

# Liver resection for hepatocellular carcinoma in patients with portal hypertension: the role of laparoscopy

Andrea Belli<sup>1</sup>, Luigi Cioffi<sup>2</sup>, Gianluca Russo<sup>2</sup>, Giulio Belli<sup>2</sup>

<sup>1</sup>Division of Surgical Oncology, Department of Abdominal Oncology, "Istituto Nazionale Tumori Fondazione G. Pascale"-IRCCS, Naples 80131, Italy; <sup>2</sup>Department of General and Hepato-Pancreato-Biliary Surgery, S. M. Loreto Nuovo Hospital, Naples 80142, Italy

Correspondence to: Andrea Belli, MD. Division of Surgical Oncology, Department of Abdominal Oncology, "Istituto Nazionale Tumori Fondazione G. Pascale"-IRCCS, Naples 80100, Italy. Email: a.belli@istitutotumori.na.it.

**Abstract:** Liver resection (LR) for hepatocellular carcinoma (HCC) in patients with chronic liver disease (CLD) is a major issue since patients are at risk of serious intraoperative and postoperative complications. The current EASL/AASLD guidelines recommend LR only in case of patients with stage A HCC with well-preserved liver function and consider the presence of portal hypertension (PHT) as a contraindication to surgery. Nevertheless, the literature on this topic is conflicting. Recently several studies reported that favorable outcomes can be achieved with a careful patients' selection in high volume centers. Laparoscopic LR, when performed by well-trained surgeons and with appropriate indications, proved to be a valid option for the surgical treatment of HCC on cirrhosis offering similar oncologic outcomes but a reduction in surgical related morbidities. Laparoscopic LR thanks to a reduction in the incidence of post-operative liver failure and ascites development in comparison to standard open LR could, in selected cases challenge alternative treatments in the treatment of HCC patients with preserved liver function and clinical signs of mild PHT.

**Keywords:** Laparoscopic; liver resection (LR); hepatocellular carcinoma (HCC); portal hypertension (PHT); cirrhosis

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## Introduction

Liver cancer is one of the leading causes of cancer death worldwide accounting for an estimated 745,500 deaths occurred during 2012 (1). Hepatocellular carcinoma (HCC) which is by far the most common primary liver malignancy has an increased incidence in patients with chronic liver disease (CLD), mostly owing to hepatitis B or C infections (2). Liver transplantation is a potentially curative treatment for HCC in patients with underlying CLD, but it cannot be applied on a large scale for several reasons (3). Therefore, other therapeutic options such as hepatic resection, percutaneous ablation techniques, transarterial chemoembolization (TACE) or systemic chemotherapy are widely applied worldwide. The choice of the optimal treatment has to be tailored on the single patient condition taking into account not only the oncologic

staging and perspective but also the degree of CLD and hepatic decompensation. In fact, patients affected by CLD are at higher risk for development of harmful post-therapies complications (4-7). Liver resection (LR) still retains a paramount role in the curative strategy of HCC in patients with an adequate liver function but the current European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Diseases (AASLD) guidelines recommend LR as preferred treatment only in case of early stage (A) single nodule of HCC in patients without signs of portal hypertension (PHT) or a bilirubin level higher than 1 mg/dL (8,9). In patients affected by CLD the development of PHT is strictly related to the degree of liver cirrhosis and its presence can complicate HCC treatment by increasing the risk of hemorrhage and liver failure. In fact, resected patients with

PHT are at higher risk of liver failure, varices rupture, and coagulation disorders caused by thrombocytopenia (7). These are all factors that can complicate the postoperative outcomes and minimize the efficacy of LR compromising the survival outcomes. Nevertheless, the literature is conflicting in considering the presence of PHT as an absolute contraindication to LR.

### Current role of liver resection (LR) in patients with portal hypertension (PHT)

In Western countries the presence of PHT is widely considered as a contraindication to LR in case of HCC, on the contrary, in the East the presence of PHT is not considered as an absolute contraindication to LR and various authors demonstrated that a low rates of postoperative mortality and morbidity can be achieved if a careful preoperative liver function evaluation is performed (10,11). The EASL/AASLD guidelines are based on the Barcelona group studies (12,13) of very small sample size and are in contrast with the result of many recent studies, also coming from Western centers. In fact, several reports coming from tertiary referral centers with an high grade of expertise in the surgical treatment of HCC demonstrated that in case of cirrhotic patients with PHT and a preserved liver function, classified by the Child-Pugh or Model for End-stage Liver Disease (MELD) score or on the basis of indocyanine green retention test (ICGR 15) value, surgical resection of up to two segments can offer similar long term outcomes when compared to those of resected patients without PHT (14-19). Furthermore, it has been reported that, when performing LR, the presence of an hepatic venous pressure gradient (HVPG)  $\geq 10$  mmHg was associated to liver failure and mortality while clinical indirect signs of PHT were not (20,21). The study by Santambrogio *et al.* also demonstrated that patients with clinically significant PHT and preserved liver function (Child-Pugh A5 class) can undergo LR with the best chances of long-term survival without postoperative impairment of liver function (22). Finally, the results of two multicenter retrospective studies collecting a huge number of patients operated in different continents give strength to the need for a re-discussion on the role of PHT as absolute contraindication to LR.

