcomes, along with overall and disease-free survival, were compared between the matched groups.* **Results:** *Liver decompensation was four-fold in the CSPH group (28.6% vs. 7.1%, p = 0.010), while rate of severe complications, including 90-days mortality, was not statistically different between patients with and without CSPH. Overall and recurrence-free survival was not inferior in patients with CSPH compared to non-CSPH group.* **Conclusions:** *The present study has demonstrated acceptable outcomes of liver resection for HCC in carefully selected Child-Pugh A cirrhotic patients, even in the presence of elevated portal pressure.*

Keywords: *Hepatocellular carcinoma. Portal hypertension. Hepatic resection. Liver decompensation. Liver function.*

Resumen

Objetivos: *La hipertensión portal clínicamente significativa (HPCS), si bien no representa una contraindicación para la resección hepática en la cirrosis, se considera un factor pronóstico determinante en los resultados posoperatorios. Este estudio se propone de estudiar los efectos de la HPCS en los resultados a corto y largo plazo tras la resección hepática por carcinoma hepatocelular (CHC).* **Métodos:** *Análisis retrospectivo mono-céntrico de 126 resecciones hepáticas por CHC en pacientes Child-Pugh A, realizadas entre el 2008 y el 2018. Los pacientes se han dividido según la presencia de HPCS, definida como gradiente de presión venoso hepático ≥ 10 mmHg. Para controlar el sesgo de selección, 42 pacientes con HPCS se han apareado con puntaje de propensión con 42 pacientes sin HPCS.* **Resultados:** *La tasa de descompensación hepática fue 4 veces superior en los pacientes con HPCS (28.6% vs. 7.1%, p = 0.010), mientras las complicaciones graves, incluyendo la mortalidad a 90 días, no se mostraron diferentes en los pacientes con y sin HPCS. La supervivencia global y libre de recidiva no fueron inferiores en los pacientes con HPCS comparados.* **Conclusiones:** *El presente estudio ha demostrado*

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resultados aceptables en la resección hepática en pacientes con cirrosis Child-Pugh A cuidadosamente seleccionados, también en presencia de hipertensión portal.

Palabras clave: *Carcinoma hepatocelular. Hipertensión portal. Resección hepática. Descompensación hepática. Función hepática.*

Introduction

Hepatocellular carcinoma (HCC) develops mainly in cirrhotic patients, who frequently present at diagnosis with signs of impaired liver function and portal hypertension. Especially in Western countries, clinically significant portal hypertension (CSPH), defined as hepatic venous pressure gradient (HVPG) ≥ 10 mmHg, has been considered an important risk factor for liver decompensation and mortality after hepatic resection for HCC[1]. Despite the most recent European Guidelines[2] do not contraindicate resection in the presence of CSPH, they warn that the risk of postoperative hepatic decompensation could be as high as 30% and liver-related mortality as high as 25%. To better clarify the role of CSPH for both short and long-term outcomes of liver resection for HCC, we reviewed our experience with hepatic resection for HCC in patients with and without CSPH.

Methods

Study design

Single institution retrospective analysis of liver resection for HCC in patients with and without significative portal hypertension performed between January 2008 and January 2018. This study was approved by the Ethical Review Board of our Institution. A hundred and twenty-six hepatic resections for HCC with curative intention were included. Resections on non-cirrhotic livers were discarded from the study population. To decrease selection bias between CSPH and non-CSPH patients, 1:1 match was performed with propensity score matching (PSM) using the nearest neighbor method. PSM was realized using the following variables: Age, sex, etiology of cirrhosis, tumor size, number of nodules, and extent of liver resection. Short- and long-term outcomes were analyzed.

Surgical criteria

Surgical candidates should fulfill all of the following criteria: (1) Preserved liver function (Child-Pugh A); (2) no clinical or radiological evidence of ascites, nor previous history of liver decompensation; (3) possibility to perform a complete R0 tumor resection leaving a sufficient liver remnant; and (4) no evidence of extrahepatic disease. These conditions being satisfied, we also considered for resection patients with macrovascular invasion, as previously reported[3], or with multinodular disease. None of the patients had a previous surgical or radiological portosystemic shunt. Clinical decision-making of every case went throughout a weekly discussion of the multidisciplinary committee devoted to HCC.

