Chapter

# Laparoscopic Liver Resection for Hepatocellular Carcinoma

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## Abstract

Hepatocellular carcinoma (HCC), remains one of the most common causes of cancer-related death globally. HCC typically arises in the setting of chronic liver disease and cirrhosis and as such, treatment must be balanced between the biology of the tumor, underlying liver function and performance status of the patient. Hepatic resection is the procedure of choice in patients with high-performance status who harbor a solitary mass (regardless of size). Before the first laparoscopic hepatectomy (LH) was described as early as 1991, open hepatectomy (OH) was the only choice for surgical treatment of liver tumors. LH indications were initially based solely on tumor location, size, and type and was only used for partial resection of the anterolateral segments. Since then, LH has been shown to share the benefits of other laparoscopic procedures, such as earlier recovery and discharge, and reduced postoperative pain; these are obtained with no differences in oncologic outcomes compared to open resection. Specific to liver resection, LH can limit the volume of intraoperative blood loss, shorten portal clamp time and decrease overall and liver-specific complications. This chapter will offer an overview of standard steps are in pursuing laparoscopic liver resection, be it for a minor segmentectomy or a lobectomy.

**Keywords:** hepatocellular carcinoma, resection, laparoscopic, technique

## 1. Introduction

Despite advances in medical, surgical and locoregional therapies, hepatocellular carcinoma (HCC), the most common primary liver cancer, remains one of the most common causes of cancer-related death globally. Hepatocellular carcinoma is the fifth most common frequently occurring cancer in men, the ninth in women and is the second leading cause of death from cancer worldwide. It is estimated that by 2025 more than 1 million individuals will be affected by liver cancer annually.

HCC typically arises in the setting of chronic liver disease and cirrhosis. In fact, the rate of disease occurrence depends upon the complex interplay between the host, disease and environmental factors. This type of liver cancer contributes to up to 40% of all patient deaths in cirrhosis, making it the single most common cause of death in this patient population. The most prominent and well researched risk factors for HCC are Hepatitis B and C infections, accounting for 50% of all cases. Furthermore, there is a clear geographical distribution in the epidemiology of hepatocellular carcinoma, with the highest incidence seen in developing countries with high rates of chronic hepatitis B and aflatoxin exposure. In contrast the lowest incidence rates are seen in some European countries that also have a lower incidence of the before mentioned risk factors. Interestingly, increasing Hepatitis B vaccination, effective Hepatitis C treatment, reducing levels of aflatoxin exposure are now shifting the global epidemiology of HCC. Metabolic disorders, including Non-Alcoholic Steatohepatitis (NASH) and diabetes mellitus, along with obesity and insulin resistance, are now emerging as direct causative factors of HCC, particularly in the West. These evolving patterns of demographic and epidemiologic characteristics bear interesting implications in the diagnosis and management of patients with HCC [1–4].

## 2. Management

Cirrhosis patients should be followed within surveillance programs, that aim for early detection of suspicious nodules and effective treatment. Diagnosis of HCC is achieved with imaging and corroborated with an increased tumor marker alpha-fetoprotein blood (AFP) testing. Percutaneous biopsy is seldomly required for diagnosis.

HCC treatment in the setting of liver cirrhosis must be balanced between the biology of the tumor, and host characteristics such as the underlying liver function, presence or not of portal hypertension and ECOG status of the patient. When evaluating a patient for resection, the functional liver remnant must be carefully assessed and its adequate vascular inflow and outflow ascertained, along with biliary drainage. In the event of marginal functional liver remnant, portal vein embolization should be entertained to decrease the possibility of post-operative liver failure.

The most common staging systems for HCC include the Barcelona Clinic Liver Cancer (BCLC), Cancer of the Liver Italian Program (CLIP), and pathologic tumor-node-metastasis (pTNM). In clinical practice, there is no ideal system that can be applicable to every patient in predicting survival [5].

## 3. The BCLC system

The Barcelona Clinic Liver Cancer (BCLC) staging system is widely used since its inception and remains the most validated and reliable system for prognostication, due to its treatment recommendations based on stage and its ability to offer predictions on patient survival. The BCLC staging system uses variables addressing tumor stage, liver functional status, physical status and cancer-related symptoms. Subsequently, the BCLC staging system can link the stages described with a treatment algorithm.

The initial authors of the BCLC staging system created a position of safety algorithm that proposes:

- Surgical resection for early HCC (i.e. stages 0 and A)
- Transarterial chemoembolization (TACE) or chemotherapy for patients with intermediate to advanced HCC – Stages B and C
- Palliative/symptomatic-only supportive treatment for patients with end-stage disease – Stage D

The combination of tumor specific staging criteria along with host specific information regarding severity of cirrhosis and symptoms have gained the BCLC staging system wide adoption by clinicians around the world. Criticisms of the BCLC staging system focus on the outdated studies the guidelines were based on and the available surgical and intensive care techniques that were available at the time these were first reported.

