Research article JHEP|Reports

Liver resection for hepatocellular carcinoma in patients with clinically significant portal hypertension

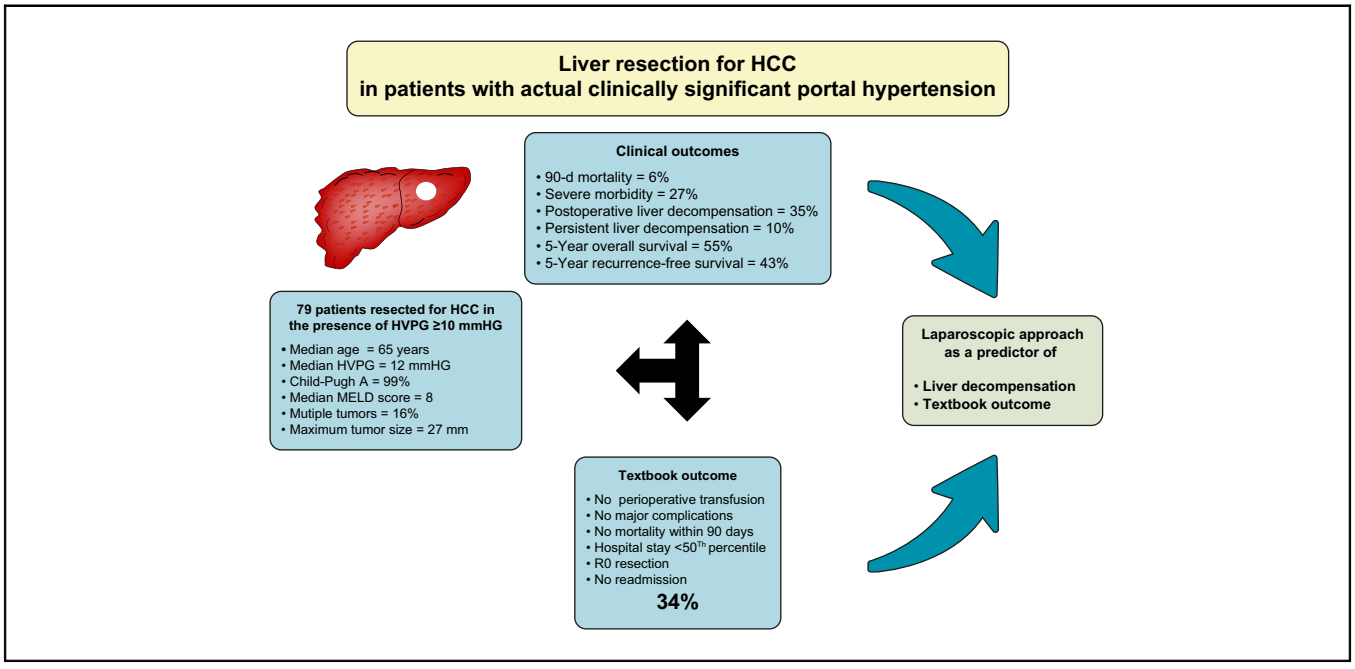
Authors

Daniel Azoulay, Emilio Ramos, Margarida Casellas-Robert, Chady Salloum, Laura Lladó, Roy Nadler, Juli Busquets, Celia Caula-Freixa, Kristel Mils, Santiago Lopez-Ben, Joan Figueras, Chetana Lim

Correspondence

daniel.azoulay@aphp.fr (D. Azoulay).

Graphical abstract



Highlights

- Patients with HCC and CSPH can undergo resection, with mortality of 6% and severe morbidity of 27%.
- Postoperative and persistent liver decompensation occurred in 35% and 10% of patients, respectively.
- Textbook outcome was achieved in 34% of patients.
- The laparoscopic approach was identified as a predictor of postoperative liver decompensation and textbook outcome.

Lay summary

Patients with cirrhosis, hepatocellular carcinoma, and clinically significant portal hypertension (defined as a hepatic venous pressure gradient ≥10 mmHg) can undergo resection with acceptable mortality, morbidity, liver decompensation rates, and a textbook outcome. These results can be achieved in selected patients with preserved liver function, good general status, and sufficient remnant liver volume.

https://doi.org/10.1016/j.jhepr.2020.100190

Research article

JHEP|Reports

Liver resection for hepatocellular carcinoma in patients with clinically significant portal hypertension

Daniel Azoulay,[1,2,*] Emilio Ramos,[3] Margarida Casellas-Robert,[4] Chady Salloum,[1] Laura Lladó,[3] Roy Nadler,[2] Juli Busquets,[3] Celia Caula-Freixa,[4] Kristel Mils,[3] Santiago Lopez-Ben,[4] Joan Figueras,[5] Chetana Lim[6]

[1]*Department of Hepato-Biliary and Pancreatic Surgery and Liver Transplantation, AP-HP Paul Brousse Hospital, Villejuif, France;* [2]*Department of Hepato-Biliary and Pancreatic Surgery and Transplantation, Sheba Medical Center, Faculty of Medicine Tel Aviv University, Tel Aviv, Israel;* [3]*Department of Hepato-Biliary and Pancreatic Surgery and Liver Transplantation, Hospital Universitari de Bellvitge, CIBERehd, Barcelona, Catalonia, Spain;* [4]*Unit of Hepato-Biliary and Pancreatic Surgery, Department of General Surgery, Hospital Universitari Dr Josep Trueta, Girona, Catalonia, Spain;* [5]*Hepato-Biliary and Pancreatic Surgery, Department of Surgery, "Sagrat Cor" Hospital University of Barcelona, Barcelona, Spain;* [6]*Department of Hepato-Biliary and Pancreatic Surgery and Liver Transplantation, AP-HP Pitié-Salpêtrière Hospital, Paris, France*