Preoperative work-up

Comprehensive pre-operative work-up included: (a) HVPG measurement by means of trans jugular catheterization of hepatic veins and was considered clinically significant when ≥10 mmHg[4,5]. Spleen major diameter and platelet count were also collected to assess their performance as surrogate criteria of CSPH[6]. (b) Hepatic tumoral burden was determined by a triphasic computed tomography (CT) scan and/or an magnetic resource imaging. (c) Extra-hepatic disease was ruled out with a thoracoabdominal CT scan and a Technetium 99m bone scintigraphy. (d) Liver segmental volumetric study (Brilliance WorkStation™, Philips). (e) Indocyanine green (ICG) clearance test to assess liver function, by injecting intravenously a bolus of 0,5 mg/Kg of body weight of the fluorescent dye ICG (ICG-PULSION, Germany), and recording the retention rate at 15 min (ICG-R15) through digital spectrophotometry (PULSION Medical System, Germany).

Surgical technique

Surgical procedure was accomplished under certain methodological standardization. We gave priority to anatomical resection, demarking borderlines either by devascularization or staining with ultrasound-guided transhepatic portal injection of methylene blue dye[7]. A systematical intraoperative ultrasound and contrast-enhanced ultrasound were performed to confirm size

and location of the known lesions and rule out any occult or radiological uncertain nodule to perform a R0 resection. Portal embolization was realized when future liver remnant was estimated to be <40% of the total liver volume[8]. Parenchymal transection was performed with harmonic scalpel (ACE®; Ethicon Endo-Surgery Inc., USA) and cavitron ultrasound aspirator (CUSA, Tyco Healthcare, USA).

These principles were modulated in the presence of some conditioning factors such as an impaired ICG-R15 and/or high HVPG. If present, (a) we performed a more expeditious liver resection with a quick multi-stapler parenchymal transection[9] after selective de-vascularization, in order to minimize bleeding and reduce the time of inflow vascular clamping (Pringle's maneuver); b) occasionally, instead of segmentectomy, we chose a non-anatomical resections with a 2 cm oncological margin, or c) we associated radio-frequency ablation (RFA) to treat newly discovered and additional nodules.

Laparoscopic technique was preferentially employed in cases of peripheral anterolateral tumor location (segment II, III, IVb, V, and VI), and only when uni-nodular disease was suspected at pre-operative study.

Post-operative follow-up

Post-operative morbidity was classified according to Clavien-Dindo[10], defining as severe morbidity a grade III or superior. Post-hepatectomy liver failure (PHLF) was defined using the "50-50" criteria (prothrombin time < 50% and total bilirubin 50 micromol/L (2.9 mg/dL) at postoperative day 5[11]. Postoperative ascites was defined as a daily ascitic drainage of at least 500 mL/day during at least 3 days or necessity of paracentesis[12]. Post-operative liver decompensation was defined as either ascites, PHLF, impaired renal function or encephalopathy classified as greater than Grade I according to the Clavien-Dindo classification[13].

Post-operative mortality was defined at 90 days after operation or any mortality during the hospital stay.

The standard follow-up after hospital discharge was with serological biomarker (alfaphoetoprotein) and dynamic thoraco-abdominal CT scan at 1 month after operation and every 3 months thereafter. In case of hepatic recurrence, we adopted quite a persistent policy for re-treatment, including liver transplantation in selected cases, re-resection, RFA and intra-arterial therapies. Overall survival was defined as the length of time patients was alive from the day of liver resection. Disease-free survival was defined as the length of time patients where alive without tumor recurrence at any location from the day of liver resection. Transplanted patients during follow-up were censored from the survival analysis from the time of transplantation.

Statistical analysis

The statistical analysis was performed using SPSS (version 25, Chicago, IL, USA). Continuous variables are expressed as median and interquartile range (IQR). Categorical variables are summarized by absolute and relative frequency. To compare variables between cohorts, unpaired Mann–Whitney, Chi-square, and Fisher's exact tests were used as appropriate. A multivariate analysis to assess pre-operative factors influencing development of post-operative severe complications (including 90-days mortality) was performed including in a binary regression model all variables with $p < 0.1$ at the univariate analysis.

Correlation between GPVH and ICG-R15 was assessed by Pearson correlation test. Overall and disease-free survival was calculated using the Kaplan–Meier method, and their comparison was performed using the log-rank test. $p < 0.05$ was considered significant.

Results

Pre-operative characteristics of the study population

Comparison of pre-operative characteristics of patients with and without CSPH is outlined in table 1. Operated patients with CSPH had more frequently viral etiology of cirrhosis (83.3 vs. 63.1%, $p = 0.020$). Despite all patients were classified as Child-Pugh grade A, and MELD punctuation was not different between the two groups, patients with CSPH had a worse preoperative liver function: Albumin (4.1 vs. 4.5 g/dL; $p = 0.034$) and ICG-R15 (11.7 vs. 8.5%, $p = 0.001$).