In fact, using modern approaches to hepatectomy and enhanced postoperative care, several authors were able to demonstrate improved perioperative outcomes and long-term survival for well selected BCLC B and in some cases BCLC C patients managed operatively. These successes point to a trend in pushing the limits of the original more conservative guidelines, thereby offering a better survival to those patients deemed to be good candidates for resection. This endeavor however has to be taken cautiously, and patients that offered resection outside class A should be managed at high volume centers and at minimum be discussed at a multispecialty tumor board. With more and more BCLC staging system patients being considered for hepatectomy, the BCLC system should be revised to reflect modern liver surgery safety standards, and BCLC stages B should not be considered as absolute contraindications to surgery [6–10].

### 3.1 Tumor-node-metastasis staging system

According to this system, the most important prognostic factors is the extent or vascular invasion (T1 without, T2 with) within the tumor. Another important prognosticator accounted for in the T portion of the TNM staging system is number of tumors (T3) and direct invasion of other organs (T4). Lymph nodes are only seldomly affected with a histologic diagnosis of HCC, therefore only rarely we observe a N1 status on these patients. Naturally, metastatic disease is denoted as M1 [11].

Although the BCLC staging system has been found to be applicable for all stages of HCC limitations of all of the other systems have been identified. For example, the AJCC (TNM) staging system has limited usefulness since a large portion of HCC patients do not undergo surgery. The most comprehensive comparison between HCC prognostic scores has recently been published by Marrero et al., who analyzed a population homogeneously including all HCC disease strata and drew a retrospective comparison between seven HCC staging systems on a prospectively enrolled cohort: the BCLC system proved to offer the best prognostic score [12].

## 4. Liver function assessment

An initial assessment of hepatic function involves liver function testing including measurement of serum levels of bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), measurement of prothrombin time (PT) expressed as international normalized ratio (INR), albumin, and platelet count (surrogate for portal hypertension). Other recommended tests include complete blood count (CBC), blood urea nitrogen (BUN), and creatinine to assess kidney function; creatinine is also an established prognostic marker in patients with liver disease. Further assessment of hepatic functional reserve prior to hepatic resection in patients with cirrhosis may be performed with different tools such as US and MRI elastography (which may provide and quantify the degree of cirrhosis-related fibrosis), and seldomly non-focal liver biopsy, and transjugular liver biopsy with pressure measurements.

The Child-Pugh classification has been traditionally used for the assessment of hepatic functional reserve in patients with cirrhosis. The Child-Pugh score incorporates laboratory measurements (i.e., serum albumin, bilirubin, PT) as well as more subjective clinical assessments of encephalopathy and ascites. It provides a general estimate of the liver function by classifying patients as having compensated (class A) or decompensated (classes B and C) cirrhosis. Advantages of the Child-Pugh score include ease of performance and the inclusion of non-laboratory, clinical parameters.

An important additional assessment of liver function not included in the Child-Pugh score is an evaluation of signs of clinically significant portal hypertension (i.e., esophagogastric varices, splenomegaly, splenorenal shunts and recanalization of the umbilical vein, thrombocytopenia). Evidence of portal hypertension may be evident on axial imagingsg (CT/MRI). Esophageal varices may be evaluated using esophagogastroduodenoscopy (EGD) or contrast-enhanced cross – sectional imaging.

The Model for End-Stage Liver Disease (MELD) is another system for the evaluation of hepatic reserve. MELD is a mathematical model based on regression analysis which employees a numerical scale ranging from 6 (best) to 40 (worst) for individuals 12 years or older. It is derived using three laboratory values (serum bilirubin, creatinine, and INR) and was originally devised to provide an assessment of mortality for patients undergoing transjugular intrahepatic portosystemic shunts (TIPS), but has been therefore incorporated as an algorithm of gauging suitability for liver transplants [13].

Which HCC patient is a candidate for resection?

Patients being considered for resection must have a high-performance status and be medically fit for what is a major operation. In general hepatic resection is the procedure of choice as a potentially curative option in patients with good liver function (generally Child-Pugh Class A without – or with mild – portal hypertension), who harbor a solitary mass (regardless of size) albeit, without major vascular invasion. In addition, the future liver remnant should be measured at minimum 20% in patients without cirrhosis and at least 40% with Child-Pugh Class A cirrhosis. Lastly, the future liver remnant should be projected to have adequate vascular and biliary inflow/outflow. Hepatic resection is controversial in patients with limited but multifocal disease and in those where tumors are seen to invade major vessels [13].

