Indications for Surgery in Cirrhotic Patients

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10.1 Introduction

Liver resection (LR) still remains one of the main curative options for hepatocellular carcinoma (HCC). When HCC is diagnosed in the cirrhotic liver, the indication for LR should be carefully established. The assessment of such patients should not consider only tumor burden, but must also necessarily include an accurate evaluation of the preoperative liver function to reduce the risk of the most feared complication following LR, that is, post-hepatectomy liver failure (PHLF). PHLF represents the most important cause of postoperative 90-day mortality and is the most commonly used measure to assess the early postoperative outcome. The evaluation of liver function includes assessment of functional reserve of the cirrhotic liver, presence of portal hypertension, extent of LR, volume of functional remnant liver (FRLV), patient performance status and comorbidities. Furthermore, LR should be carefully evaluated against liver transplantation, when this can be a chance of cure, and other potentially curative therapies such as ablation.

10.2 Hepatic Functional Reserve Assessment

Several tools are available to evaluate liver function and to stratify the risk of PHLF, but there is no general agreement on the best to be used worldwide.

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10.2.1 Child-Turcotte-Pugh Score

The Child-Turcotte-Pugh score is frequently used because it is a simple system including five easily available variables. In the majority of Western [1, 2] and Eastern guidelines [3] there is a wide consensus that patients with cirrhosis Child-Pugh A are good candidates for LR. However, PHLF may occur also in Child-Pugh A patients [4], because the score does not capture different levels of liver function in the same class of patients. This drawback, defined as the "floor effect" [4], is often associated with the use of the Child-Pugh score, which usually works better in patients with decompensated cirrhosis than in patients with preserved liver function where identifying those with elevated risk of PHLF is crucial.

10.2.2 Model for End-Stage Liver Disease

The model for end-stage liver disease (MELD), developed to predict survival following transjugular intrahepatic portosystemic shunt procedure, is another easily available tool that is effective in predicting PHLF, but once again it has limited capacity for risk stratification in patients not affected by end-stage cirrhosis. Recent evidence has shown that good candidates for LR should have a MELD score $\leq$10 and therefore it was recently included in the European Association for the Study of the Liver (EASL) guidelines, with Child-Pugh score, for treatment allocation [2, 5, 6]. Indeed, above this cut-off the reported morbidity rate reached 50%, with an unacceptable risk of irreversible PHLF (up to 15%) [5, 6].

10.2.3 Indocyanine Green Clearance Test

More accurate liver function evaluation can be obtained with the use of other tests, including the indocyanine green (ICG) clearance test, widely used in Asia. It is a dynamic method for studying liver function. It evaluates the hepatic clearance of indocyanine green 15 min after intravenous administration (ICG-R15) [7, 8]. The safe cut-off ICG retention rate at 15 min, which allows major hepatectomy, is around 10% [9]. A decision algorithm developed by Makuuchi guides the extent of hepatectomy. Three variables are included: ascites, serum total bilirubin level and ICG-R15 [9]. The presence of ascites with serum total bilirubin level $\geq$2 mg/dL is an absolute contraindication for LR. In patients without ascites and normal serum total bilirubin level, the extent of LR is planned according to the ICG-R15 value: major LR should only be performed in patients with ICG-R15 <10–20%, and limited LR when ICG-R15 is <40% [9]. Therefore the ICG-R15 may be useful for guiding the extent of LR and for stratifying the risk of PHLF in Child-Pugh A patients.

10.2.4 Other Liver Function Scoring Systems

Other scoring systems have been proposed to overcome the limitations of the Child-Pugh classification. These are used in different centers, according to different local expertise levels and protocols. These include: the aspartate transaminase-to-platelet ratio index (APRI) score [10], the albumin-bilirubin (ALBI) score [11], the albumin-indocyanine green evaluation (ALICE) score [12] and the bilirubin-cholinesterase (BILCHE) score [13].

10.2.5 Evaluation of Portal Hypertension

According to the EASL guidelines [2], clinical signs of portal hypertension (PH) include the presence of esophageal varices, or splenomegaly (diameter >12 cm) and platelet count <100,000/mm^3. Non-invasive assessment of fibrosis grade by liver stiffness measurement with transient elastography is an additional effective tool for assessing the degree of PH, which has gained more clinical diffusion than invasive measurement of HVGP. The degree of liver stiffness may identify patients at risk of PHLF, with a significant risk of PHLF being predicted by liver stiffness >12–14 kPa [14]. The presence of PH is a significant prognostic factor affecting postoperative outcome [2]. In such patients the risk of PHLF following major LR is >30% with a 90-day postoperative mortality reaching 25%. However, PH in itself should not be considered an absolute contraindication to LR if liver function is preserved. In selected Child-Pugh A patients, with PH and well-compensated cirrhosis, limited LR can be performed with competitive survival outcomes [15–17]. For this reason, the role of PH in evaluating the indication for LR should always be balanced with the extent of resection and liver function tests.