Median tumor size was significantly smaller in the CSPH group (33 vs. 40 mm, $p = 0.006$) and, in this group, major hepatectomies were less frequently performed (19% vs. 31%), while non-anatomical wedge resections were more commonly executed compared to the non-CSPH group (16.7 vs. 2.4%) ($p = 0.009$). Laparoscopy was equally employed in the two groups (21.4% in the CSPH group compared to 19.0% in the non-CSPH group, $p = 0.752$).

Surrogate criteria of portal hypertension (spleen diameter and platelet count) had a 97.6% specificity

Table 1. Demographic and clinical characteristics of the entire study population and according to the presence of clinically significative portal hypertension (CSPH). Data are expressed as median (interquartile range) or number (percentage), when indicated

Characteristic	All patients	Non-CSPH (n = 84)	CSPH (n = 42)	p
Age (years)	62 (54-71)	63 (55-72)	60 (54-67)	0.116
Gender, male (%)	112 (88.9)	77 (91.7)	35 (83.3)	0.162
Cause of cirrhosis				
HCV or HBV (%)	88 (69.8)	53 (63.1)	35 (83.3)	0.020
NASH or alcohol (%)	46 (36.5)	33 (39.3)	13 (31.0)	0.360
Bilirubin (mg/dL)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.846
Albumin (g/dL)	4.3 (3.5-4.8)	4.5 (3.6-5.1)	4.1 (3.1-4.5)	0.034
Creatinine (mg/dL)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.991
MELD score	6.4 (6.4-7.4)	6.4 (6.4-7.4)	6.4 (6.4-7.4)	0.608
Platelet count (10^3/mm^3)	158.0 (121.5-213.3)	184.5 (148.3-230-8)	102.5 (83.8-135.3)	< 0.0001
Spleen diameter (cm)	11.0 (9.8-12.3)	10.1 (9.3-11.2)	12.5 (11.7-14.3)	< 0.0001
HVPG (mmHg)	9.0 (6.0-11.5)	7.0 (4.9-8.5)	12.0 (11.4-14.1)	< 0.0001
ICG-R15	9.5 (5.8-15.1)	8.5 (5.1-12.4)	11.7 (9.2-17.4)	0.001
ICG-R15 ≥ 10% (%)	39.7 (47.6)	27 (38.0)	23 (67.6)	0.004
AFP (ng/ml)	12 (5-74)	10 (5-43)	21 (9-94)	0.083
Tumor size (mm)	35 (25-50)	40 (30-60)	33 (22-40)	0.006
≥ 3 nodules (%)	21 (16.7)	11 (13.1)	10 (23.8)	0.128
BCLC classification				0.334
Stage 0	15 (11.9)	8 (9.5)	7 (16.7)	
Stage A	73 (57.9)	53 (63.1)	20 (47.6)	
Stage B	25 (19.8)	16 (19.0)	9 (21,4)	
Stage C	13 (10.3)	7 (8.3)	6 (14.3)	
Preoperative portal embolization (%)	3 (2.4)	1 (1.2)	2 (4.8)	0.215
Extension of hepatectomy				0.009
Major (≥ 3 segments) (%)	34 (27.0)	26 (31.0)	8 (19.0)	
Bi-segmentectomy/	83 (65.9)	56 (66.7)	27 (64.3)	
Segmentectomy (%)				
Non-anatomical resection (%)	9 (7.1)	2 (2.4)	7 (16.7)	
Associated RFA (%)	30 (23.8)	20 (23.8)	10 (23.8)	1.000
Laparoscopy (%)	25 (19.8)	16 (19.0)	9 (21.4)	0.752

AFP: Alpha-fetoprotein; BCLC: Barcelona Clinic Liver Cancer; HBV: Hepatitis B virus; HCV: Hepatitis C virus; ICG-R15: Indocyanine green retention rate at 15 min; MELD: Model of end-stage liver disease; NASH: Non-alcoholic steatohepatitis; RFA: Radiofrequency ablation.

identifying CSPH, but a sensitivity of only 35.7%, with an accuracy of 77.0%.

Propensity score match outcomes

The 42 patients with CSPH were matched 1:1- to 42 patients without portal hypertension (thus discarding 42 patients from this group), obtaining a new cohort of 84 patients, now adjusted for covariate differences mainly due to selection bias. Pre-operative characteristics of the matched cohort are summarized in table 2. Analysis of perioperative and long-term oncological outcomes is based on the matched cohort.