## 5. Partial hepatectomy

Surgical removal of a portion of a patient's liver (partial hepatectomy) is beneficial in removing the tumor that it harbors and thereby limiting its growth and spread to other organs. Partial hepatectomy for well-selected patients with HCC can nowadays be performed with low operative morbidity (<25%) and mortality (≤2–5%). Results of large retrospective studies have shown 5-year survival rates for patients with preserved liver function and early-stage HCC of approximately 70%.

Since liver resection for patients with HCC includes removal of functional liver parenchyma in the setting of underlying liver disease, careful patient selection, based on patient characteristics as well as characteristics of the liver and the tumor(s), is essential. Beyond functional liver remnant volume and adequacy of vascular inflow & outflow, technical considerations related to tumor and liver anatomy, must be taken into account before a patient is determined to have potentially resectable disease.

Resection is recommended only in the setting of preserved liver function. The Child-Pugh score provides an estimate of liver function, although it has been suggested that it is more useful as a tool to rule out patients for liver resection (i.e., serving as a means to identify patients with substantially decompensated liver disease). An evaluation of the presence of significant portal hypertension is also an important part of the surgical assessment.

## 6. Operative approach: open vs. laparoscopic hepatectomy

Before the first laparoscopic hepatectomy (LH) was described as early as 1991, open hepatectomy (OH) was the only choice for surgical treatment of liver tumors. LH indications were initially based solely on tumor location, size, and type and was only used for partial resection of the anterolateral segments.

Several studies have been conducted comparing laparoscopic liver resection (LLR) versus open liver resection (OLR) for hepatocellular carcinoma (HCC), however, the optimal therapeutic approach has not been established [10, 14–20].

A 2019 systematic review and meta-analysis by the Department of Hepatobiliary Surgery of Bengbu Medical College analyzed 17 studies comparing OH and LH. This metanalysis included 2004 patients and showed the following findings: For short-term outcomes, LH was associated with less blood loss, lower blood transfusion rates, reduced occurrence of postoperative complications, wider surgical margin, shorter postoperative hospital stay, and declined rate of mortality (all $P < 0.05$). However, there was no significant difference in operation time ($P = 0.67$) between the two groups, whereas tumor size was larger in OH ($P = 0.004$). As for long-term outcomes, 1-, 3-, 5-year OS and 1-year DFS were higher in LH group (all $P < 0.05$). Nevertheless, there were no significant differences in 3- and 5-year DFS ($P = 0.23$ and 0.83, respectively) [18].

Another 2018 European systematic review and meta-analysis of individual patient data by Meidai Kasai et al. also compared outcomes of LH and OH. A total of 917 patients were divided into the laparoscopic (427) and open (490) groups from 8 selected studies. Interestingly, the hospital stay was significantly shorter, and the total morbidity was lower in the laparoscopic group. When classified by severity, the incidence of postoperative minor complications was lower in the LH group, however, that of major complications was not significantly different. The operative time was longer in the laparoscopic group; however, intraoperative blood loss, perioperative mortality, and blood transfusions were comparable between the two groups. The overall survival in the patients with colorectal liver metastases and hepatocellular carcinoma was not significantly different between the two groups in this metaanalysis [20].

It is clear that LLR has the same benefits as other laparoscopic procedures, such as earlier, recovery and discharge, and reduced postoperative pain. It is also important to underline the many benefits of the laparoscopic approach are obtained while there are no differences in oncologic outcomes compared to OLR. Furthermore, the studies showed the specific advantages of LLR: lower volume of blood loss, shorter portal clamp time and less overall and liver-specific complications, for selected patients and within the technical capabilities of each experienced center. LLR also allows for better visibility and manipulation in a small operative field under some conditions, such as repeat hepatectomy with adhesions. Laparoscopic surgery makes subsequent abdominal operations easier by reducing adhesions. It was reported that the salvage transplantation after previous LLR is associated with reductions of operation time, blood loss, and transfusion requirements, compared to that after OLR. Therefore, it is advantageous not only in reducing future adhesions but also in decreasing the need for adhesiolysis in repeat abdominal exploration.

The safety and feasibility of LLR and its short-term benefits for the patients with HCC and CLD have also been well demonstrated. Reduction of surgery-induced stress by LLR, especially in the patients with HCC and CLD, decreases the risk of refractory ascites due to the preservation of venous and lymphatic collateral flows. In result, this reduces the risk of water or electrolyte imbalances and hypoproteinemia that could lead to liver failure.