JHEP Reports **2021.** https://doi.org/10.1016/j.jhepr.2020.100190

Background & Aims: Liver resection (LR) in patients with hepatocellular carcinoma (HCC) and clinically significant portal hypertension (CSPH) defined as a hepatic venous pressure gradient (HVPG) ≥10 mmHg is not encouraged. Here, we reappraised the outcomes of patients with cirrhosis and CSPH who underwent LR for HCC in highly specialised liver centres.
Methods: This was a retrospective multicentre study from 1999 to 2019. Predictors for postoperative liver decompensation and textbook outcomes were identified.
Results: In total, 79 patients with a median age of 65 years were included. The Child-Pugh grade was A in 99% of patients, and the median model for end-stage liver disease (MELD) score was 8. The median HVPG was 12 mmHg. Major hepatectomies and laparoscopies were performed in 28% and 34% of patients, respectively. Ninety-day mortality and severe morbidity rates were 6% and 27%, respectively. Postoperative and persistent liver decompensation occurred in 35% and 10% of patients at 3 months. Predictors of liver decompensation included increased preoperative HVPG ($p = 0.004$), increased serum total bilirubin ($p = 0.02$), and open approach ($p = 0.03$). Of the patients, 34% achieved a textbook outcome, of which the laparoscopic approach was the sole predictor ($p = 0.004$). The 5-year overall survival and recurrence-free survival rates were 55% and 43%, respectively.
Conclusions: Patients with cirrhosis, HCC and HVPG ≥10 mmHg can undergo LR with acceptable mortality, morbidity, and liver decompensation rates. The laparoscopic approach was the sole predictor of a textbook outcome.

Introduction

Liver resection (LR) is one of the few first-line curative options for patients with cirrhosis, very-early/early-stage hepatocellular carcinoma (HCC) and preserved liver function.[1]

In this setting of LR, portal hypertension (PHT) has been associated with increased postoperative morbidity and liver decompensation,[2,3] which led to PHT being considered a formal contraindication for LR.[4] Recently, updated guidelines from the European Association for the Study of the Liver (EASL) opened the door to LR for HCC in patients with PHT by endorsing a risk algorithm for postoperative liver decompensation.[5] This algorithm includes the hierarchical interaction of three preoperative variables in the following order: presence of PHT; extent of resection; and model for end-stage liver disease (MELD) score. However, this algorithm was determined from a series of LRs performed with an open approach, in which PHT was defined by the presence of indirect signs for this condition,[4] whereas the laparoscopic approach decreases the risk of liver surgery,[6–9] and the actual measurement of the hepatic venous pressure gradient (HVPG), which is the current gold-standard method for ascertaining clinically significant PHT (CSPH, defined as HVPG ≥10 mm Hg), highlights the limited sensitivity and specificity of indirect signs.[10,11]

This background motivated the creation of a consortium of specialised liver centres in which all non-surgical and surgical approaches, including laparoscopy, are available and where HVPG measurement is routine in the preoperative assessment before LR for HCC in patients with cirrhosis. Here, we assessed the short-term and oncological outcomes of selected patients with CSPH after LR for HCC, taking into account patient-oriented outcomes. Reasonable results, namely a reasonable rate of postoperative liver decompensation and the possibility of achieving a textbook outcome, including in technically difficult cases, would promote reconsideration of the indications for resection in the selected group of patients with cirrhosis and CSPH.

Keywords: Hepatectomy; Hepatic venous pressure gradient; Clinically significant portal hypertension; Postoperative liver decompensation; Textbook outcome.
Received 20 August 2020; received in revised form 10 September 2020; accepted 16 September 2020; available online 8 October 2020
* Corresponding author. Address: Centre Hépato-Biliaire, AP-HP Hôpital Paul Brousse, Avenue Paul Vaillant Couturier, 94000 Villejuif, France.
E-mail address: daniel.azoulay@aphp.fr (D. Azoulay).

Materials and methods

Study design

The study population included all consecutive patients with cirrhosis and preoperative CSPH, as assessed by HVPG

measurement, who underwent LR for HCC between November 1999 and March 2019 in three Western liver centres (Henri Mondor Hospital, Créteil, France; Universitari Dr Josep Trueta Hospital, Girona, Spain; and Universitari de Bellvitge Hospital, Barcelona, Spain).

The primary endpoint was to assess the safety of LR in patients with preoperative CSPH, evaluated as 90-day mortality and morbidity. Secondary endpoints included the occurrence of postoperative liver decompensation, a textbook outcome, and long-term oncological outcomes. The study protocol was designed according to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the institutional review boards of the three centres.

Study population

The diagnosis of HCC relied on the acknowledged diagnostic criteria of HCC. First, to be considered potential candidates for LR, patients had to fulfil the following criteria: no previous history of ascites, variceal rupture, or spontaneous encephalopathy; no prohibitive comorbidities; Child-Pugh class A liver function or class B, provided this was because of biliary obstruction; and a plan for a complete macroscopic resection combined with a sufficient future remnant liver volume upon preoperative computed tomography (CT) volumetric assessment [following percutaneous portal vein embolisation (PVE) whenever needed[12]]. The alpha-fetoprotein (AFP) level was not considered in the decision for surgery. Second, all of the above-selected patients underwent preoperative PHT assessment, including transjugular HVPG measurement complying with technical recommendations,[13] CT and upper gastrointestinal endoscopy. Briefly, within the 2 weeks before surgery, HVPG measurements were performed in fasting conditions under local anaesthesia. The right jugular vein was canalised under ultrasonographic guidance. A 7-French balloon-tipped catheter ('Fogarty' Edwards Lifesciences LLC, Irvine, CA, USA) was guided into the main right or middle hepatic vein for measurements of wedged and free HVPs to calculate the HVPG. All measurements were taken in triplicate and averaged to obtain the baseline HVPG. HVPG ≥10 mmHg indicated the presence of CSPH[14] regardless of the presence of oesophageal varices, thrombopenia, or splenomegaly.

The presence of oesophageal varices or the coexistence of a platelet count $<10^9$/L and splenomegaly >120 mm in diameter were considered surrogates of CSPH.[15] At this stage, patients with HVPG ≥30 mmHg were arbitrarily excluded from resection. The indications for surgery, planned resection, and the chosen approach were homogenous across centres (see later) and decided during board meetings at each liver centre.