Post-operative complications

Rate of intraoperative red blood cells transfusion and median operative time was similar in the two groups (Table 3).

Table 2. Demographic and clinical characteristics of the propensity score matched groups according to the presence of clinically significative portal hypertension (CSPH). Data are expressed as median (interquartile range) or number (percentage), when indicated

Characteristic	Non-CSPH (n = 42)	CSPH (n = 42)	p
Age (years)	58 (52-68)	60.6 (9.4)	0.707
Gender, male (%)	36 (85.7)	35 (83.3)	0.763
Cause of cirrhosis			
HCV or HBV (%)	33 (78.6)	35 (83.3)	0.578
NASH or alcohol (%)	13 (31.0)	13 (31.0)	1.000
Bilirubin (mg/dL)	1.0 (1.0-1.0)	1.1 (1.0-1.0)	0.071
Albumin (g/dL)	4.3 (3.6-4.8)	4.1 (3.1-4.5)	0.105
Creatinine (mg/dL)	1.0 (1.0-1.0)	1.0 (1.0-1.0)	0.133
MELD score	6.4 (6.4-6.4)	6.4 (6.4-7.4)	0.141
Platelet count (10^3/mm^3)	178 (138-223)	103 (84-135)	< 0.0001
Spleen diameter (cm)	10.5 (9.6-11.5)	12.5 (11.7-14.3)	< 0.0001
HVPG (mmHg)	7.0 (5.3-8.6)	12.0 (11.4-14.1)	< 0.0001
ICG-R15	8.4 (5.1-13.4)	11.7 (9.2-17.4)	0.013
ICG-R15 ≥ 10% (%)	13 (39.4)	23 (67.3)	0.020
AFP (ng/ml)	12 (5-79)	21 (9-94)	0.316
Tumor size (mm)	30 (20-41)	33 (22-40)	0.896
≥ 3 nodules (%)	9 (21.4)	10 (23.8)	0.794
BCLC classification			0.641
Stage 0	8 (19.0)	7 (16.7)	
Stage A	24 (57.1)	20 (47.6)	
Stage B	7 (16.7)	9 (21.4)	
Stage C	3 (7.1)	6 (14.3)	
Pre-operative portal embolization (%)	0 (0.0)	2 (4.8)	0.247
Extension of hepatectomy			0.105
Major (≥ 3 segments) (%)	5 (11.9)	8 (19.0)	
Bi-segmentectomy/ Segmentectomy (%)	35 (83.3)	27 (64.3)	
Non-anatomical resection (%)	2 (4.8)	7 (16.7)	
Associated RFA (%)	13 (31.0)	10 (23.8)	0.463
Laparoscopy (%)	10 (23.8)	9 (21.4)	0.794

HCV: hepatitis C virus; HBV: hepatitis B virus, NASH: non-alcoholic steatohepatitis; MELD: model of end-stage liver disease; ICG-R15: indocyanine green retention rate at 15 min; AFP: alphaphoetoprotein; BCLC: Barcelona clinic liver cancer; RFA: radiofrequency ablation.

There was no 90-days mortality in the non-CSPH matched cohort, while two patients with CSPH (4.8%) died after surgery (p = 0.247): The first as consequence of liver failure, and the second due to multiple organ failure after hemorrhagic shock and multiple transfusions. Both deaths occurred at the beginning of the study period (2008). Rate of postoperative severe complications (Clavien-Dindo III-V) was not different in the two groups (23.8% in the CSPH group and 21.4% in non-CSPH group, p = 0.794). PHLF occurred in three patients with CSPH and in none of the patients without CSPH (7.3 vs. 0%, respectively; p = 0.120). Rates of post-operative ascites, liver decompensation, and minor complications were superior in the patients with elevated portal pressure with significative differences (Table 3). Median hospital stay was not different between groups (7.5 vs. 6.5 days, in CSPH and non-CSPH groups, respectively, p = 0.383).

Table 3. Post-operative general complications, liver specific complications, and hospital stay in the studied patients. Data are expressed as median (interquartile range) or number (percentage), when indicated

	Non-CSPH (n = 42)	CSPH (n = 42)	p
Pringle maneuver (min)	23 (14-40)	13 (11-21)	0.105
Perioperative RBC transfusion (%)	5 (12.5)	7 (16.7)	0.594
Operative time (min)	261 (220-310)	263 (220-353)	0.758
Minor complication (Grade I-II) (%)	3 (7.1)	10 (23.8)	0.034
Severe complication (Grade III-V) (%)	9 (21.4)	10 (23.8)	0.794
90-days mortality (%)	0 (0.0)	2 (4.8)	0.247
Post-operative ascites (%)	4 (9.5)	15 (35.7)	0.004
Liver failure ("50-50" criteria) (%)	0 (0.0)	3 (7.1)	0.120
Liver decompensation (Grade II-V) (%)	3 (7.1)	12 (28.6)	0.010
In-hospital stay (days)	6.5 (5.0-11.5)	7.5 (5.0-14.8)	0.383

CSPH: clinically significant portal hypertension; RBC: red blood cells.