10.2.6 Extent of Liver Resection and Functional Remnant Liver Volume Evaluation

A critical issue is the FRLV following LR. A computed tomography (CT)-based volumetric assessment is generally used to evaluate the FRLV; a value ranging from 40% to 50% may be considered the safe limit for LR in the cirrhotic liver to prevent severe PHLF [18] (Figs. 10.1, 10.2 and 10.3). For this reason, strategies to increase FRLV or reduce the HCC and expand resectability have been developed: portal vein embolization (PVE) (Fig. 10.1); preoperative transarterial chemoembolization (TACE) alone (Fig. 10.2), or followed by PVE [19]; combined hepatic vein embolization and PVE (liver venous deprivation) [20]; radioembolization with yttrium-90 microspheres [21]; portal vein ligation for staged hepatectomy (ALPPS) procedure [22].

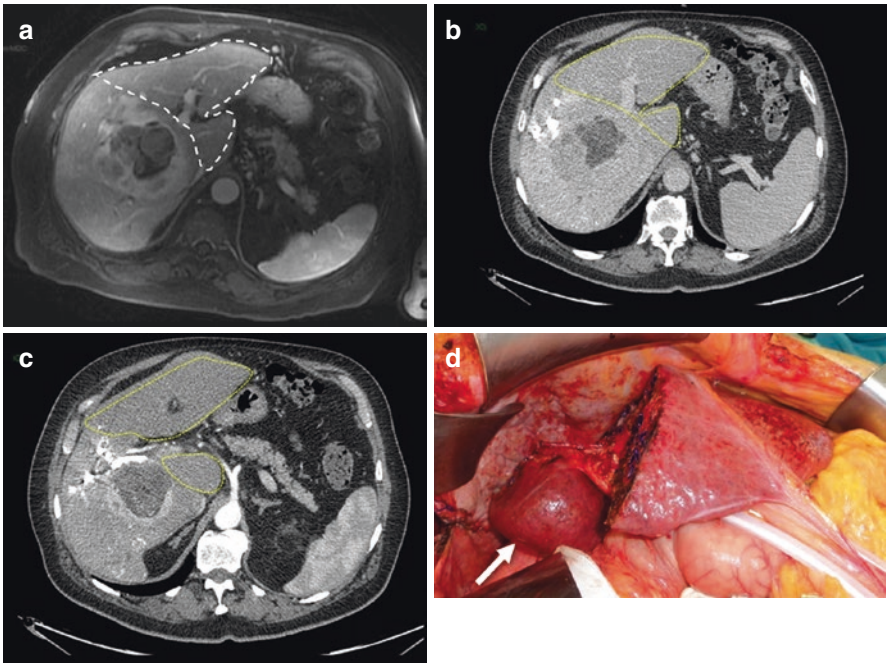

Fig. 10.1 Sixty-six-year-old male. (**a**) CT scan: large hepatocellular carcinoma on non-alcoholic fatty liver disease-related cirrhosis. Indication for right hepatectomy; small functional remnant liver volume (FRLV) (32%). (**b**, **c**) CT scan after right portal vein embolization: FRLV 43%. (**d**) Right hepatectomy. Note the caudate lobe hypertrophy (white arrow)

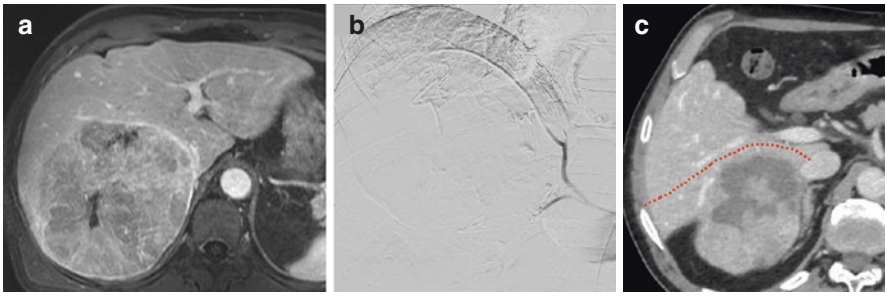

Fig. 10.2 Seventy-year-old male. (**a**) CT scan: large right lobe hepatocellular carcinoma. (**b**) Selective transarterial chemoembolization (TACE). (**c**) CT scan after TACE: tumor shrinkage and partial necrosis. Indication for right posterior sectionectomy (S6–S7)