Surgical approach and complexity of liver resection

Laparoscopic approach, repeat hepatectomy, or anatomical resection were performed whenever possible. The laparoscopic approach was chosen according to the guidelines of the World Consensus Conference on Laparoscopic Surgery.[16,17]

The technical difficulty of each procedure was evaluated based on a 3-level classification validated for both the laparoscopic and open approaches.[18,19] Briefly, this comprised three levels of technical difficulty [low, wedge resection and left lateral sectionectomy; moderate, anterolateral segmentectomy (from segments II to VI) and left hepatectomy; and high: posterosuperior segmentectomy (segments VII, VIII, and I), right and extended right hepatectomy, right posterior sectionectomy, central hepatectomy, and extended left hepatectomy].

Major resection was defined as resection ≥3 contiguous Couinaud's segments. Morbidity was evaluated according to the comprehensive complication index described by Slankamenac *et al.*[20] (available at www.assessurgery.com/calculator_single/). Severe morbidity was defined by a Comprehensive Complication Index (CCI) ≥26.2, which refers to 1 complication of Clavien-Dindo grade IIIa.[21]

Liver complications (grade A or higher) included liver failure,[22] bile leakage,[23] and haemorrhage,[24] as defined by the International Study Group on Liver Surgery. Postoperative ascites and encephalopathy were defined based on the definition of Moore *et al.*[25] and Vilstrup *et al.*,[26] respectively. Non-liver complications included cardiopulmonary and infectious complications and acute kidney injury.[27]

Three binary composite endpoints were used: postoperative liver decompensation; persistent liver decompensation at 3 months; and textbook outcome. Postoperative liver decompensation was defined as present when at least 1 of the following complications occurred within 3 months after resection: liver failure; ascites; or encephalopathy. Persistent liver decompensation was defined as present when at least 1 of the following three liver complications occurred at 3 months after resection: jaundice and/or ascites and/or encephalopathy.[28] A textbook outcome was achieved when all 6 of the following criteria were met: no perioperative transfusion; no major postoperative complications (CCI <26.2); no mortality within 90 days or during the hospital stay; hospital stay <50th percentile of the total cohort (≤8 days); R0 resection (≥1 mm), and no readmission.[29–32]

Postoperative mortality included any death within 90 days or during hospitalisation for LR. Readmission included any hospitalisation occurring after discharge within 90 days following LR.

Follow-up

Patients were followed up every 4 months for the first 2 years and every 6 months thereafter. Tumour recurrence and liver status were monitored, and patients were treated according to disease presentation. HCC recurrence, persistent liver decompensation, or death were recorded as major impact events. Follow-up for this study was completed on 11 April 2020.

Statistical analysis

Continuous variables were expressed as the median and 25–75th IQR. Categorical variables were expressed as numbers and percentages. Student's *t* test, the Mann-Whitney *U* test and Fisher's exact test were used as appropriate.

Overall survival was defined as the period between the date of hepatectomy and the date of death or last follow-up. Recurrence-free survival was defined as the period between the date of hepatectomy and the date of first recurrence or death.

Two multivariate regression logistic analyses were performed to identify the independent predictors of: (1) postoperative liver decompensation; and (2) textbook outcome. All pre- and intraoperative variables associated with these two latter composite endpoints in the univariable analysis (p <0.1) were included in the multivariate analysis. Statistical analysis was performed using Statview version 5.0 (SAS Institute, Inc., Cary, NC, USA). The present study complied with RECORD guidelines.[33]

Results

Study population

During the study period, a total of 375 consecutive patients with HCC and liver cirrhosis who had LRs underwent HVPG assessment before surgery. The study population comprised 79 (21%) patients with preoperative CSPH, namely, those with HVPG ≥10 mmHg. The baseline characteristics of the study population are shown in Table 1. Viral infection (63%) was the most common cause of cirrhosis. The Child-Pugh grade of 78 (99%) patients was A, and the median MELD score was 8 (IQR: 6–9). The median HVPG was 12 mmHg (IQR: 11–15, range 10–26 mmHg). Indirect signs of CSPH were observed in 31 (39%) patients: oesophageal varices were present in 26 (33%) and splenomegaly and thrombopenia in 12 (15%). Only 7 (9%) patients met all the surrogate criteria for CSPH, and 28 (35%) patients had none of them. Tumours presented as a single nodule in 66 patients (84%), and the median size of the largest nodule was 27 (IQR: 18–35) mm.

Table 2 shows the detailed intraoperative events. The open approach was used in 52 (66%) patients, and the laparoscopic approach was used in 27 (34%) patients, with 1 case (4%) of conversion to the open approach. The latter was evaluated in the laparoscopic group on an intent-to-treat basis. Minor LR was performed in 72% (n = 65) of patients. Eleven (14%) patients needed intraoperative blood transfusion.

Ninety-day mortality and morbidity

Overall, the 90-day mortality rate was 6% (n = 5; Table 3); 3 and 2 patients had major and minor resections, respectively. All patients had postoperative liver decompensation, and 3 had persistent liver decompensation at 3 months. Causes of death included persistent liver decompensation in 3 patients (liver failure in 2 patients and ascites in 1 patient), new onset of ascites in 1 patient, and postoperative diffuse portal vein thrombosis in 1 patient.

The details of postoperative complications are shown in Table 3. Overall, 53 of 79 patients developed postoperative complications (morbidity rate = 67%) with a median CCI of 8.7 (0–30). Major complications (CCI ≥26.2) occurred in 21 (27%) patients.

Postoperative ascites, liver failure, haemorrhage, and bile leakage occurred in 25 (3%), 6 (8%), 6 (8%), and 3 (4%) patients, respectively. The median hospital stay was 14 (IQR: 8–19) days. Nine (10%) patients needed readmission.

Table 1. Baseline clinical, laboratory and tumour characteristics of the study population.