Long-term outcomes

After a median follow-up period of 8.5 years, survival was not different in the two groups: 1, 3-, and 5-years overall survival rates were 85.7, 64.0, and 46.1% in the patients with portal hypertension versus 92.9, 70.1, and 51.6% in patients without it, (p = 0.604) (Fig. 1A). No difference was found in disease-free survival between the groups, being 61.3, 44.4, and 30.4% and 59.5, 29.5, and 20.7% at 1, 3, and 5 years in CSPH group and non-CSPH group, respectively (p = 0.296) (Fig. 1B).

Univariate and multivariate analysis

Uni- and multivariate analyses were performed on the entire study population. Table 4 shows that, among 13 pre-operative variables analyzed, the development of severe post-operative complications (Clavien-Dindo Grade III-V, thus including 90-days mortality) was significantly associated with a number of nodules ≥ 3, a MELD score ≥ 8, and a tumor diameter ≥ 50 mm. It is noteworthy that neither the presence of clinically significant portal hypertension (OR = 1.232, 95% C.I.: 0.507-2.991, p = 0.645), nor a pathologic ICG-R15 (OR = 1,269, 95% C.I.: 0.487-3.307, p = 0.625), were associated with severe post-operative complications. HVPG and ICG-R15 values positively correlated with moderate strength (r = 0.497; p < 0.001).

In multivariate logistic regression model, only multinodular disease (≥ 3 tumors) and pre-operative MELD ≥ 8 resulted to be factors independently associated with severe post-operative complications and death (OR = 5.927, 95% C.I.: 1.624-21.603, p = 0.007 and OR = 5.190, 95% C.I.: 1.546-17.421, p = 0.008, respectively, being the AUC of the model 0.738).

Discussion

This study demonstrates that, in selected Child A patients, hepatic resection for HCC can be performed safely and with acceptable long-term survival, despite the presence of CSPH.

CSPH has been considered in the Western Countries for almost two decades a formal contraindication for hepatic resection, since a prospective study realized on 29 patients by the group of the Barcelona Clinic of Liver Cancer (BCLC)(1) found that, at 3 months after operation, 11 out of 15 patients with HVPG ≥ 10 mmHg developed hepatic decompensation with uncontrollable ascites, low quality of life, and reduced survival. Until recently, the European and American guidelines for the treatment of HCC adopted this criterion of exclusion and addressed patients with HVPG ≥ 10 mmHg to other treatment options.

Measurement of the HVPG is considered the most accurate way to assess the presence of CSPH[14], although only few centers worldwide use it as a routine exam to screen surgical candidates, due to its invasiveness and logistic requirements. Indirect signs of portal hypertension, such as the presence of esophageal varices and/or splenomegaly (major diameter > 12 cm) with a platelet count < 100,000/mm^3, as proposed by BCLC(6), although are more widely used, might under- or over-estimate the real value of portal pressure[15,16]. Interestingly, a recent systematic review and meta-analysis by Liu et al.[17] summarizes the short- and long-term outcomes of 4029 patients from 16 studies, of whom 1256 (31.2%) with CSPH. While globally, patients with CSPH had worse outcomes compared to the non-CSPH patients, in the analysis of sub-groups (sorted by geographical origin and way of measurement of CSPH), the Authors found that European patients whose portal hypertension had been assessed by indirect criteria showed a similar performance compared to patients with no-CSPH. Assuming that CSPH was a real negative prognostic