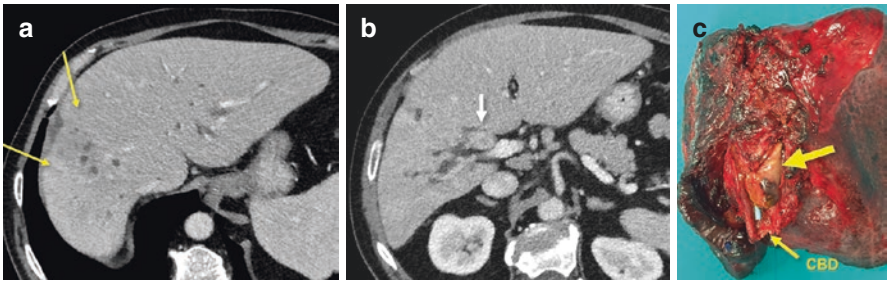

Fig. 10.3 Sixty-two-year-old male. (**a**) CT scan showing a large infiltrative right lobe hepatocellular carcinoma (arrows). (**b**) Biliary thrombosis (white arrow). (**c**) Specimen after right hepatectomy with left hepaticojejunostomy; endobiliary tumor thrombus (thick arrow)

10.3 Indications According to Tumor Stage, Survival Benefit, and Technical Considerations

Accurate tumor staging is crucial to evaluate the indication for LR. The Barcelona Clínic Liver Cancer (BCLC) staging system is one of the most widely used in Western countries [2]. It provides a survival benefit-based treatment algorithm, associated with a prognostic staging system consisting of four variables: tumor burden, degree of liver function, general condition of the patient and treatment efficacy. According to the BCLC system, LR is restricted to a selected group of patients without PH, with very early (single nodule <2 cm) or early (tumors within the Milan criteria: single nodule ≤5 cm or 2–3 nodules ≤3 cm) tumor stage (BCLC stage 0–A). However, this type of treatment algorithm may prove rigid, as it gives only one treatment option for each tumor stage and it is not open to treatment alternatives [23]. This algorithm is not regularly followed in real-life clinical practice throughout the world. In fact, several studies have shown a potential role of surgery also for patients with large multinodular and macrovascular invasive HCC, classified as BCLC stage B/C, or with biliary invasion (Fig. 10.3). A recent multicenter study [24] reported that about 50% of patients with intermediate or advanced stage HCC (BCLC stage B/C) are routinely treated with LR in tertiary referral centers worldwide. Furthermore, the study showed that the 5-year overall survival (OS) of BCLC stage B/C patients following LR was 57% and 38%, respectively.

Based on these observations, with the aim of improving the accuracy of treatment indications for HCC in cirrhotic patients, the concept of "therapeutic hierarchy" strategies has been proposed, which introduces a relative independence between the choice of treatment and the stage of disease [23]. This allows us to tailor the indications to the single patient and avoid the risk of undertreatment with the rigid application of a simple stage-linked treatment algorithm. However, the decision of the first treatment is complex because it requires consideration of several factors that can only be evaluated within a multidisciplinary dedicated team of experts.

As regards the indication for LR, from the technical point of view, one significant improvement was the introduction and wide diffusion of minimally invasive LR for HCC in cirrhotic patients: currently, HCC is the most frequent indication for a laparoscopic LR [25]. The advantages of minimally invasive surgery are particularly significant in cirrhotic patients, with overall better perioperative outcomes than open surgery, and in particular with a lower incidence of PHLF and of postoperative ascites. This has made it possible to consider the extension of surgical indications to selected Child B patients [26]. Furthermore, the significantly reduced surgical risk of laparoscopic LR for HCC in cirrhotic patients, particularly for small HCC, allows reappraisal of the competitive indications between ablation and surgery, in favor of resection. Laparoscopic LR also has a significant role in patients with indications for liver transplantation, as a bridge treatment before transplant, with advantages relating not only to limited postoperative adhesions but also to the possibility of obtaining relevant prognostic information from the surgical specimen before a definitive indication for transplantation.

10.4 Need for a Multidisciplinary Evaluation in High-Volume Centers

It should be highlighted that the indications for LR in cirrhotic patients should be assessed in a multidisciplinary setting in high-volume centers, where the presence of experienced liver and transplant surgeons, hepatologists, anesthesiologists, interventional radiologists and endoscopists, specialized dietitians together with dedicated intensive care unit and high-level nursing care, may all contribute to prevent mortality following LR. Recent advances in surgical technique, patient selection, and perioperative management have contributed to decrease the postoperative mortality rate to <5% in most centers following LR for HCC. However, although reduced by accurate patient selection, the occurrence of postoperative complications, may be unavoidable even in high-volume centers. A new parameter proposed to assess the quality of care during hospitalization is failure to rescue (FTR), defined as the probability of postoperative death among patients with a major complication. FTR reflects the ability to rescue a patient with a major complication from the risk of death. FTR has been shown to decrease significantly with increasing hospital volumes. A recent multicenter Italian study [27] on 1935 patients undergoing resection, showed that the risk of major complications and mortality was related to comorbidities, cirrhosis severity, and complexity of surgery, but these factors were not correlated with FTR. Indeed, the center's volume was the only independent predictor related to severe complications, mortality, and FTR. In other words, the ability to rescue a patient from a major complication was strictly correlated with the center's volume and was significantly lower in high-volume centers. Centralization could be one prerequisite for proper indications and improved outcomes following LR for HCC.

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