Hepatological Evaluation and Biomarkers

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Valerio Giannelli, Shirin Demma, Adriano Pellicelli, and Giuseppe Maria Ettorre

7.1 Introduction

Most patients with hepatocellular carcinoma (HCC) have underlying liver disease [1]. The need to predict the risk of post-hepatectomy liver failure (PHLF) should be of greater interest before performing a liver resection in a cirrhotic patient, especially if the indication is hepatocellular carcinoma (HCC), which can be treated with other options, including liver transplantation, thermoablation or effective palliative techniques, such as chemoembolization or radioembolization.

The task of the hepatologist, in supporting the surgical team, is to help in identifying the cirrhotic patient at greater risk of clinical decompensation of portal hypertension, up to the fearful development of postsurgical liver failure. In this chapter, we explain how the evaluation must go beyond the simple measurement of the well-known parameters of liver function. Over the past decade there has been substantial progress in hepatic resection for hepatocarcinoma (HCC) [2], which can be explained by a better selection of surgical candidates and improvement of pre- and postoperative management [3]. Nevertheless, liver failure after major resection in cirrhosis is still associated with high morbidity and mortality [4], and the fear of such complications therefore continues to limit the therapeutic possibilities of hepatic resection in patients with HCC. Liver surgery for hepatocellular carcinoma (HCC) remains limited by two major aspects: a sufficient remnant of liver volume

V. Giannelli (✉) · A. Pellicelli
Liver Unit, Department of Transplantation, San Camillo-Forlanini Hospital, Rome, Italy
e-mail: vgiannelli@scamilloforlanini.rm.it; apellicelli@scamilloforlanini.rm.it

S. Demma · G. M. Ettorre
General Surgery and Transplantation Unit, Department of Transplantation, San Camillo-Forlanini Hospital, Rome, Italy
e-mail: sdemma@scamilloforlanini.rm.it; gmettorre@scamilloforlanini.rm.it

G. M. Ettorre (ed.), *Hepatocellular Carcinoma*, Updates in Surgery,
https://doi.org/10.1007/978-3-031-09371-5_7

must be preserved [5] and, second, ischemic injury to remnant liver cells should be reduced as much as possible to minimize reperfusion injury. The threshold below which the liver remnant becomes insufficient depends on different variables, the most commonly proposed being age, etiologies of liver disease, grade of hepatic disease and portal hypertension, and hepatic functional reserve [6].

Age alone does not contraindicate liver resection. In previous studies on liver resection for HCC, the age of 70 years was reported as one of the negative predictive factors for postoperative survival. The most recent literature has, however, refuted this result and to date a careful selection of the elderly patient allows one to obtain survivals similar to those of younger patients [6].

7.1.1 Etiologies of Liver Disease: Metabolic-Associated Fatty Liver Disease

Among the different etiologies of liver disease, particular consideration in patients evaluated for liver resection should be given to hepatic steatosis, a constantly increasing cause of liver disease. Growing attention is being paid to advanced steatosis as it seems to compromise or delay liver regeneration after major resection. The risk of resection begins to increase in the case of steatosis involving more than 30% of hepatocytes [7]. Experimental data indicate that macro-type steatosis, rather than micro-steatosis, increases surgical risk. In cases of steatosis involving 30–60% of hepatocytes, larger resections should be carefully evaluated. In cases of steatosis >60% of hepatocytes, the resections should be limited (<2 hepatic segments and preferably an enucleation is advisable) [8].

In the case of a suspicion of advanced steatosis, it is recommended to perform a liver biopsy to exclude a critical burden of steatosis and eventually plan a preoperative medical treatment. The suspicion of hepatic steatosis should go beyond the simple external evaluation of body mass index or composition or the presence of diabetes, as demonstrated in a seminal study on liver resection in metabolic-associated fatty liver disease (MAFLD), where 31.9% of patients with hepatic steatosis did not show any signs of metabolic syndrome nor a history of alcohol abuse and were not treated with steatogenic chemotherapy (i.e., irinotecan) before liver resection [7].

In these patients, histological evaluation allows to assess the presence of non-alcoholic steatohepatitis (NASH) and the degree of fibrosis. Reddy et al. found that patients with NASH had higher 90-day overall mortality (56.9% vs. 37.3%; $p = 0.008$) and any hepatic-related morbidity (28.4% vs. 15.7%; $p = 0.043$), compared with corresponding controls. This includes a higher rate of postoperative hepatic decompensation (16.7% vs. 6.9%; $p = 0.049$) and a higher risk of post-hepatectomy liver insufficiency (6.9% vs. 2.0%; $p = 0.170$). On multivariable logistic regression, resection of four or more segments (OR 9.4; 95% CI: 4.1–21.5; $p < 0.001$), and NASH (OR 2.7; 95% CI: 1.0–6.1; $p = 0.016$) were independently associated with any hepatic-related morbidity. Hence liver inflammation is the key feature to include among the negative predictive factors of liver

resection outcome in patients with MAFLD [7]. A more recent study performed in an Asian cohort of patients also found that liver failure of all grades was higher in the MAFLD group compared with other etiologies (29.5% vs. 9.5% moderate liver failure, and 20.1% vs. 7.2% severe liver failure; $p < 0.0001$). Extrahepatic complications, such as cardiac disease (11.8% vs. 6.8%; $p = 0.02$) and pulmonary embolism (2% vs. 0.4%; $p = 0.01$) were also higher in the MAFLD group compared with other etiologies [9]. A drawback of these studies is the absence of a clear distinction between MAFLD and NASH.

