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RESEARCH ARTICLE

Safety of laparoscopic hepatectomy in patients with hepatocellular carcinoma and portal hypertension: interim analysis of an open prospective study

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Abstract

Background The laparoscopic approach might increase the number of cirrhotic patients with hepatocellular carcinoma (HCC) indicated for liver resection, otherwise contraindicated due to portal hypertension. The goal of this study was to confirm the safety of laparoscopic liver resection (LLR) in patients with portal hypertension.

Methods This prospective, single-center, open study (ClinicalTrials.gov ID: NCT02145013) included all consecutive cirrhotic patients who underwent LLR for HCC from 2014 to 2017. Short-term outcomes were compared between patients with and without clinically significant portal hypertension (CSPH, defined by hepatic venous pressure gradient ≥ 10 mmHg).

Results The study population included 45 patients, comprising 27 patients (60%) in the no CSPH group and 18 patients (40%) in the CSPH group. All planned procedures could be performed. The two groups did not differ in the extent of resection, transfusion, duration of clamping, and need for conversion. Overall, the 90-day mortality and severe morbidity rates were nil. Moderate morbidity was significantly higher in the CSPH group (39 vs. 4%, $p = 0.01$); however, the two groups did not differ in the rate of unresolved liver decompensation. Intensive care unit and hospital stays were significantly longer in the CSPH group. At 2 years, overall survival was 77% in the no CSPH group and 100% in the CSPH group ($p = 0.17$), and recurrence-free survival was 55% in the no CSPH group and 79% in the CSPH group ($p = 0.10$).

Conclusion LLR is safe in BCLC 0-A patients with CSPH, with no mortality and good short-term outcomes. Re-evaluation of the BCLC guidelines is needed.

Keywords Liver resection · Hepatocellular carcinoma · Laparoscopic · Clinically significant portal hypertension · Hepatic venous pressure gradient

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According to the Barcelona Clinic Liver Cancer (BCLC) classification and management guidelines for hepatocellular carcinoma (HCC) [1], patients with clinically significant portal hypertension (CSPH), defined by hepatic venous pressure gradient (HVPG) ≥ 10 mmHg, are denied surgery even if they fulfill all other criteria for classification as BCLC stage 0-A, i.e., potentially resectable.

Until recently, two curative intent options have been available for BCLC stage 0-A patients. The first option, concordant with the BCLC guidelines, is evaluating patients for liver transplantation. While this option is ideal in terms of potential cure, it is not a viable option in a large proportion of patients due to (i) the current organ shortage and (ii) the long wait time associated with the risk of drop out due to tumor progression, which increases by the presence of CSPH [2]. Further, liver transplantation is not an option for the major

subset of patients ≥ 70 years old. The second option, straying from the BCLC guidelines, is proceeding with surgery despite CSPH; patients fulfilling all criteria for resection but with HVPG ≥ 10 mmHg accounted for 7–51.7% of a recent series (Table 1) [3–10]. Indeed, four recent meta-analyses [11–14] identified CSPH as an independent predictor of impaired short-term and long-term outcomes following liver resection for HCC in patients with compensated cirrhosis.

On the other hand, although there are no randomized controlled studies comparing laparoscopic liver resection (LLR) versus open liver resection for HCC, the current data strongly indicate [15–17] that when both options are available, LLR yields decreased intraoperative blood loss, transfusion requirements, liver failure rates, postoperative ascites, and liver specific complications together with similar oncological results [15]. These accumulated findings raised

Table 1 Studies defining CSPH by HVPG ≥ 10 mmHg and reporting data on LLR for HCC