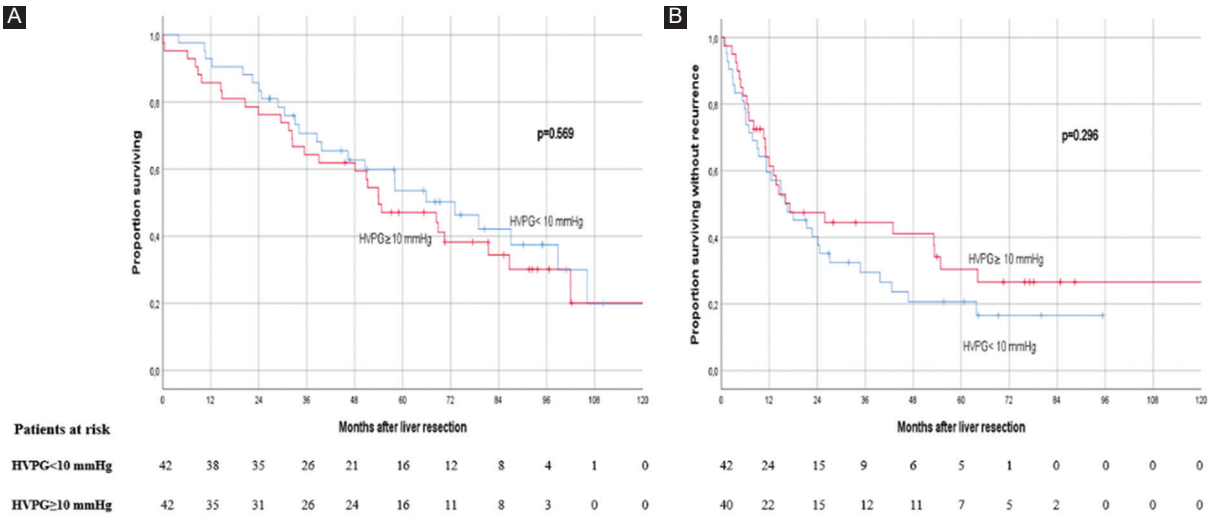

Figure 1. A: *Overall survival in the two groups.* **B:** *Disease-free survival in the two groups. In blue, patients without clinically significant portal hypertension (CSPH); in red, patients with CSPH. a: p = 0.604 (non-CSPH vs. CSPH); b: p = 0.296 (non-CSPH vs. CSPH) (log rank test).*

Table 4. Univariate and multivariate analysis of the influence of pre-operative factors and surgical technique on the development of severe postoperative complications and mortality (Clavien-Dindo Grade III-V) in the whole study cohort (n = 126)

Variables	Univariate analysis (p)	Odds ratio	95% CI	P
Age ≥ 65 years	0.259	-	-	-
Male sex	0.436	-	-	-
Viral hepatitis	0.946	-	-	-
HVPG ≥ 10 mmHg	0.645	-	-	-
MELD score ≥ 8	0.033	5.190	1.546-17.421	0.008
ICG-R15 ≥ 10%	0.625	-	-	-
3 or more nodules	0.041	5.927	1.624-21.603	0.007
Macrovascular invasion	0.072	2.130	0.494-9.182	n.s.
Tumor diameter ≥ 50 mm	0.029	2.644	0.547-5.257	n.s.
Previous treatment	0.901	-	-	-
Major hepatectomy	0.069	1.460	0.442-4.823	n.s.
Associated RFA	0.771	-	-	-
Open surgery versus Laparoscopy	0.081	1.624	0.306-8.612	n.s.

HVPG: Hepatic vein pressure gradient; ICG-R15: Indocyanine green retention rate at 15 min; MELD: Model of end-stage liver disease; RFA: Radiofrequency ablation; n.s.: Not significant, CI: confidence interval.

factor, the method of measurement could have selected some false positive patients in that subgroup, thus justifying the better outcomes.

In the present study, considering the HVPG measurement as the gold standard, the sensitivity of surrogate criteria for detecting CSPH (based on the spleen diameter and platelet count) was only 35.7%.

Another interesting result of this study is that, also in patients with HCC, ICG-R15 directly correlates with the HVGP. As previously observed by Lisotti et al.[18], ICG-R15 could accurately predict the presence of CSPH and esophageal varices in Child A cirrhotic patients. A matter of concern in the preoperative planification might be how to interpret a concomitant

impaired ICG clearance and the presence of CSPH. In our series of 42 patients with CSPH measured by trans jugular catheter detection, we performed eight (19%) major hepatectomies, none of which provoked a liver failure. Despite five of those patients presented with an ICG-R15≥10%, volume safety threshold of at least 40% of total liver volume[8] was respected in all cases. In carefully selected patents with well-preserved liver function and portal hypertension, a pathological ICG clearance might not necessarily mean a much higher operative risk, as it could represent only the degree of hepatic blood flow resistance[19].