7.2 Methods to Evaluate Liver Function and Hepatic Reserve Before Surgery

The safety of resective liver surgery in patients with cirrhosis has significantly improved in the last decade, but mortality related to surgery is still estimated between 3% and 15% [3]. Post-hepatectomy liver failure (PHLF) is the most feared complication, with a mortality rate of up to 50%. In this chapter, for the definition of PHLF we adopted the classification given by the International Study Group of Liver Surgery in 2011. According to this definition, the parameters to define the three grades (A, B, C) of PHLF are based on hepatic (INR/neurologic symptoms), renal (acute kidney injury criteria) and pulmonary function (arterial oxygen saturation) [10]. For convenience, we will use the definition of "mild" (INR between 1.5 and 2 + grade I–II of hepatic encephalopathy) or "severe" (INR > 2 + grade III–IV hepatic encephalopathy) to mean those PHLF in which there was a deviation from the regular clinical management without or with invasive treatment, respectively.

7.2.1 Predictors of Post-hepatectomy Liver Failure

Invasive portal pressure measurement is one of the most important and more concordantly evaluated indicators of outcome. Moreover, a hepatic venous pressure gradient (HVPG) >6 mmHg indicates the presence of cirrhosis more accurately than liver histology [11]. Also in the case of compensated cirrhosis without esophageal varices, a further stratification is warranted, based on the measurement of portal pressure, which is most commonly assessed by the invasive (transjugular) measurement of HVPG, consisting of the difference between the wedged (or balloon-occluded) hepatic venous pressure and the free hepatic venous pressure. The HVPG accurately reflects portal pressure in sinusoidal causes of portal hypertension [12]. Although it is fairly easy to perform and safe, accurate measurement requires specific training [13]. For this reason, the number of studies conducted to assess the role of the HVPG as a prognostic factor are also limited in number, although the conclusions are fairly solid and concordant [14, 15]. The stratification of compensated cirrhosis has also been based on the HVPG results, with HVPG between 5 and 10 mmHg indicating mild portal

hypertension and above 10 mmHg indicating a clinically significant portal hypertension (CSPH) at risk of ascites, encephalopathy, jaundice and varices [12].

The first reports on HVPG assessment before liver resection were published in 1996 and 1999 by the Barcelona Clinic Liver Cancer group and included a small series of patients applying for hepatic resection (29 and 43 patients, respectively) [12]. Based on these two studies, the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) recommended in their guidelines the use of HVPG in the selection of hepatic resection candidates (indicating HVPG < 10 mmHg and normal bilirubin as key positive predictors of survival in patients undergoing resection). More recently, a French multicenter study on more than 300 patients confirmed that among the 20 patients with PHLF, HVPG was a strong independent predictor of worse outcome. PHLF was 8.3 vs. 50% (p = 0.001) if HVPG was below or above 10 mmHg, respectively. However, the latest published EASL HCC guidelines mitigate the role of HVPG > 10 mmHg as a contraindication to surgery, and suggest that the role of portal hypertension in deciding on eligibility for resection of HCC should not be absolute but always balanced with the extent of hepatectomy and liver function indicators [16]. We also believe that resection decisions must also be taken on the basis of the localization of the hepatic nodule; for instance, the posterior sectors are burdened with greater technical difficulties [17]. The predictive value of HVPG is further enhanced when combined with the MELD score, using for the latter the value of 10 as a cut-off. In patients with HVPG ≥ 10 mmHg but with a MELD score <10, severe PHLF occurred in 14.3% of cases when an enucleation was performed, whereas this percentage increased up to 66.7% in cases of more extended hepatectomies (more than 2 segments).