Author [reference], year	Study period	Study population		Laparoscopic procedure, % (*N*)		Liver decompensation, % (*N*)		Operative mortality, % (*N*)	
		Total (*N*)	CSPH versus no CSPH % (*N*)	Total (*N*)	CSPH versus no CSPH	Total	CSPH versus no CSPH	Total	CSPH versus no CSPH
Bruix et al. [4], 1996	1991–1994	29	51.7 (15) versus 48.3 (14)	0	–	37.9 (11/29)(1)	37.9 (11/15) versus 0 (0/14), $p < 0.0001$**	3.4 (1/29)	6.7 (1/15) versus 0 (0/14), $p = 0.99$**
Llovet et al. [7], 1999	1989–1997	43	49 (21) versus 51 (22)	0	–	NA	–	7 (3/43)	NA
Stremitzer et al. [9]	2000–20009	39	7.7 (3) versus 92.3 (36)	NA	–	NA	–	2.6 (1/39)	NA
Truant et al. [10], 2011[a]	2002–2009	37	43.2 (16/37) versus 56.8 (21/37)	40.4 (36/89)	52.6 (10/19) versus 47.4 (9/19)	NA	NA	4.5 (4/89)	NA
Boleslawski et al. [3], 2012	2007–2009	40	45 (18) versus 55% (22)	32.5 (13/40)[b]	61.5 (8/13) versus 38.5 (5/13)	50 (20/40)(2)	NA	15 (6/40)	27.8 (5/18) versus 4.5 (1/22), $p = 0.07$**
Cuchetti et al. [5], 2016	2009–2014	70	49 (34) versus 51 (36)	2.9 (2/70)	0 (0/2) versus 100 (2/2)	30 (21/70)(3)	50 (17/34) versus 4.8 (4/36), $p = 0.001$	0	–
Lim et al. [6], 2017	2014–2016	65	21.5 (14) versus 78.5 (51)	38.5 (25/65)	28 (7/25) versus 72 (18/25)	10.8 (7/65)(1)	14.3 (1/14) versus 85.7 (6/51), $p = 0.62$**	4.6 (3/65)	0 (0/14) versus 5.9 (3/51), $p = 0.99$**
Molina et al. [8], 2017[c]	2006–2016	45	33.3 (15) versus 66.7 (30)	100 (45/45)	–	6.7 (3/45)(4)	13.3 (2/15) versus 0 (0/30), $p = 0.04$**	0	–
Present study, 2018	2014–2017	45	40 (18) versus 60 (27)	100 (45/45)	–	2 (1/45)(1)	6 (1/18) versus 0 (1/27), $p = 0.22$	0	–

HVPG hepatic venous pressure gradient, *CSPH* clinically significant portal hypertension, *NA* not available

Liver decompensation: (1) jaundice, ascites, or encephalopathy after 3 months after surgery; (2) serum bilirubin level over 5 mg/dL on or after postoperative day 5, coagulopathy (INR exceeding 2.0 associated with hemorrhagic complications requiring transfusion), hepatic encephalopathy, and/or abdominal ascites (drainage volumes more than 500 mL/day after day 3) within 90 days after surgery; (3) posthepatectomy liver failure grade B/C according to ISGLS; (4) transient ascites

[a]The study population includes a total of 89 patients but only 37 patients had preoperative HVPG (including 19 patients with LLR and 18 with open liver resection)

[b]Four patients who need a conversion to laparotomy was excluded from the calculation

[c]After propensity score matching

***p* values were calculated by the authors on the basis of data reported in studies

the questions regarding whether LLR could be considered a third option to improve the safety of surgery in patients with CSPH and whether these patients could have similar outcomes as patients without CSPH. Thus far, only one retrospective study specifically compared the outcomes after LLR between patients with and without HVPG ≥ 10 mmHg, and promising, similar results were reported for both patient groups [8]. The above findings represented the impetus for the present analysis, which was based on data acquired in an open prospective study. Herein, we compared the safety of LLR for HCC in cirrhotic patients with CSPH versus those without CSPH, as assessed by the gold standard HVPG measurement.

Materials and methods

The present analysis relied on the data from a registered single-center, prospective, open study assessing the outcomes of liver resection in patients with HCC (ClinicalTrials.gov ID: NCT02145013) [6]. Recruitment included all consecutive patients referred for HCC and potential candidates for liver resection since January 1, 2014. The study population of the present analysis included all consecutive patients with single HCC on cross imaging that developed in a cirrhotic liver, with normal liver function and with or without CSPH (see definition below). The study was approved by the local institutional review board and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Preoperative management