Variables	Study population (79 patients)
Age (years)	65 (59–70)
Male gender, yes	65 (82)
Body mass index (kg/m^2)	29 (25–31)
ASA score >2	38 (48)
Previous treatment before resection	18 (23)
Hepatectomy	2 (3)
Local destruction	2 (3)
TACE	12 (15)
Sorafenib	2 (3)
Child-Pugh class (A/B)	78 (99)/1 (1)
HVPG (mmHg)	12 (11–15)
Surrogate criteria of CSPH	31 (39)
Oesophageal varices	26 (33)
Splenomegaly and thrombopenia*	12 (15)
Viral infection	50 (63)
MELD score	8 (6–9)
Pre-resection blood tests	
Serum albumin (g/L)	40 (37–43)
Serum total bilirubin (μmol/L)	12 (8–18)
Platelet (/10^5/ml)	133 (101–167)
Serum creatinine (μmol/L)	83 (67–92)
AFP (ng/ml)	8 (4–38)
Multiple nodules	13 (16)
Maximum tumour size (mm)	27 (18–35)
Resection margin (mm)	5 (2–10)
Satellite nodules	9 (11)
Macrovascular invasion	3 (4)
Microvascular invasion	25 (32)
Poor differentiated tumours	5 (6)

Results are presented as median (IQR) or n (%).
AFP, α-fetoprotein; ASA, American Society of Anesthesiologists; CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; MELD, Model for End-Stage Liver Disease; LLR, laparoscopic liver resection; TACE, transarterial chemoembolisation.
* Splenomegaly >120 mm in diameter and platelet count <100,000/ml.

Table 2. Surgical procedures and intraoperative characteristics.

Variable	Study population (79 patients)
Portal vein embolisation	5 (6)
Repeat hepatectomy	2 (3)
Laparoscopic hepatectomy	27 (34)
Anatomical resection*	45 (57)
Type of surgical procedure	
Wedge resection	34 (43)
Segmentectomy	17 (22)
Bisegmentectomy	14 (18)
Major hepatectomy†	14 (18)
Left-sided hepatectomy	5 (6)
Right-sided hepatectomy	9 (11)
Multiple hepatectomies	6 (8)
Associated procedures‡	8 (10)
Technical difficulty grade (low/moderate/high)	44 (56)/14 (18)/21 (27)
Inflow clamping	66 (84)
Duration of inflow clamping (min)	30 (10–48)
Duration of operation (min)	240 (180–300)
Blood loss (ml)	200 (110–611)
Blood transfusion	11 (14)
Red blood cell units (mean ± SD)	1.3 ± 0.8
Intraoperative mortality	0 (0)

Results are presented as median (IQR) or n (%), unless indicated otherwise.
* Defined as any type of systematic resection of the portal areas based on Couinaud classification.
† Major hepatectomy defined by resection ≥3 Couinaud segments.
‡ Associated procedures included partial hepatectomy (3 patients), local destruction (2 patients), portal thrombectomy (1 patient), opening of the diaphragm (1 patient), portal thrombectomy, and opening of the diaphragm (1 patient).

Postoperative liver decompensation

Overall, 28 (35%) patients developed at least 1 sign of postoperative liver decompensation, including ascites in 25 patients, jaundice in 6, and encephalopathy in 3. Among them, 5 (18%, 5/28) died within 90 days of surgery (see later). An increased preoperative HVPG value [p = 0.004; odds ratio (OR) = 1.5; 95% CI = 1.1–1.9], increased elevated preoperative serum total bilirubin (p = 0.02; OR = 1.1; 95% CI = 1.0–1.3), and open approach (p = 0.03; OR = 8.7; 95% CI = 1.2–63.9) were independent predictors of postoperative liver decompensation (Table 4).

At 3 months following resection, 8 (10%) patients had persistent liver decompensation: 5 had refractory ascites, 2 had jaundice and ascites, and 1 had encephalopathy. Four (50%, 4/8) of them died within 12 months following surgery.

Textbook outcomes

A textbook outcome was achieved in 27 (34%) patients. The distributions of each textbook outcome criterion are shown in

Table 3. Short and long-term outcomes.

Outcome	N =79
Any perioperative morbidity	53 (67)
CCI	8.7 (0–28)
Severe morbidity (CCI ≥26.2)	21 (27)
Combined medical, surgical and/or liver-related complications	16 (20)
Medical complications only	14 (18)
Infection	14 (18)
Cardiac and respiratory	14 (18)
Acute kidney injury	4 (5)
Surgical complication only	7 (9)
Wound complications	3 (4)
Haemorrhage	6 (8)
Fluid collections requiring percutaneous drainage	10 (13)
Surgical reintervention	2 (3)
Liver-related complications only	16 (20)
Ascites	25 (3)
Biliary fistula	3 (4)
Encephalopathy	3 (4)
Liver failure	6 (8)
Postoperative liver decompensation	28 (35)
Persistent liver decompensation at 3 months	8 (10)
Jaundice and ascites	2 (3)
Ascites	5 (6)
Encephalopathy	1 (1)
Postoperative hospital stay (days)	8 (6–15)
Mortality	
90-day mortality	5 (6)
1-year mortality	9 (11)
HCC recurrence	36 (46)
Timing (months following resection)	22 (1–43)
Intrahepatic/extrahepatic/both recurrence	33 (92)/2 (6)/1 (2)
Curative treatment*	14 (39)
Treatment type†	
Liver transplantation	3 (8)
Re-hepatectomy	2 (6)
Local destruction	9 (25)
TACE	10 (28)
Combination local destruction and chemotherapy	1 (3)
Best supportive care	11 (31)
Postoperative follow-up (months)	39 (18–56)

Results are presented as median (IQR) or n (%).
CCI, Comprehensive Complication Index; TACE, transarterial chemoembolisation.
* Curative treatment included transplantation, surgery and local destruction.
† The most effective treatment was retained when a multimodal management was implemented.

Figure 1. In the multivariate analysis, the laparoscopic approach emerged as the sole independent predictor associated with textbook outcome (p = 0.004, OR = 5.6; 95% CI = 1.7–18.2; Table 5). Textbook outcomes were achieved in 63% and 19% (p = 0.0001) of patients who underwent laparoscopic and open LR, respectively. A textbook outcome was observed in 7% and 40% (p = 0.02) of patients who underwent major and minor LR, respectively. A textbook outcome was achieved in 43%, 43%, and 10% (p = 0.02) of patients submitted to surgeries graded as low, moderate, and high difficulty, respectively. A textbook outcome was achieved in 56%, 37%, 0%, and 0% of patients with tumours classified as Barcelona-Clinic Liver Cancer (BCLC) 0, A, B, and C, respectively (p = 0.01).