In patients with an HVPG > 10 mmHg and MELD ≥10, severe PHLF occurred in 87.5%, even in the case of limited resections. Less than 20% of the patients enrolled experienced a normal and uneventful postoperative course in spite of having a pressure gradient ≥10 mmHg [13]. Therefore, the most appropriate approach to avoid excluding patients who might otherwise benefit from a curative HCC resection, or who might otherwise take too high a surgical risk, is to use a multiparametric algorithm as the one recently proposed by Citterio et al. and then endorsed by EASL [18]. According to this hierarchical interaction (portal pressure + extent of resection + MELD score), HVPG > 10 mmHg or indirect evidence of CSPH are no longer an absolute contraindication for HCC resection in patients with cirrhosis, if MELD is below 10 and the resection limited. Other studies which included patients with HVPG > 10 mmHg found an acceptable risk of PHLF of about 5–30%, with an acceptable 36-month survival (about 75%) [19]. In the case of HVPG > 10 mmHg, we should select those with a good performance status (PS 0–1), with preserved liver function (MELD <10), and without any sign of clinical decompensation of liver cirrhosis (only Child A5–6), including the absence of esophageal varices.

7.2.2 Biomarkers and Dynamic Test to Recognize Liver Function and Its Reserve Capacity

Among the various biomarkers used to investigate liver function, certainly the most validated are bilirubin values preresection and coagulation status. The use of hepatic clearance of indocyanine green (ICG) has been widely used in Asian countries for surgical decision making. ICG is a dark bluish-green tricarbocyanine dye that rapidly binds to plasma lipoprotein and is metabolized completely and solely by hepatocytes. ICG clearance can be measured by giving a single intravenous injection (around 0.5 mg/kg) and determining the blood level 15 min later (ICG-R15) [14]. The normal values of the ICG-R15 range between 8% and 14%. Patients with clearance kinetics of less than 14% are considered fit for major hepatectomy, whereas those with >20%, a major hepatectomy should be not recommended. According to some authors, in patients with a retention between 14% and 20%, surgery should be proposed only if the liver remnant is >50% [5]. ICG can be measured directly by using a fingertip optical sensor, which allows a continuous measurement of serum ICG concentration [12]. Much of the experience of using ICG before surgery comes from studies conducted on Asian patients, with a high prevalence of early HBV-related cirrhosis. Makuuchi et al. in a seminal study conducted on a large sample of Asian patients proposed an algorithm based on ICG-R15, ascites, bilirubin levels and the extent of liver resection [20]. However, in a recent French multicenter study on 343 patients, applying the Imamura and Makuuchi criteria, as many as 13 patients would not have been candidate for resection surgery due to a high estimated risk of PHLF, while in the French experience 92% of them were alive at the surveillance after 3 months [15].

7.2.3 MELD Score

Another algorithm to assess the operational risk, elaborated with the intention of having a quick and simple evaluation tool, is based on the use of MELD <10, associated with natremia for those with MELD 9–10. In an external validation, also this algorithm failed its reproducibility.

7.2.4 Fibrosis Biomarkers and Noninvasive Evaluation of Portal Hypertension

With regard to fibrosis biomarkers, no study conducted so far has shown a correlation between their serum levels and the development of clinically significant portal hypertension. Platelet counts also have less than 0.75 accuracy at the AUROC (area under the receiver operating characteristic) curve.

On the other hand, noninvasive tests are increasingly being used to improve prediction of CSPH. Liver stiffness measurement (LSM) is the most validated test for indirect portal pressure measurement, although its correlation with HVPG is not

excellent (AUROC 0.67–0.86) [21]. Our advice is to use, in order to assess patients at risk of HVPG > 10 mmHg a cut-off of LSM equal to 20–25 kPa (AUROC 0.93 for CSPH) [22]. Spleen elastometry (SEM) has been tested in a more limited number of studies, but a cut-off <40 kPa is highly sensitive (98%) to rule out HVPG > 10 mmHg, while SEM > 50 kPa is 90% specific for CSPH. The liver surface nodularity (LSN) score performed at CT or ultrasound [23] predicts HVPG > 10 mmHg in 88%. While the diameter of the spleen as well as that of the portal vein have a lower accuracy. A recent portal hypertension score has been proposed to combine LSM and LSN to improve the detection reliability for CSPH to more than 75% [24].

7.3 Conclusion

In accordance with the recent EASL guidelines on noninvasive liver disease severity and prognosis evaluation methods, we believe that HVPG remains the only validated tool for an exact assessment of portal hypertension severity and cannot be substituted by noninvasive techniques [25].

In conclusion, none of the proposed algorithms based on biomarkers of liver function has entered routine surgical practice. Clinicians and surgeons engaged in resective liver surgery know that portal hypertension is the most important prognostic factor associated with PHLF. In consideration of the logistic difficulty to perform invasive portal pressure measurement on all surgical candidates, our idea is to first study patients with noninvasive methods and to refer to a center with a hepatic hemodynamics team those at high risk of clinically significant portal hypertension. Liver function should obviously not be neglected but integrated in a multiparametric consideration, bearing in mind that in patients with bilirubin between 27 and 33 mmol/L or MELD scores about 10 and portal hypertension, surgical consideration should not be denied *a priori*. A short delay of surgical resection, allowing better clinical management, is recommendable in these cases.

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