Cirrhosis was based on non-invasive criteria or histology (METAVIR F4). In patients without preoperative histology, diagnosis of cirrhosis required the association of morphological changes of the liver including reduction in the size of the right lobe, enlargement of the left and caudate lobes, enlargement of liver/spleen size-based, and presence of indirect signs of portal hypertension (esophageal varices, portosystemic shunts, repermeabilization of the umbilical vein) based on ultrasound, computed tomography and magnetic resonance imaging. Diagnosis of HCC on the identification of the typical features of HCC (hypervascular in the arterial phase with washout in the portal venous or delayed phases) obtained by computed tomography scan or magnetic resonance imaging according to the accepted guidelines [1, 18]. All patients underwent a standard workup [6] as well as transjugular HVPG measurements in compliance with technical recommendations [19]. The groups of patients without and with CSPH were defined by HVPG < or ≥ 10 mmHg, respectively [20]. Ascites (absent in all patients included in the present study by definition of the study population) or the presence of esophageal varices on endoscopy were considered surrogates of CSPH [21].

Patients were selected for surgery at a multidisciplinary meeting dedicated to primary liver tumors provided that the following criteria were fulfilled: (i) absence of a history of ascites, variceal rupture, or encephalopathy; (ii) absence of prohibitive comorbidities; (iii) Child-Pugh class A liver function or class B, provided the impaired function was due to biliary obstruction; and (iv) successful planning of a complete macroscopic resection combined with a sufficient future remnant liver volume upon preoperative computed tomography volumetric assessment. AFP level was not considered in the decision for resection. The laparoscopic approach was chosen according to the guidelines of the World Consensus Conference on Laparoscopic Surgery [22, 23]. Patients initially deemed both resectable and transplantable were enrolled for salvage liver transplantation strategy [24, 25]. Rescue transplantation was an available option in case of postoperative irreversible liver decompensation. No treatment for HCC was administered before surgery. The usual relevant preoperative variables were retrieved and are available in Table 2.

Laparoscopic liver resection and surgical technique

The surgical techniques for laparoscopic [16, 26, 27] and robot-assisted laparoscopic [28–30] liver resections used in the study center have been described in detail elsewhere. Whenever needed, vascular clamping was performed by intermittent extra-corporeal [31, 32] clamping of the liver pedicle, with 10 min of clamping and 5 min of unclamping. One abdominal drain was placed near the transection surface in all cases.

The following intraoperative variables were retrieved: laparoscopic or robot-assisted laparoscopy, clamping time, blood loss, transfusion, conversion to open surgery, and duration of operation. Patients who were converted to open surgery were analyzed on an intended-approach basis, i.e., with the results of their initial group.

Definitions of complications

Postoperative mortality and morbidity were assessed within 90 days of surgery or at any time during hospitalization for surgery. Postoperative liver failure was defined based on the 50–50 criteria on day 5 or at any time, thereafter [33]. Massive ascites was defined as an abdominal drain output of > 500 mL/day for > 3 days despite a reduction in sodium intake to 40 mEq/day and diuretic therapy with furosemide and spironolactone if needed. Acute kidney injury was defined according to the Kidney Disease Improving Global Outcomes consensus criteria [34]. According to the BCLC group, unresolved