Long-term oncological outcomes

During the follow-up period, recurrence occurred in 36 (46%) patients with a median delay of 22 months (IQR: 1–43). The first recurrence was intrahepatic in most cases (33 patients, 92%). Curative treatment could be applied in 14 (39%) patients, including liver transplantation, rehepatectomy, and local destruction in 8%, 6%, and 25% of patients, respectively.

The 1-, 3-, and 5-year overall survival rates were 89%, 73%, and 55%, respectively (Figure 2). The 1-, 3-, and 5-year recurrence-free survival rates were 82%, 62%, and 43%, respectively (Figure 2).

Discussion

In the present series, LR for HCC in selected patients with cirrhosis and actual CSPH, as assessed by HVPG measurement, was performed with acceptable results not only in terms of standard medical-centered outcomes, including 90-day mortality (6%), overall morbidity (67%), and 5-year overall survival (55%), but also in terms of patient-centered outcomes, with textbook outcomes achieved in one-third of patients across the various technical difficulty and BCLC grades. In addition, our selection criteria increased the number of LRs for HCC by 21%.

The updated EASL guidelines endorse a risk algorithm for postoperative decompensation following LR for HCC,[5] which includes the hierarchical interaction of three variables in the following order: presence of PHT; extent of resection; and MELD score. In these guidelines, CSPH is no longer a formal contraindication for the resection of HCC in patients with cirrhosis, provided that this is balanced by the extent of LR and liver function. Importantly, the above-mentioned algorithm was developed from a series of surgeries all performed with an open approach, in which CSPH was defined by the presence of indirect signs for this condition[4]; however, the laparoscopic approach *per se* is acknowledged to decrease the risk of liver surgery,[6,8,34] and surrogates of CSPH lack sensitivity and specificity compared with the HVPG measurement[10,11,35,36] and >50% of compensated patients, as in our study population, with HVPG ≥10 mmHg might have no varices and normal or almost normal platelet count.[36] In this subset of well-selected patients with HVPG ≥10 mmHg, some centres, following the guidelines, reported reasonable surgical and acceptable long-term oncological outcomes, with postoperative liver decompensation ranging from 6% to 33% and 3-year survival ranging from 72% to 79%.[28,37,38]

Clearly, the present series only included selected patients with good general condition [52% with American Society of Anesthesiologists (ASA) score <2], a preserved liver condition (99% with Child-Pugh A, median MELD score of 8), and favourable tumour biology (84% with single nodules, median tumour size of 27 mm, median AFP level = 8 ng/ml). Nevertheless, it comprised a full spectrum of the three aspects of tumours across the BCLC classification, of the magnitude of surgical procedures from non-anatomical to major resections, and of technical complexity. The mortality and morbidity rates as well as the postoperative liver decompensation incidence achieved here do not require further comment, because they were concordant with those reported by other series including patients with CSPH defined by HVPG ≥10 mmHg.[2,28,37,38] We consider that the comparison of these results to those obtained when the criteria per the guidelines to proceed for surgery are met, is at least debatable, if even clinically sound, because these guidelines target both the best perioperative outcome and longest survival time possible following surgery for the ideal surgical candidates. We acknowledge the value of guideline recommendations and expected results, but we also consider it meaningful to clinicians and patients to provide a comparison between surgical management and the best non-surgical management for clinical

Table 4. Uni- and multivariable analysis of variables associated with postoperative liver decompensation.

Variable	Postoperative liver decompensation		Univariate *p* value	Multivariate *p* value [OR (95% CI)]
	Yes (n = 28)	No (n = 51)		
Age (years)	66 (59–70)	65 (58–70)	0.90	
Male sex	24 (86)	41 (80)	0.55	
BMI (kg/m^2)	28 (22–31)	29 (25–32)	0.24	
ASA score >2	11 (39)	27 (53)	0.25	
Viral aetiology	21 (75)	29 (57)	0.11	
Previous treatment	8 (29)	10 (20)	0.36	
Repeat hepatectomy	0 (0)	2 (4)	0.29	
Child-Pugh class B	0 (0)	1 (2)	0.46	
HVPG (mmHg)	14 (12–20)	11 (10–13)	<0.0001	0.004 [1.5 (1.1–1.9)]
Indirect signs of CSPH	13 (46)	18 (35)	0.33	
Oesophageal varices	11 (39)	15 (29)	0.37	
Splenomegaly and thrombopenia	5 (18)	7 (14)	0.62	
MELD score	8 (6–10)	8 (6–9)	0.40	
Creatinine (μmol/L)	75 (67–95)	83 (69–92)	0.60	
Serum total bilirubin (μmol/L)	16 (11–23)	11 (8–15)	0.002	0.02 [1.1 (1.0–1.3)]
Serum albumin (g/L)	37 (34–41)	41 (38–44)	0.03	0.93
Platelet (10^5/mm^3)	130 (95–164)	135 (104–167)	0.36	
Portal vein embolisation	4 (14)	1 (2)	0.03	0.99
Major resection	9 (32)	5 (10)	0.01	0.67
Open approach	23 (82)	29 (57)	0.02	0.03 [8.7 (1.2–63.9)]
Anatomical resection	18 (64)	26 (51)	0.25	
Associated procedures	4 (14)	4 (8)	0.36	
Inflow clamping	23 (82)	43 (84)	0.80	
Operative time (min)	230 (184–344)	240 (180–300)	0.34	
Blood transfusion	8 (29)	3 (6)	0.005	0.20
High grade of technical difficulty	17 (61)	18 (35)	0.03	0.33

Results are presented as median (IQR) or n (%).
ASA, American Society of Anesthesiologists; CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; MELD, Model for End-Stage Liver Disease; OR, odds ratio.