Comparing outcomes with a matched cohort without CSPH, but similar oncologic characteristic and extent of liver resection, we reported clearly a higher rate of postoperative ascites in the CSPH group. In addition, the development of liver decompensation, which include ascites, renal impairment, encephalopathy, jaundice, and/or coagulation disorders, all being classified as greater than Grade I according to Clavien-Dindo, was approximately 4-fold in patients with CSPH.

In our experience, the majority of ascitic decompensations could be managed by standard diuretic treatment, infusion of albumin and, occasionally, by paracentesis. As a matter of fact, average hospital stay was not significantly affected by the presence of CSPH.

Our results are in line with other published series[16,20-23]: Hepatic resection is safe and effective in patients with CSPH and short- and long-term results are similar to those of patients with normal portal pressure, assuming that patients presented a well preserved liver function (Child-Pugh A).

These positive outcomes are partially considered in the latest European guidelines (EASL-EORTC)[2], that state that the decision of hepatic resection should be based on multi-parametric assessment that considers portal hypertension, liver function, extent of hepatectomy, expected volume of the future liver remnant, performance status and patients' co-morbidities, to obtain a perioperative mortality of less than 3% and liver failure rate of < 5%. In the same guidelines, besides these recommendations, it is stated that, in presence of CSPH, liver-related mortality could be as high as 25% and liver decompensation superior to 30% in the case of major resections. In our opinion, this information is in contradiction with the former statement and could be difficult to interpret and somehow misleading. EASL-EORTC guidelines endorsed a hierarchical tree of risk factors for liver decompensation based on the study of Citterio et al.[13], which established that presence of portal hypertension (stated on surrogate criteria), MELD ≥ 9 and major hepatectomy were the three main determinants of decompensation and liver related mortality. In the present study, we focused uni- and multivariate analysis on severe general post-operative complications according to Clavien-Dindo scale, which, in our opinion, classifies better the clinical impact of a complication rather than the quite broad definition of liver decompensation. We could demonstrate an acceptable outcome for 42 patients operated with a HVPG ≥ 10 mmHg (including 36% of patients classified as BCLC Stages B and C) with a mortality < 5%, a rate of severe complications < 25%, and 5 years overall and recurrence-free survival of 46.1 and 30.4%, respectively.

The recent work by Azoulay et al.[16] retrospectively analyzes the outcomes of a multi-center cohort of 79 patients with CSPH determined by pressure gradient measurement after resection for HCC. Although the BCLC stage of their cohort is not explicitly detailed, they obtained short- and long-term outcomes comparable to ours. Moreover, they found that laparoscopic approach (34% of total procedures), was the only predictor of a textbook outcome and, also, that open surgery was an independent predictor of liver decompensation. In our series, laparoscopic resection was performed in 21.4% of the patients with CSPH. A very likely selection bias ("easier" resections and uni-nodular disease) and the small number of patients in this category, make difficult in our analysis to interpret any possible effect of laparoscopy in patients with portal hypertension.

This study presents some limitations to be pointed out. First, this is a retrospective study, even if the main study variable (HVPG) was systematically recollected in all surgical candidates. In second place, we must acknowledge the small sample size: We were not able to find a statistical difference in PHLF between the groups, although this is seemingly due to problem of underpower and type II error. In addition, despite the use of propensity score matching, still it could interfere in the results our ability to select better surgical candidates.

Despite feasibility and safety of liver resection in patient with CSPH have been already attested in several studies, it is still considered a no-go zone in most centers. These patients are usually offered either liver transplantation (which might not be readily available due to shortage of grafts or impracticable because of inclusion criteria), or non-curative treatments. This

work adds to the now accumulating evidence on surgery in CSPH, emphasizes on the importance of trans jugular measurement of pressure gradient for the classification of portal hypertension, and calls for bigger prospective studies in this field.

Conclusion

Carefully selected patients with preserved Child A cirrhosis can benefit of hepatic resection for treatment of HCC even in the presence of CSPH, accepting an augmented risk of developing liver decompensation (mainly treatable ascites) but not of severe post-operative complications. Provided that an intense follow-up is realized to treat recurrences, long-term survival of these patients is not inferior to that of patients with a non-pathological portal pressure.

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Conflicts of interest

The authors have no conflicts of interest to declare.