Table 2 Baseline characteristics of LLR in patients with versus without CSPH

	Total ($N=45$)	No CSPH $n=27$ (60%)	CSPH $n=18$ (40%)	p Value
Clinical				
Male sex, *n* (%)	34 (76)	23 (85)	11 (61)	0.07
Age (years)	65 (49–85)	65 (49–85)	64 (52–83)	0.81
Age ≥ 70 years	16 (36)	10 (37)	6 (33)	0.80
BMI (kg/m^2)	26 (19–47)	27 (20–37)	26 (19–47)	0.48
ASA class, *n* (%)				0.93
1	9 (20)	5 (19)	4 (22)	
2	25 (56)	15 (56)	10 (56)	
3	11 (24)	7 (26)	4 (22)	
Previous hepatectomy, *n* (%)	7 (16)	4 (15)	3 (17)	0.59
HVPG (mmHg)	8 (2–26)	6 (2–9)	14 (10–26)	< 0.0001
Indirect signs of PHT[a], *n* (%)	22 (49)	10 (37)	12 (67)	0.051
Child-Pugh grade A/B, *n* (%)	44 (98)/1 (2)	26 (96)/1 (4)	18 (100)/0 (0)	0.41
MELD score	8 (6–11)	7 (6–10)	8 (6–11)	0.08
Underlying liver disease, *n* (%)				0.28
Alcohol	7 (16)	7 (26)	1 (6)	
Virus	25 (56)	13 (48)	12 (67)	
Metabolic syndrome	4 (9)	2 (7)	2 (11)	
Hemochromatosis	2 (4)	2 (7)	0 (0)	
Healthy	2 (4)	2 (7)	0 (0)	
Alcohol and metabolic syndrome	5 (11)	2 (7)	3 (17)	
Preoperative BCLC staging A/B	42 (93)/3 (7)	26 (96)/1 (4)	16 (89)/2 (11)	0.33
Preoperative blood tests				
AST (IU/L)	39 (19–178)	37 (19–178)	41 (27–96)	0.97
ALT (IU/L)	35 (14–120)	36 (15–120)	33 (14–95)	0.62
Total bilirubin (μmol/L)	11 (5–48)	12 (5–48)	11 (5–31)	0.86
Albumin (g/dL)	40 (28–48)	41 (28–48)	37 (30–47)	0.01
Platelet/10^5/mm^3	139 (62–440)	143 (74–440)	109 (62–183)	0.009
Prothrombin ratio (% of normal)	86 (60–100)	86 (60–100)	88 (63–100)	0.84
Creatinine (μmol/L)	79 (38–121)	76 (38–121)	84 (38–119)	0.56
AFP (ng/mL)	7 (1–2899)	5 (1–2899)	8 (2–928)	0.66

CSPH clinically significant portal hypertension, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *HVPG* hepatic venous pressure gradient, *MELD* model for end stage liver disease, *BCLC* Barcelona Clinic Liver Cancer, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *AFP* alpha-fetoprotein

[a]Presence of esophageal varices at endoscopy [21]

liver decompensation (ULD) was defined based on the presence of at least one sign of hepatic decompensation (jaundice, ascites, or encephalopathy) 3 months after surgery in patients who presented at least one of these signs during the postoperative period [4]. Re-admission occurring within 30 days of discharge was also evaluated.

Postoperative complications were classified according to the Clavien–Dindo classification system [35] and further categorized as minor (I–II) or major (III–IV). The highest grade was used in cases of multiple complications.

Specimen analysis

Data on tumor size, number of nodules, macrovascular/microvascular invasion, satellite nodules, and margin of resection were retrieved. Tumors were characterized as well (grade 1), moderately (grade 2), or poorly (grade 3) differentiated according to modified Edmondson and Steiner criteria [36]. In specimens with heterogeneous grades of differentiation, the poorest grade was utilized. Following the specimen analysis, the patients were categorized into two groups: high

risk of recurrence for those who exhibited macrovascular or microvascular invasion and/or additional nodules and/or satellites nodules and low risk of recurrence for those who did not exhibit any of these parameters [37, 38].

Cost analysis

The mean estimated costs (in €) per patient to the French Public Health System were calculated and compared between groups. The cost data were estimated based on reimbursements to the public hospitals by the ''health care insurance system.'' Euros amounts for Groupe Homogène de Malades (GHM), which is derived from the diagnosis-related group (DRG), were determined from the hospitals and the Agence technique de l'information sur l'hospitalisation (ATIH). The GHM-based reimbursements were calculated based on cost-to-charge ratios, using national median charges and discharges for specific GHMs. For GHM coding, a severity-refined GHM system was defined by associated diagnosis and major complications as modifiers for various reimbursements. The GHM code 07C09 was used for hepatectomies for malignant tumors. The cost depends not only on medical diagnoses but also on additional financial supplements calculated according to the severity of the treated conditions (from grade 1–4) as well as on the number of days in intensive care unit. Thus, a supplement of 860.35 € per days in intensive care unit is added with the cost.

Follow-up

Data were evaluated on January 31, 2018. Following discharge, patients were followed up at the outpatient clinic every 3 months for the first 2 years and every 6 months thereafter.

All relevant events including unresolved or newly developed liver decompensation, tumor recurrence, liver transplantation, and death were recorded.

Statistical analysis

Continuous variables, reported as medians and range, were compared using the Mann–Whitney test. Categorical data, presented as frequencies (%), were compared using the Chi square test or Fischer's exact test, as appropriate. All statistical analyses were performed using SPSS software, version 23 (Chicago IL, USA). The present study complies with the RECORD guidelines [39]. All the co-authors had access to the study data and had reviewed and approved the final manuscript.