decision-making and on an intent-to-treat basis. Given the paucity of data published, the natural outcome of patients treated on an intent-to-treat basis is not well known, but median survival has been reported to be <36 months.[1]

Textbook outcome is a composite endpoint that integrates a selection of relevant peri- and postoperative outcomes, and represents the ideal postoperative course following a surgical procedure. Evaluating textbook outcome among patients with cirrhosis, CSPH and HCC is particularly interesting not only because it gives an overview of the overall quality of care following LR for HCC, but also because it shows that ideal perioperative outcomes can be achieved in these non-ideal patients. In the present series, a textbook outcome was achieved overall in one-third of patients, including 7% and 23% of those who underwent major hepatectomies and moderate/highly complex surgery, respectively. This composite criterion is one of the latest patient-centered outcomes[39,40] added to improve the vital patient–doctor decision process[41] to proceed for surgery, including the provision of tool aids for decisions, recommendations from guidelines and consensus conferences.

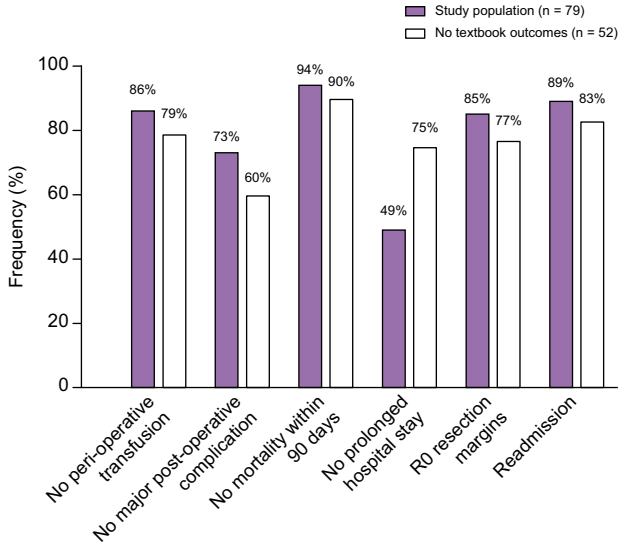


Fig. 1. Distribution of each textbook outcome criterion.

Interestingly, the laparoscopic approach was the sole independent predictor of a textbook outcome in the present series of *a priori* high-risk patients. Unsurprisingly, patients with very/early HCC were more likely to achieve a textbook outcome than were those with more advanced tumour stages (BCLC B/C). Patients with minor and low-difficulty LRs were also more likely to achieve a textbook outcome than were those with major and moderate/high-difficulty LRs. Overall, the textbook rate observed in the present series was lower than that reported in a previous series (62.3%).[32] There are several possible reasons for this difference, including the baseline characteristics of the patients (70.1% with ASA score <2, 36.2% with only cirrhosis) and the definition of the textbook outcome itself.

This study was retrospective. However, the data were obtained from a multicentric prospectively maintained database, making this series of LRs in patients with cirrhosis and confirmed CSPH the largest available. Given that the main objective of this study was to reappraise the outcomes in this highly selected group of patients in terms of the effects of the laparoscopic surgery and the assessment of textbook outcome, rather than to confirm what previous studies had already shown in terms of feasibility and safety, we did not compare our study population with patients with HVPG <10 mmHg as controls. The most

Table 5. Uni- and multivariable analysis of variables associated with a textbook outcome.

Variable	Textbook outcomes		Univariate *p* value	Multivariate *p* value [OR (95% CI)]
	Yes (n = 27)	No (n = 52)		
Age (years)	64 (59–71)	66 (44–69)	0.59	
Male sex	21 (78)	44 (85)	0.45	
Body mass index (kg/m^2)	27 (24–30)	30 (26–32)	0.19	
ASA score >2	14 (52)	24 (46)	0.63	
Virus-related cirrhosis	16 (59)	34 (65)	0.59	
Previous treatment	4 (15)	14 (27)	0.22	
Repeat hepatectomy	1 (4)	1 (2)	0.63	
Child-Pugh class B	0 (0)	1 (2)	0.47	
HVPG (mmHg)	11 (10–14)	12 (11–16)	0.13	
Indirect signs of CSPH	12 (44)	19 (37)	0.49	
Oesophageal varices	10 (37)	16 (31)	0.57	
Splenomegaly and thrombopenia	4 (15)	8 (15)	0.95	
MELD score	8 (6–9)	8 (6–9)	0.57	
Creatinine (μmol/L)	84 (70–91)	78 (67–97)	0.48	
Total Bilirubin (μmol/L)	11 (8–15)	14 (9–19)	0.06	0.21
Albumin (g/L)	42 (39–44)	39 (36–42)	0.05	0.43
Platelet (10^5/mm^3)	127 (96–167)	134 (104–164)	0.30	
Portal vein embolisation	0 (0)	5 (10)	0.10	0.99
Major resection	1 (4)	13 (25)	0.02	0.70
Laparoscopic approach	10 (37)	42 (81)	0.0001	0.003 [7.2 (2.0–25.6)]
Anatomical resection	14 (52)	30 (58)	0.62	
Associated procedures	1 (4)	7 (13)	0.17	
Inflow clamping	6 (22)	7 (13)	0.32	
Operative time (min)	230 (180–293)	240 (188–334)	0.17	
High grade of technical difficulty	8 (30)	27 (52)	0.06	0.13

Results are presented as median (interquartile range) or n (%).
ASA, American Society of Anesthesiologists; CSPH, clinically significant portal hypertension; HVPG, hepatic venous pressure gradient; MELD, Model for End-Stage Liver Disease; OR, odds ratio.

appropriate control group would be patients with HVPG ≥10 mmHg who did not undergo surgery. Ideally, a randomised controlled trial comparing resection to non-resection management in the selected population (*i.e.* in patients with 10 mmHg < HVPG <30 mmHg, good general status and preserved liver and kidney function, and low MELD score) would be performed. However, considering the results obtained here, we are not convinced that this trial would be ethical, if ever feasible, because of the limited number of eligible patients.

