Research Article

JOURNAL OF HEPATOLOGY

Hepatic venous pressure gradient in the preoperative assessment of patients with resectable hepatocellular carcinoma

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Backgrounds & Aims: To assess the relationship existing between hepatic venous pressure gradient (HVPG) and the occurrence of post-hepatectomy liver failure (PHLF) grade B/C after resection of hepatocellular carcinoma (HCC) and persistent worsening of liver function.

Methods: Data from 70 consecutive prospectively enrolled HCC patients undergoing resection were collected and analysed. PHLF grade B/C was defined by the International Study Group of Liver Surgery recommendations. The appearance of unresolved decompensation was also analysed.

Results: Postoperative and 90-day mortality were null. The median HVPG value was 9 mmHg (range: 4–18) and the median Model for End-stage Liver Disease (MELD) score was 8 (range: 6–14); 34 patients had an HVPG $\geqslant$10 mmHg (48.6%). Forty-nine patients had an uneventful (Grade A) postoperative course, including 17 with an HVPG $\geqslant$10 mmHg (24.2% of 70 patients). Grade B complications occurred in 20 patients (3 with an HVPG <10 mmHg and 17 with an HVPG $\geqslant$10 mmHg; p <0.001); only one grade C complication occurred in a patient with an HVPG <10 mmHg, subsequently successfully undergoing liver transplantation. Median MELD score returned to preoperative values after a transient postoperative increase, regardless of the HVPG values; after three months, it returned to the preoperative of 8 in patients with an HVPG <10 mmHg and of 9 in patients with an HVPG $\geqslant$10 mmHg (p = 0.077 and 0.076 at paired test, respectively).

Conclusions: The hepatic venous pressure gradient can be used before surgery to stratify the risk of PHLF but the proposed cut-off of 10 mmHg excludes approximately one-quarter of the patients who would benefit from surgery without short to mid-term postoperative sequelae.

Keywords: Portal hypertension; Hepatic venous pressure gradient; Hepatocellular carcinoma; Surgery; Survival.

Received 13 March 2015; received in revised form 17 August 2015; accepted 17 August 2015; available online 29 August 2015

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Abbreviations: HVPG, hepatic venous pressure gradient; HCC, hepatocellular carcinoma; PHLF, post-hepatectomy liver failure; MELD, Model for End-stage Liver Disease; PH, portal hypertension; EASL, European Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; CSPH, clinically significant portal hypertension; BCLC, Barcelona Clinic Liver Cancer; kPa, kilo-Pascal.

Introduction

Hepatocellular carcinoma (HCC) is the most frequent primary hepatic tumour in patients with liver cirrhosis [1]. Patients having well-compensated liver disease in the absence of clinically significant portal hypertension (PH) are considered optimal candidates for hepatic resection (HR), thanks to the very low risk of worsening of the postoperative liver function and excellent long-term survival [2]. Accordingly, the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) guidelines consider elevated PH to be a contraindication for resection due to the relatively higher risk of postoperative liver decompensation [1,3]. In particular, resection should be reserved for patients with very well-preserved liver function, defined as normal bilirubin with either hepatic venous pressure gradient (HVPG) <10 mmHg or platelet count $\geqslant$100,000 [1,3]. Measurement of the HVPG is considered the gold standard for assessing the presence of clinically significant portal hypertension (CSPH) whereas much debate still exists as to whether the indirect signs of PH, such as the presence of esophageal varices detected by endoscopy or splenomegaly (major diameter >12 cm) with a platelet count <100,000/mm^3, can be considered adequate predictors of PH severity in surgical series [4–8]. At present, the literature regarding the role of the HVPG in risk stratification for postoperative liver failure (PHLF) in HCC patients is surprisingly poor when compared with the weight of the guideline recommendations. In Eastern countries, evaluation for surgery is based on the indocyanine green retention rate (ICG-R) and, in Western countries, many, if not most, centers do not routinely perform venous pressure measurements [2,9]. The first reports regarding the HVPG in HR candidates were published in 1996 and 1999 by the Barcelona Clinic Liver Cancer (BCLC) group and included 29 and 43 surgical patients, respectively [10,11]. On the basis of these two seminal studies, the EASL and the AASLD wrote the current guidelines regarding the role of the HVPG in selecting candidates for resection. For more than a decade, no additional evidence was provided to support these findings [4]. In 2012, two prospective

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studies were published [8,12]; one of these was again from the BCLC group [12] and included a maximum of 46 resected patients having a maximum HVPG value of 12.5 mmHg [12]. Thus, at present there seems to be a great need for additional studies to strengthen the evidence of the current recommendations. The main aim of the present study was to investigate the usefulness of the HVPG in the risk stratification for PHLF, as defined in 2012 by the International Study Group of Liver Surgery (ISGLS) in the largest prospective cohort of patients enrolled to date. Residual mid-term liver function, previously defined as the appearance of unresolved decompensation [10–12], and the competing role of the MELD score as well as patient survival were analysed.