The aim of the interim analysis of this open prospective study was to assess the safety and short-term outcomes of LLR in patients with portal hypertension. Given a potential inclusion of 40–50 patients with resectable HCC per year at Henri Mondor Hospital, including 10–15 HCC patients with cirrhosis suitable for laparoscopic hepatectomy, the expected number of patients for this interim analysis would be at least 40 patients with a minimum follow-up time of 1 month.

Results

Patient characteristics

During the 4-year study period, 187 patients were enrolled and resected in the prospective open study. Of these, 57 patients, comprising 45 cirrhotic and 12 non-cirrhotic patients, underwent minimally invasive liver resection. The study population of the present analysis included the 45 cirrhotic patients, of which 18 (40%) had CSPH and 27 (60%) did not have CSPH. The HVPG was significantly higher ($p < 10–4$) in the CSPH group, and the proportion of patients with indirect surrogates of PHT (i.e., with esophageal varices) was higher in the CSPH group, although this difference did not reach significance ($p = 0.051$).

The clinical course following HVPG measurement was uneventful in all patients. Patients of the CSPH group were more likely to have lower albumin ($p = 0.01$) and platelet counts ($p = 0.009$). As shown in Table 2, none of the other comparisons of preoperative variables showed a significant difference between the two groups, including sex ($p = 0.07$), age ($p = 0.81$), proportion of patients ≥ 70 years old (36% of the study population, $p = 0.80$), previous history of liver resection ($p = 0.59$), Child-Pugh class, MELD score ($p = 0.08$), kidney and liver function tests ($p = 0.56$), and AFP level ($p = 0.66$).

Intraoperative outcomes

All planned procedures could be performed. As shown in Table 3, none of the compared intraoperative variables, including laparoscopic or robot-assisted laparoscopic approach ($p = 0.41$), need for conversion to open surgery ($p = 0.67$), extent of resection ($p = 0.29$), duration of clamping ($p = 0.13$), need for blood transfusion ($p = 0.12$), and duration of operation ($p = 0.41$), significantly differed between the two groups. Although not statistically significant, there was a trend toward more frequent use of portal clamping ($p = 0.051$) and increased blood loss ($p = 0.07$) in the CSPH group.

Mortality and morbidity

The 90-day overall mortality rate was nil in both groups (Table 4). In addition, the two groups did not differ in terms of postoperative liver failure ($p = 0.08$), ascites ($p = 0.33$), acute kidney injury ($p = 0.13$), liver

Table 3 Intraoperative outcomes of LLR in patients with versus without CSPH

	Total $N=45$	No CSPH $n=27$ (60%)	CSPH $n=18$ (40%)	p Value
Robot-assisted/laparoscopic approach, *n* (%)	12 (27)/33 (73)	6 (22)/21 (78)	6 (33)/12 (67)	0.41
Anatomical resection, *n* (%)	22 (49)	16 (59)	6 (33)	0.09
Site				0.64
Right lobe	14	8	6	
Left lobe	27	17	10	
Bilobar	1	0	1	
Segment I	3	1	1	
Location				0.94
Antero-lateral (segments 2–6)	39	23	16	
Postero-lateral (segments 7–8)	3	2	1	
Segment I	3	2	1	
Extent of resection (minor/major), *n* (%)	43/2	18/0	25/2	0.24
Partial hepatectomy	23 (51)	11 (41)	12 (67)	
Segmentectomy	8 (18)	6 (22)	2 (11)	
I	3	2	1	
IV	2	2	0	
VI	3	2	1	
Left lateral sectionectomy	12 (27)	8 (30)	4 (22)	
Left hepatectomy	2 (4)	2 (7)	0 (0)	
Conversion to open	4 (9)	2 (7)	2 (11)	0.67
Clamping	22 (49)	10 (37)	12 (67)	0.051
Total clamping time (min)	29 (8–100)	26 (8–100)	30 (10–50)	0.13
Blood loss (mL)	200 (20–1700)	125 (20–1000)	300 (20–1700)	0.07
Blood red cell transfusion, yes, *n* (%)	1 (2)	1 (4)	0 (0)	0.41
Operative time (min)	230 (90–480)	220 (90–480)	240 (100–360)	0.41

CSPH clinically significant portal hypertension

decompensation ($p=0.13$), or ULD ($p=0.22$). According to the Clavien–Dindo classification, the severe morbidity rate was nil in both groups, and the moderate morbidity rate was significantly higher in the CSPH group ($p=0.003$). The rate of pulmonary complications was significantly higher in the CSPH group ($p=0.01$). Intensive care unit ($p=0.02$) and total hospital stays ($p=0.02$) were significantly longer in the CSPH group. Neither re-admission nor rescue transplantation occurred in any group.