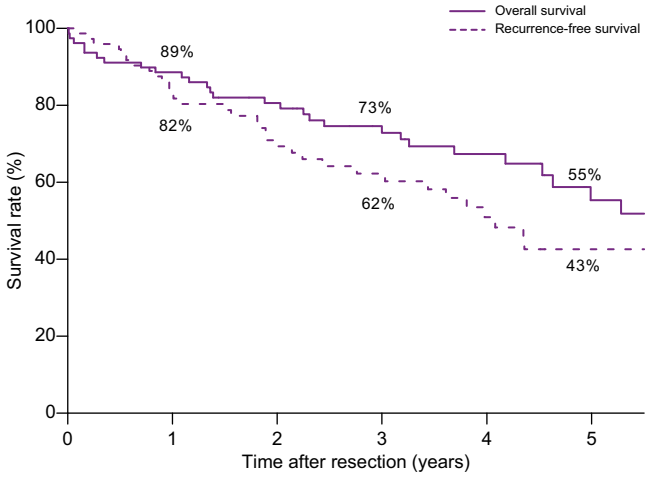


Fig. 2. Overall survival (OS) and recurrence-free survival (RFS) rates of the study population.

Liver transplantation is the best available treatment for patients with HCC and PHT, but the shortage of liver grafts, strict inclusion criteria (*e.g.* age, comorbidities, and tumour characteristics) together with the risks of dropout from the waiting list because of PHT[42] could preclude access for a large number of candidates. Interestingly, 56% (n = 44) of patients in the present series were initially transplantable based on the acknowledged transplantation criteria.

The low rate of posthepatectomy liver failure (8%, n = 6 in this series) methodologically hampered a sound multivariate analysis to identify the independent predictors of this major complication. This event was rare in this series compared with others, again because of the stringent selection of candidates for surgery. Finally, the number of patients did not allow us to perform a subanalysis regarding a potential effect of centre difference or era difference on outcomes.

Conclusions

Patients with cirrhosis, HCC, and measured CSPH (*i.e.* HVPG ≥10 mmHg) can be resected with acceptable rates of mortality, morbidity, liver decompensation, and even a textbook outcome. These results can be achieved in selected patients with preserved liver function, good general status, and sufficient remnant liver volume.

Abbreviations

AFP, alpha-fetoprotein; ASA, American Society of Anesthesiologists; BCLC, Barcelona-Clinic Liver Cancer; CCI, Comprehensive Complication Index; CSPH, clinically significant portal hypertension; CT, computed tomography; EASL, European Association for the Study of the Liver; HVPG, hepatic venous pressure gradient; MELD, model for end-stage liver disease; LLR,

laparoscopic liver resection; LR, liver resection; PHT, portal hypertension; PVE, portal vein embolisation; TACE, transarterial chemoembolisation.

Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: DA, CL; acquisition, analysis and interpretation of data: all authors; drafting of manuscript: DA, CL, CS; critical revision of manuscript for important intellectual content: ER, MCR, LL, RN, JB, CCF, KM, SLB, JF; final approval of manuscript: all authors.

Data availability

The data that support the findings of this study are available on request from the corresponding author.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhepr.2020.100190.

References

[1] EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol 2018;69:182–236.

[2] 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;111:1018–1022.

[3] Cescon M, Vetrone G, Grazi GL, Ramacciato G, Ercolani G, Ravaioli M, et al. Trends in perioperative outcome after hepatic resection: analysis of 1500 consecutive unselected cases over 20 years. Ann Surg 2009;249:995–1002.

[4] Llovet JM, Bru C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis 1999;19:329–338.

[5] 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;151:846–853.

[6] Han HS, Shehta A, Ahn S, Yoon YS, Cho JY, Choi Y. Laparoscopic versus open liver resection for hepatocellular carcinoma: case-matched study with propensity score matching. J Hepatol 2015;63:643–650.

[7] Ciria R, Gomez-Luque I, Ocana S, Cipriani F, Halls M, Briceño J, et al. A systematic review and meta-analysis comparing the short- and long-term outcomes for laparoscopic and open liver resections for hepatocellular carcinoma: updated results from the European Guidelines Meeting on Laparoscopic Liver Surgery, Southampton, UK, 2017. Ann Surg Oncol 2018;26:252–263.

[8] Sposito C, Battiston C, Facciorusso A, Mazzola M, Muscarà C, Scotti M, et al. Propensity score analysis of outcomes following laparoscopic or open liver resection for hepatocellular carcinoma. Br J Surg 2016;103:871–880.

[9] Nomi T, Hirokawa F, Kaibori M, Ueno M, Tanaka S, Hokuto D, et al. Laparoscopic versus open liver resection for hepatocellular carcinoma in elderly patients: a multi-centre propensity score-based analysis. Surg Endosc 2019;34:658–666.

[10] Qamar AA, Grace ND, Groszmann RJ, Garcia-Tsao G, Bosch J, Burroughs AK, et al. Platelet count is not a predictor of the presence or development of gastroesophageal varices in cirrhosis. Hepatology 2008;47:153–159.

[11] Berzigotti A, Seijo S, Arena U, Abraldes JG, Vizzutti F, García-Pagán JC, et al. Elastography, spleen size, and platelet count identify portal hypertension in patients with compensated cirrhosis. Gastroenterology 2012;144:102–111.

[12] Azoulay D, Castaing D, Krissat J, Smail A, Hargreaves GM, 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;232:665–672.

[13] Bosch J, Abraldes JG, Berzigotti A, Garcia-Pagan JC. The clinical use of HVPG measurements in chronic liver disease. Nat Rev Gastroenterol Hepatol 2009;6:573–582.

[14] Bosch J, Garcia-Pagan JC, Berzigotti A, Abraldes JG. Measurement of portal pressure and its role in the management of chronic liver disease. Semin Liver Dis 2006;26:348–362.

[15] Berzigotti A, Reig M, Abraldes JG, Bosch J, Bruix J. Portal hypertension and the outcome of surgery for hepatocellular carcinoma in compensated cirrhosis: a systematic review and meta-analysis. Hepatology 2014;61:526–536.