The first study by Torzilli *et al.* (23) collected 2,046 patients (10% with F1 to F3 esophageal varices) and demonstrated the safety and the benefit of LR in selected patients classified as Barcelona Clinic Liver Cancer (BCLC) B and C stage even in case of PHT. The

BRIDGE study (24) collected 8,656 patients (3,103 with PHT) and demonstrated that in patients submitted to OLR the presence of PHT alone (defined as the presence of either splenomegaly, platelet count  $<100,000/\mu\text{L}$  or varices) without ascites had no statistically significant impact on survival outcomes when compared to optimal candidate to open LR without signs of PHT. Indeed, the EASL/AASLD guidelines define the presence of PHT as the measurement of an HVPG  $\geq 10$  mmHg. Unfortunately, HVPG measurement needs technical expertise and is an invasive procedure which is not widely performed in clinical practice worldwide. Therefore, the presence of clinical signs is widely adopted as surrogates for the diagnosis of PHT. The EASL/AASLD guidelines seem to be able to select the best candidates for resection and to allocate to different treatments non-optimal patients, nevertheless there is possibly a room to expand the indication for LR to patient with moderate clinical signs of PHT.

### Potential role of laparoscopic liver resection (LR)

In the decision making process guiding the choice of the appropriate treatment for HCC when considering LR nowadays clinicians have to take into account also the possibility to consider the option of laparoscopic LR. In fact, laparoscopic LR is now offered to patients, with selected indications, in many centers worldwide. HCC, which mainly occurs on the background of liver cirrhosis, is by far the most reported indication for laparoscopic LR in case of malignancy (25). This is probably due to the fact that the benefit of a minimally invasive approach seems to be more pronounced in case of cirrhotic patients. In fact, laparoscopic LR can offer additional benefit if performed in patients affected by CLD and cirrhosis by minimizing abdominal wall trauma, liver compression-manipulation and extensive liver mobilization (often no need for transection of the round ligament and the re-canalized umbilical vein or other liver suspensory ligament). These are all factors that allow to preserve collateral blood and lymphatic circulation and reduce the risk of postoperative liver failure, the development of postoperative intractable ascites (which can be per-se a life treating complication) and the rate of overall postoperative morbidity. From an analysis of the literature 21 comparative studies (26-46) focused on the comparison of open and laparoscopic LR for HCC are currently available in the English literature (47) and 11 of them analyzed post-operative ascites development and reported a reduction in its incidence associated to laparoscopic

LR. Interestingly in the study by Truant *et al.* (39), including patients affected by PHT, despite similar magnitude of LR and PHT levels patients operated on by laparoscopy showed lower morbidity and mortality in terms of severe complications related to ascites than patients operated by open approach (0% *vs.* 33% death rate) without differences in 5-year, disease-free and overall survival (OS). In addition, from the cooperative effort done in 2014 at the second international consensus conference on laparoscopic liver surgery held in Morioka-Iwate, the most updated and comprehensive systematic review and meta-analysis available in the literature (48) has been recently published highlighting a reduction in both postoperative liver failure and post-operative ascites development in case of laparoscopic LR performed for HCC complicated by CLD. From an oncologic perspective has been also demonstrated that stratifying patients for factors well known to relate with outcomes, when compared to standard open LR, laparoscopic LR for HCC on cirrhosis can offer similar long-term oncologic outcomes both in term of OS and recurrence free survival (RFS) (32,49). This has been confirmed by the meta-analysis by Morise *et al.* (48) and Xiong *et al.* (50) which did not find any difference in the oncologic outcomes between open and laparoscopic LR. The latter meta-analysis also examined ascites development and postoperative liver failure after laparoscopic LR and reported reduced incidences of both when compared to open LR for the treatment of HCC complicated by CLD.

Finally, although LR resection is strongly challenged by alternative treatment such as tumor ablation and TACE especially in terms of overall morbidity, recently new evidences on the treatment of HCC in patients with PHT appeared in the literature. In the study by Faitot *et al.* (51) the authors observed, on explanted specimens of patients submitted to liver transplant, a reduction in the efficiency of TACE (a 3-fold lower pathological response rate) in patients with PHT when compared to patients without PHT. This data raise questions on the appropriateness of TACE as preferred option in case of patients with PHT and otherwise suitable to minor laparoscopic LR which can offer a complete tumor removal with a reduced incidence of post-operative liver failure and ascites formation in comparison to open LR. In addition the study by Qiu *et al.* (52) demonstrated that when comparing by a propensity score matching analysis the outcomes of LR and tumor ablation in hepatitis B virus-related HCC patients with PHT, LR proved to offer a consistent survival benefit without increasing the incidence of grade II-IV complications

(Clavien-Dindo classification). Therefore, laparoscopic LR more than alternative should be probably considered complementary to percutaneous ablation in the treatment of early HCC even in case of PHT. When adequate expertise in both open and minimally invasive liver surgery are available laparoscopic LR could be offered to patients deserving minor resections of peripherally located lesions, while percutaneous ablation could be preferred in case of small deeply located HCC. In fact, in case of peripherally located lesions percutaneous ablation can carry a high risk of tumor seeding while laparoscopic LR can be safely carried out in dedicated centers and can offer the possibility of an accurate pathological and genetic assessment of tumor biology and surrounding liver parenchyma which could drive in a near future more tailored approaches.

Therefore, even if patients with preserved liver function and PHT would not be considered as optimal candidates for LR by the current EASL/AASLD guidelines, in a single patient perspective surgery could probably still offer the best survival outcomes than any other available treatment option in selected cases. In conclusion from an analysis of the currently available literature it seems that at least a proportion of patients with HCC and clinical signs of mild PHT can be offered LR expecting good results and that when technically feasible laparoscopic LR should be considered as a viable option. Laparoscopic LR thanks to a reduction of post-operative liver failure and ascites development in comparison to standard open LR could, in selected cases challenge alternative treatments in the treatment of HCC patients with preserved liver function and clinical signs of mild PHT. A dedicated randomized controlled trial or a multicenter collection of cases would be advisable in order to investigate the role of laparoscopic LR in this clinical setting.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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