Specimen analysis

No significant differences were found between the groups for largest tumor size ($p=0.69$), presence of additional nodule(s) ($p=0.67$), surgical margins ($p=0.85$), R1 resection ($p=0.33$), tumor differentiation ($p=0.13$), and microvascular invasion ($p=0.29$; Table 5). Patients without CSPH were more likely to have a higher rate of satellite nodules (30 vs. 6%, $p=0.05$). Fourteen (52%) patients in the no CPSH group and 6 (33%) patients in the CSPH group had high histological risk of tumor recurrence ($p=0.22$).

Results of cost analysis

Postoperative-costs were significantly higher for the CSPH group (20 518 €) compared to the no CSPH group (13 873 €, $p=0.042$).

Mid-term outcomes

No patient was lost to follow-up. The median follow-up time of the study population was 18 months (range 1–42 months). The median follow-up time was 9 months (range 1–40 months) for the CSPH group and 21 months (range 2–42 months) for the no CSPH group ($p=0.10$). Recurrence occurred within a median time period of 11 months in each group, including in 11 (41%) patients of the no CSPH group and in 2 (11%) patients of the CSPH group ($p=0.03$). Liver transplantation was performed in 3 patients from the no CSPH group and in 1 patient from the CSPH group ($p=0.52$).

Intention-to-treat 1- and 2-year overall survival (OS) rates calculated from the time of surgery were 91 and 77% for the no CPSH group and 100 and 100% for the CSPH group

Table 4 Morbidity and mortality of LLR in patients with versus without CSPH

	Total $N=45$	No CSPH $n=27$ (60%)	CSPH $n=18$ (40%)	p Value
90-Day mortality, *n* (%)	0 (0)	0 (0)	0 (0)	–
Overall morbidity, *n* (%)	8 (18)	1 (4)	7 (39)	0.003
Severe morbidity (≥ Dindo grade III)	0 (0)	0 (0)	0 (0)	–
Dindo–Clavien grading				0.001
0	35 (78)	26 (96)	9 (50)	
I	1 (2)	0 (0)	1 (6)	
II	9 (20)	1 (4)	8 (44)	
Liver-specific complications				
Ascites	3 (7)	1 (4)	2 (11)	0.33
Liver failure	2 (4)	0 (0)	2 (11)	0.08
Biliary fistula	0 (0)	0 (0)	0 (0)	–
Hemorrhage	0 (0)	0 (0)	0 (0)	–
AKI	4 (9)	1 (4)	3 (17)	0.13
General complications				
Cardiac	2 (4)	1 (4)	1 (6)	0.77
Pulmonary	4 (9)	0 (0)	4 (22)	0.01
Neurologic	2 (4)	0 (0)	2 (11)	0.08
Infectious	2 (4)	0 (0)	2 (11)	0.08
Reoperation	0 (0)	0 (0)	0 (0)	–
Percutaneous drainage	0 (0)	0 (0)	0 (0)	–
ICU stay (days)	5 (1–36)	3 (1–7)	6 (2–36)	0.02
Hospital stay (days)	6 (2–48)	5 (2–12)	7 (3–48)	0.02
Readmission within 30 days after discharge	0 (0)	0 (0)	0 (0)	–
Unresolved liver decompensation	1 (2)	0 (0)	1 (6)	0.22

CSPH clinically significant portal hypertension, *AKI* acute kidney injury, *ICU* intensive care unit