[16] Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, et al. The international position on laparoscopic liver surgery: the Louisville Statement, 2008. Ann Surg 2009;250:825–830.

[17] Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han HS, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. Ann Surg 2015;261:619–629.

[18] Kawaguchi Y, Fuks D, Kokudo N, Gayet B. Difficulty of laparoscopic liver resection: proposal for a new classification. Ann Surg 2017;267:13–17.

[19] Kawaguchi Y, Hasegawa K, Tzeng CD, Mizuno T, Arita J, Sakamoto Y, et al. Performance of a modified three-level classification in stratifying open liver resection procedures in terms of complexity and postoperative morbidity. Br J Surg 2019;107:258–267.

[20] Slankamenac K, Graf R, Barkun J, Puhan MA, Clavien PA. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. Ann Surg 2013;258:1–7.

[21] Cloyd JM, Mizuno T, Kawaguchi Y, Lillemoe HA, Karagkounis G, Omichi K, et al. Comprehensive complication index validates improved outcomes over time despite increased complexity in 3707 consecutive hepatectomies. Ann Surg 2018;271:724–731.

[22] Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the international study group of liver surgery (ISGLS). Surgery 2011;149:713–724.

[23] Koch M, Garden OJ, Padbury R, Rahbari NN, Adam R, Capussotti L, et al. Bile leakage after hepatobiliary and pancreatic surgery: a definition and grading of severity by the International Study Group of Liver Surgery. Surgery 2011;149:680–688.

[24] Rahbari NN, Garden OJ, Padbury R, Maddern G, Koch M, Hugh TJ, et al. Post-hepatectomy haemorrhage: a definition and grading by the international study group of liver surgery (ISGLS). HPB (Oxford) 2011;13:528–535.

[25] Moore KP, Wong F, Gines P, Bernardi M, Ochs A, Salerno F, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003;38:258–266.

[26] Vilstrup H, Amodio P, Bajaj J, Cordoba J, Ferenci P, Mullen KD, et al. Hepatic encephalopathy in chronic liver disease: 2014 Practice guideline by the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver. Hepatology 2014;60:715–735.

[27] Lim C, Audureau E, Salloum C, Levesque E, Lahat E, Merle JC, et al. Acute kidney injury following hepatectomy for hepatocellular carcinoma: incidence, risk factors and prognostic value. HPB (Oxford) 2016;18:540–548.

[28] Lim C, Salloum C, Osseis M, Lahat E, Gómez-Gavara C, Compagnon P, et al. Short-term outcomes following hepatectomy for hepatocellular carcinoma within and beyond the BCLC guidelines: a prospective study. HPB (Oxford) 2017;20:222–230.

[29] Mehta R, Tsilimigras DI, Paredes AZ, Sahara K, Dillhoff M, Cloyd JM, et al. Dedicated cancer centers are more likely to achieve a textbook outcome following hepatopancreatic surgery. Ann Surg Oncol 2020;27:1889–1897.

[30] Merath K, Chen Q, Bagante F, Alexandrescu S, Marques HP, Aldrighetti L, et al. A multi-institutional international analysis of textbook outcomes among patients undergoing curative-intent resection of intrahepatic cholangiocarcinoma. JAMA Surg 2019;154:e190571.

[31] Merath K, Chen Q, Bagante F, Beal E, Akgul O, Dillhoff M, et al. Textbook outcomes among medicare patients undergoing hepatopancreatic surgery. Ann Surg 2020;271:1116–1123.

[32] Tsilimigras DI, Mehta R, Merath K, Bagante F, Paredes AZ, Farooq A, et al. Hospital variation in textbook outcomes following curative-intent resection of hepatocellular carcinoma: an international multi-institutional analysis. HPB (Oxford) 2020;22:1305–1313.

[33] Benchimol EI, Langan S, Guttmann A. Call to RECORD: the need for complete reporting of research using routinely collected health data. J Clin Epidemiol 2012;66:703–705.

[34] Lim C, Osseis M, Lahat E, Doussot A, Sotirov D, Hemery F, et al. Safety of laparoscopic hepatectomy in patients with hepatocellular carcinoma and portal hypertension: interim analysis of an open prospective study. Surg Endosc 2019;33:811–820.

[35] Llop E, Berzigotti A, Reig M, Erice E, Reverter E, Seijo S, et al. Assessment of portal hypertension by transient elastography in patients with compensated cirrhosis and potentially resectable liver tumors. J Hepatol 2011;56:103–108.

[36] Berzigotti A, Gilabert R, Abraldes JG, Nicolau C, Bru C, Bosch J, et al. Noninvasive prediction of clinically significant portal hypertension and esophageal varices in patients with compensated liver cirrhosis. Am J Gastroenterol 2008;103:1159–1167.
[37] Boleslawski E, Petrovai G, Truant S, Dharancy S, Duhamel A, Salleron J, et al. Hepatic venous pressure gradient in the assessment of portal hypertension before liver resection in patients with cirrhosis. Br J Surg 2012;99:855–863.
[38] Cucchetti A, Cescon M, Golfieri R, Piscaglia F, Renzulli M, Neri F, et al. Hepatic venous pressure gradient in the preoperative assessment of patients with resectable hepatocellular carcinoma. J Hepatol 2015;64:79–86.
[39] Shulman M, Myles P. Measuring perioperative outcome. Curr Opin Anaesthesiol 2016;29:733–738.
[40] Moonesinghe SR, Jackson AIR, Boney O, Stevenson N, Chan MTV, Cook TM, et al. Systematic review and consensus definitions for the standardised endpoints in perioperative medicine initiative: patient-centred outcomes. Br J Anaesth 2019;123:664–670.
[41] Barry MJ, Edgman-Levitan S. Shared decision making–pinnacle of patient-centered care. N Engl J Med 2012;366:780–781.
[42] Faitot F, Allard MA, Pittau G, iacio O, Adam R, Castaing D, et al. Impact of clinically evident portal hypertension on the course of hepatocellular carcinoma in patients listed for liver transplantation. Hepatology 2015;62:179–187.