Ethical disclosures

Protection of human and animal subjects. The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Bruix J, Castells A, Bosch J, Feu F, Fuster J, Garcia-Pagan JC, et al. Surgical resection of hepatocellular carcinoma in cirrhotic patients: prognostic value of preoperative portal pressure. Gastroenterology. 1996;111:1018-22.
2. Llovet JM, Ducreux M, Lencioni R, Di Bisceglie AM, Galle PR, Dufour JF, et al. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2018;56:908-43.
3. Cortese S, Morales J, Martín L, Kayser S, Colón A, Ramón E, et al. Hepatic resection with thrombectomy in the treatment of hepatocellular carcinoma associated with macrovascular invasion. Cir Esp (Engl Ed). 2019;98:9-17.
4. Groszmann RJ, Garcia-Tsao G, Bosch J, Grace ND, Burroughs AK, Planas R, et al. Beta-blockers to prevent gastroesophageal varices in patients with cirrhosis. N Engl J Med. 2005;353:2254-61.
5. Ripoll C, Groszmann R, Garcia-Tsao G, Grace N, Burroughs A, Planas R, et al. hepatic venous pressure gradient predicts clinical decompensation in patients with compensated cirrhosis. Gastroenterology. 2007;133:481-8.
6. Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. 1999;19:329-38.
7. Makuuchi M, Yamakaki S, Hasegawa H. Ultrasonically guided liver surgery. Jpn J Ultrason Med. 1980;7:45-9.
8. Azoulay D, Castaing D, Krissat J, Smail A, Marin Hargreaves G, Lemoine A, et al. Percutaneous portal vein embolization increases the feasibility and safety of major liver resection for hepatocellular carcinoma in injured liver. Ann Surg. 2000;232:665-72.
9. Schemmer P, Bruns H, Weitz J, Schmidt J, Büchler M. Liver transection using vascular stapler: a review. HPB (Oxford). 2008;10:249-52.
10. Dindo D, Demartines N, Clavien PA. Classification of surgical complications. A new proposal with evaluation in a Cohort of 6336 patients and results of a survey. Ann Surg. 2004;240:205-13.
11. Balzan S, Belghiti J, Farges O, Ogata S, Sauvanet A, Delefosse D, et al. The 50-50 criteria on postoperative day 5. Ann Surg. 2005;242:824-9.
12. Azoulay D, Eshkenazy R, Andreani P, Castaing D, Adam R, Ichai P, et al. *In situ* hypothermic perfusion of the liver versus standard total vascular exclusion for complex liver resection. Ann Surg. 2005;241:277-85.
13. Citterio D, Facciorusso A, Sposito C, Rota R, Bhoori S, Mazzaferro V. Hierarchic interaction of factors associated with liver decompensation after resection for hepatocellular carcinoma. JAMA Surg. 2016;151:846-53.
14. Bosch J, Abraldes JG, Berzigotti A, García-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol. 2009;6:573-82.
15. Casellas-Robert M, Lim C, Lopez-Ben S, Lladó L, Salloum C, Codina-Font J, et al. Laparoscopic liver resection for hepatocellular carcinoma in child-pugh a patients with and without portal hypertension: a multicentre study. World J Surg. 2020;44:3915-22.
16. Azoulay D, Ramos E, Casellas-Robert M, Salloum C, Lladó L, Nadler R, et al. Liver resection for hepatocellular carcinoma in patients with clinically significant portal hypertension. JHEP Rep. 2021;3:100190.
17. Liu J, Zhang H, Xia Y, Yang T, Gao Y, Li J, et al. Impact of clinically significant portal hypertension on outcomes after partial hepatectomy for hepatocellular carcinoma: a systematic review and meta-analysis. HPB (Oxford). 2019;21:1-13.
18. Lisotti A, Azzaroli F, Buonfiglioli F, Montagnani M, Cecinato P, Turco L, et al. Indocyanine green retention test as a noninvasive marker of portal hypertension and esophageal varices in compensated liver cirrhosis. Hepatology. 2014;59:643-50.
19. Schneider PD. Preoperative assessment of liver function. Surg Clin North Am. 2004;84:355-73.
20. Ishizawa T, Hasegawa K, Aoki T, Takahashi M, Inoue Y, Sano K, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. Gastroenterology. 2008;134:1908-16.
21. Capussotti L, Ferrero A, Viganò L, Muratore A, Polastri R, Bouzari H. Portal hypertension: contraindication to liver surgery? World J Surg. 2006;30:992-9.
22. Cucchetti A, Ercolani G, Vivarelli M, Cescon M, Ravaioli M, Ramacciato G, et al. Is portal hypertension a contraindication to hepatic resection? Ann Surg. 2009;250:922-8.
23. Santambrogio R, Kluger MD, Costa M, Belli A, Barabino M, Laurent A, et al. Hepatic resection for hepatocellular carcinoma in patients with child-pugh's A cirrhosis: is clinical evidence of portal hypertension a contraindication? HPB (Oxford). 2013;15:78-84.