Table 5 Histopathological characteristics of patients without versus with CSPH

	Total $N=45$	No CSPH $n=27$ (60%)	CSPH $n=18$ (40%)	p Value
Maximum tumor size (mm)	27 ± 19	28 ± 13	26 ± 25	0.69
Multiple nodules (> 1 nodule)	4 (9)	2 (7)	2 (11)	0.67
Surgical margins (mm)	11 ± 14	11 ± 13	10 ± 14	0.85
R1 resection (margin < 1 mm), *n* (%)	3 (7)	1 (4)	2 (11)	0.33
Microvascular invasion, *n* (%)	14 (31)	10 (37)	4 (22)	0.29
Satellite nodules, *n* (%)	9 (20)	8 (30)	1 (6)	0.05
Differentiation[a]				0.13
Well	15 (33)	6 (22)	9 (50)	
Moderate	28 (62)	20 (74)	8 (44)	
Poor	0 (0)	0 (0)	0 (0)	
High risk of recurrence[b], *n* (%)	20 (44)	14 (52)	6 (33)	0.22

CSPH clinically significant portal hypertension

[a]Including 1 case of hepatocholangiocarcinoma in each group

[b]High risk of recurrence defined by the presence of microvascular invasion and/or additional nodules or satellite nodules [38, 39]

($p=0.17$), respectively. The 1- and 2-year recurrence-free survival (RFS) rates were 66 and 55% for the no CSPH patients and 94 and 79% for the CSPH patients ($p=0.10$), respectively. None of the patients in the CSPH group died within the first year after surgery, and 39% (7/18) of these patients reached the median follow-up.

RFS rates at 1 and 2 years in the group with high risk of recurrence were 55 and 55%, respectively, and RFS rates in the low-risk group were 90 and 69%, respectively ($p = 0.15$).

Subset of patients ≥ 70 years old

No significant difference was observed in terms of presence of CSPH between patients ≥ 70 years and those < 70 years (37.5% [6/16] vs. 41.4% [12/29], $p = 0.80$). A robotic approach was used in the same proportion of patients in each group (≥ 70 years: 41.7% [5/12] vs. < 70 years: 58.3% [7/12], $p = 0.61$). Overall, the 90-day mortality rate was nil, and the morbidity rate was 25%. The median durations of ICU and hospital stays were 1 and 7 days, respectively. In this subset of patients, survival at 1 and 2 years was 90 and 72%, respectively.

Subset of HCC patients with CPSH who underwent robotic hepatectomy

Among the 12 patients who underwent robotic hepatectomy, 6 (50%) had CSPH. All but one (who underwent bisegmentectomy) CSPH patients underwent robotic minor non anatomical resection for tumors located in the antero-lateral segments of the liver (i.e., from segments II to segments VI). The rate of conversion to laparoscopic open surgery was nil. Two patients required inflow clamping during resection. There was no intraoperative blood transfusion. Overall, the 90-day mortality rate was nil, and the morbidity rate was 17% (1/6).

Discussion

The present prospective, open study shows that expanding LLR for HCC to selected cirrhotic patients with CSPH defined by HVPG ≥ 10 mmHg can (i) achieve a zero mortality rate and a zero severe morbidity rate and (ii) increase the feasibility of surgery by 40% at the cost of significant increases in the moderate morbidity rate and the duration of stay compared to patients without CSPH.

Concordant with previous studies [3, 7, 40], 40% of the present patients with potentially resectable HCC had HVPG ≥ 10 mmHg. Among these patients, only 67% had acknowledged surrogates of CSPH [21], i.e., esophageal varices (ascites, which is also a surrogate, was not present in any patient by definition of the study population). In contrast, up to 37% of patients without CSPH had varices. This underlines the limits of most previous studies that have recommended either for or against liver resection in patients with CSPH when the diagnosis of CSPH relies on surrogates (either acknowledged or highly debated surrogates, such as splenomegaly with platelet counts lower than 100,000/m^3 [21]).

The HVPG values in our CSPH group were concordant with those reported in the few previously reported surgical series that used this criterion [2, 5, 8]. The comparison of intraoperative events between the two groups did not reveal significant differences in any variables (Table 3). Conversion to open surgery was needed in 9% of patients in our series compared with 23% of patients in Molina's study [7]. We assume the lower need for conversion that we observed resulted from better view of the operating field and easier control of bleeding owing to (i) a higher rate of clamping in the CSPH group in our series (67 vs. 38%), (ii) the use of robotic assistance in 27% of patients of our series versus none in Molina's study, and (iii) the extra-corporeal technique of clamping in our series allowing more complete clamping compared with the intra-corporeal technique used in Molina's study.