Methods and patients

From October 2009 to November 2014, 217 patients having HCC were resected at our centre. Of them, 70 patients with resectable HCC, with or without clinical signs of portal hypertension [6], prospectively enrolled, were offered and accepted to participate in this longitudinal observational study after approval by the local institutional review board. The observational nature of the study was explained to the patients, and informed consent was obtained in each case, according to the Declaration of Helsinki. The policy of our centre regarding HCC resectability and the role of liver function tests has already been published. Briefly, we consider patients as potential candidates for resection on the basis of the MELD score and, more recently, with the help of liver stiffness measurement to confirm the degree of liver fibrosis [13,14]. Briefly, we considered candidates, even for major hepatectomies, those patients having a liver stiffness value <15 kPa and a MELD score of 6–7; in patients having a MELD score $\geqslant$10 and/or liver stiffness value above 20 kPa, resection was proposed, and performed, only if a limited curative resection (with adequate future remnant liver volume) could be planned, and/or as a bridge therapy in the setting of a liver transplantation strategy [13,15]. In those patients with borderline MELD scores and/or liver stiffness values, we allowed the removal of not more than one/two segments but limited curative resection was always the preferred approach. The HVPG value alone was not considered as a determinant for refusing resection in our centre. Patient demographics, laboratory and radiological data, tumour pathology and operative data were collected for all subjects undergoing curative (R0) hepatectomy. None of the patients in the present study population underwent preoperative portal vein embolization. Intra-operative ultrasound was performed systematically in order to detect additional nodules not revealed preoperatively and to ascertain a tumour-free margin of at least 1 cm. During parenchymal transection, clamping manoeuvres was always adopted to control for bleeding; central venous pressure was maintained under 5–6 mmHg to prevent from bleeding from hepatic veins. Candidates for liver resection for recurrent tumours were excluded from the study. All 70 patients had chronic hepatitis with or without cirrhosis and belonged to Child–Pugh class A.

HVPG measurement

Patients underwent hepatic vein catheterisation within a maximum of three weeks before surgery. The procedures were performed by three experienced radiologists with at least ten years of expertise in this setting. Under local anaesthesia, a 7F venous catheter introducer was placed in the right basilic vein of the right forearm using the Seldinger technique. Thereafter, a 8.5–11 mm balloon-tipped catheter was advanced into the right hepatic vein to measure the wedged and the free hepatic venous pressures using an external electromechanical transducer and polygraph. The HVPG was calculated as the difference between the wedged and the free hepatic pressures, as previously described [16,17]. All measurements were carried out in triplicate as previously described [16,17].

Endpoints of the study

The main endpoint of the study was to assess the relationship existing between the HVPG and the development of PHLF grade B/C, immediately after resection as well as in the mid-term, as already previously reported and more recently suggested by expert opinions [4,10–12,18]. To this end, three months after HR, the patients were re-evaluated with a computed tomography scan and biochemical exams in order to detect tumour recurrence and to assess residual liver function [10–12]. The PHLF was defined here on the basis of the ISGLS recommendations, showing a good relationship with postoperative survival in recent series [19,20]. In particular, PHLF grade A corresponds to a substantial regular postoperative course whereas grade B results in a deviation from the regular clinical management but manageable without invasive treatment, and grade C results in a deviation from the regular clinical management requiring invasive treatment. A detailed report of postoperative complications was recorded during the postoperative course and has been presented here. The 50–50 criteria were also recorded [21]. Finally, overall survival was computed for completeness of results.

Statistical analysis

Continuous variables were expressed as medians and ranges, and the values in the different subgroups were compared using the unpaired Mann-Whitney test (for comparison between groups) or the paired Wilcoxon Signed Rank test (for comparison of postoperative MELD score course within groups). Categorical variables were expressed as prevalence, and the subgroups were compared using the Fisher's exact test. Overall survival was computed from the day of surgery until the death of the patient; liver transplantation and the last follow-up visit were treated as censoring events (end of observations: 1 May 2015). Differences in survival were investigated using the Kaplan–Meier estimate and the log-rank test. The accuracy of the HVPG in predicting PHLF grade B/C was assessed by measuring the area under the receiver operating characteristic curve (AUROC). Differences between AUROCs were compared using the Hanley-McNeil method. Positive and negative predictive values (PPV and NPV) for the HVPG cut-off point of $\geqslant$10 mmHg were calculated and reported. Relationships between MELD score, HVPG and liver stiffness values were investigated using both linear regression models and non-linear regression models. A significance level of 0.05 was used in all analyses. The statistical analysis was carried out using SPSS Version 13.0 software (SPSS, Chicago, IL) and MedCalc for Windows, version 12.5 (MedCalc Software, Ostend, Belgium).

Results

The entire study population had a median age of 62 years (range: 40–84) and a median MELD score of 8 (range: 6–14). All patients belonged to Child–Pugh class A. The HVPG measurement was successful in all 70 patients but two (2.9%) developed basilic vein thrombosis after the procedure which was treated with heparin with no delay in the surgical procedure. The median HVPG value was 9 mmHg (range: 4–18) and 34 patients had an HVPG $\geqslant$10 mmHg (48.6%). Baseline clinical characteristics of the entire study population, and of the subgroups according to the HVPG cut-off, are reported in Table 1. As expected, patients with an HVPG $\geqslant$10 mmHg had higher international normalized ratios (INRs) ($p = 0.025$), lower platelet counts ($p = 0.001$), higher prevalence of oesophageal varices at endoscopy ($p = 0.003$) and slightly higher MELD scores ($p = 0.010$); these patients also had smaller tumours ($p = 0.023$), had more frequently F4 fibrosis stage ($p = 0.003$) and more frequently underwent limited resections ($p = 0.013$) in comparison to patients with an HVPG <10 mmHg.

Postoperative complications

The postoperative (during in-hospital course) and 90-day mortalities were null. The median in-hospital stay was 8 days (range: 5–55). Forty-nine patients had an uneventful postoperative course (70.0%); of them, 17 had an HVPG $\geqslant$10 mmHg (24.2% of the 70 patients). Grade B complications occurred in 20 patients: three with an HVPG <10 mmHg (8.3%) and 17 with an HVPG $\geqslant$10 mmHg (50.0%; p <0.001). Only one grade C complication occurred in a patient having an HVPG <10 mmHg and this was the only case in which the 50–50 criterion on postoperative day 5 was fulfilled. This patient had a tumour burden within our transplantability criteria and underwent a right hepatectomy,