In the present analysis, ULD was observed in a single patient who subsequently survived. ULD was the cornerstone contraindication for liver resection in the seminal report by the BCLC group [4], and CSPH was identified as the only independent predictor of ULD, as well as in a subsequent report from the same team [41]. Ascites was observed in 7% of the study population and in 11% of the CSPH group (vs. 4% in the no CSPH group, $p = 0.33$), concordant with previous reports (7–45% [3, 5, 8]). The advantages of laparoscopy, such as the ability to preserve the abdominal wall, the contained spontaneous portacaval shunts, and the round ligament, have contributed to the low rate of postoperative ascites [42].

Interestingly, in the present series, one-third of the patients of the CSPH group were ≥ 70 years old, and these patients are usually deemed not transplantable. This elderly population not only represents an increasing proportion of the general population but is also particularly vulnerable to HCC [43]. LLR in our subset of these patients was associated with no postoperative mortality, a morbidity rate of 25%, and good mid-term results, which further endorse the use of the laparoscopic approach in these patients who would traditionally be recommended to undergo ablative procedures. Not surprising, the financial cost of surgery in patients with CSPH was significantly increased as compared to those without CSPH. However, this cost (and its effectiveness in term of years of life gained) remains to be compared to the cost of other options available in these patients, i.e., mainly radiofrequency and/or liver transplantation [44].

The main strengths of the present study are (i) its prospective nature, (ii) the recruitment of a large number of highly selected patients during a short period, and (iii) the fact that it was performed in a specialized unit by surgeons with extensive experience in laparoscopic and robot-assisted LLR. The main drawback of the present study is

the limited follow-up time. However, considering that our patients and their mid-term results are similar to those reported by Molina et al. [8], the patients in the present study should be expected to achieve comparable promising results. A controlled study comparing, for example, LLR to radiofrequency ablation would be ideal to prove the superiority of one procedure over the other. However, considering the results obtained here together with the results of other series, such a randomized controlled study would be ethically questionable. So far only a small subset (24%) of enrolled patients could benefit from the laparoscopic approach. We assume this proportion should increase in the near future due to the rapid progresses of this approach including with robotic assistance. The present study opens the door to show that the laparoscopic approach may provide a surgical alternative for patients who were previously deemed resectable based on technical and liver function assessments but non-operable due to CSPH. Yet, the small sample size does not allow for full comparison between patients with CSPH and those without CPSH. However, the series reported here is prospective, includes a large number of highly selected patients with cirrhosis accrued over a much shorter period as compared to other series on the same topic (as shown in Table 1, only 13–45 such patients who underwent LLR could be included in large centres during a period ranging from 2 to 10 years). Also, all patients in the present study were managed with a homogeneous selection process for laparoscopic approach, which allows us to reach robust conclusions regarding mid-term outcomes.

Almost two decades ago, the adoption of BCLC criteria was a major step forward in the intent-to-treat selection of HCC candidates for liver resection [4, 41]. Yet, the strict application of BCLC criteria, originally derived from the analysis of a cohort of 29 patients, excludes from resection a substantial number of HCC patients due to CSPH who could be resected with a curative intent as shown the results of the present prospective study. The latter added to others [45] claim for a re-appraisal of the value of CSPH in these criteria.

In conclusion, the present report shows that the advantages of laparoscopy also apply to patients with CSPH. By using the laparoscopic approach, the formal contraindication for surgical resection in cirrhotic patients with HCC due to CSPH may become null and void in the near future. Rebalancing the risk benefit ratio, the laparoscopic approach may provide a surgical side-path in the BCLC algorithm for patients who were previously deemed resectable based on technical and liver function assessments but non-operable due to CSPH. Therefore, the BCLC guidelines for resection of HCC should be re-evaluated.

Compliance with Ethical Standards

Disclosures Dr. Chetana Lim, Dr. Michael Osseis, Dr. Eylon Lahat, Dr. Alexandre Doussot, Dr. Dobromir Sotirov, Dr. Francois Hemery, Dr. Marc Lantéri-Minet, Pr. Cyrille Feray, Dr. Chady Salloum, and Pr. Daniel Azoulay have no conflicts of interest or financial ties to disclose.

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