Although currently there is no established adjuvant therapy for patients with hepatocellular carcinoma who undergo resection, patients do recover fully faster after laparoscopic hepatectomy. As such, when future effective adjuvant modalities emerge, patients who undergo laparoscopic resection will be fully recovered and ready to receive these much sooner than patients who undergo an open resection. This has been shown in patients with colorectal liver metastasis who undergo laparoscopic liver resection to have a prognostic benefit compared to patients who undergo an open resection.

## 7. Technical considerations

In general, "peripheral" liver segments can be resected laparoscopically much easier than "central". This applies to the left lateral segment (II & III) and to segments V & VI). Segments adjacent to the diaphragm (segments II, VII, VIII), are more challenging to access and safely resect laparoscopically. A thoracoscopic approach could be considered in these situations, but this is accompanied by the challenges of entering the pleural space and lack of quick hepatic hilum access, should one be needed intraoperatively. In addition a formal hepatic lobectomy is more challenging laparoscopically than it is open. It is therefore intuitive for a novice laparoscopic surgeon to start performing the easier, peripheral, resections first, and build a routine in mobilizing the liver, addressing problems, controlling hemorrhage etc., before embarking in bigger resections. The reported learning curve is 50 cases before a surgeon can take on more challenging cases, including laparoscopic lobectomy. It should be emphasized that during the first 50 cases, conversion rate can be as high as 50%, which is never worrisome and should never be considered a sign of failure. In almost all case, conversion is a sign of surgical maturity on behalf of the surgeon.

In is important to underline that the key initial steps are standard in pursuing laparoscopic liver resection, be it for a minor segmentectomy or a lobectomy. Set up, important for all surgical operations, is of paramount significance when it comes to LLR. The wrong setup can render a straightforward case into a very difficult one, necessitating needless conversion to open exploration. During LLR there is no surgical hand in the abdomen to gently but swiftly retract the liver and enable its mobilization, and/or tamponade a bleeding vessel. Surgical ingenuity has led to utilization of gravity to assist in retracting and mobilization, or the opposite in the event of hemorrhage during LLR.

We present herein a step by step laparoscopic approach through a video which highlights key points including surgical set up, placement of trocars, full mobilization of a liver lobe, facilitating access and resection of lesions in subdiaphragmatic hepatic segments through a minimally invasive peritoneal approach.

## 8. Technique

The video presented herein concerns the laparoscopic resection of a 2 cm liver mass in segment 7. The patient had a solid mass but in Computed Tomography and Magnetic Resonance imaging, and was FDG avid on PET CT. The patient, an otherwise healthy 51-year-old woman, with no past medical or surgical history. Of note, the patient provided consent to use the recorded video of her operation while protecting her privacy and maintaining her anonymity. In this video, we summarize key steps/technical tips with laparoscopic liver resections from our experience with minimally invasive hepatectomies, and highlight the challenges of subdiaphragmatic liver lesion resections. As mentioned, several key maneuvers are highlighted which apply to laparoscopic liver resection, of all segments.

One of the most important key elements of laparoscopic liver resection especially for resection of the right lobe, is positioning the patient in a full left lateral decubitus position, with the patient's trunk at 90-degree angle to the operating room table and the right upper extremity position securely over the patient's right chest. Drawing from the experience of laparoscopic adrenalectomies, the full left lateral position allows for easier, lateral access to the right lobe of the liver. "Jackknifing" the table opens up the working space at the far right of the abdominal musculature even more.

This approach is taking advantage of the weight of the liver itself, which is rotated medially by gravity as mobilization progresses, and obviates the need for an additional port for a liver retractor. An arm rest for the patient's right upper extremity should be employed to position it at a comfortable position over and above the upper right chest. Appropriate padding should be placed under the left axilla and at all pressure points of the trunk. The patient's abdomen, particularly the right upper quadrant at a minimum, should be left unobstructed for laparoscopic port placement but also for a quick laparotomy (through a generous right subcostal incision), should the need arise intraoperatively. The patient's body should be secured on the operating table in a fashion that will enable steep Trendelenburg and reverse Trendelenburg positioning, as well as rotation of the table to the right and left without patient slipping. We favor a belt around the patient's hip as well as stop latches at the lower spine and suprapubic areas. Intravenous fluid administration should be kept to a minimum until parenchymal transection, as is true for all liver resections.

Initially, just three 5 mm ports are placed, as shown in image 1, one for a high definition 5 mm camera and two for the laparoscopic instruments. Insufflation of the abdomen is instituted at a pressure of 12 mm Hg, with the ability to increase the intra-abdominal pressure up to 20 mm Hg should venous or low-pressure parenchymal bleeding is encountered. Depending on the most beneficial camera view and angle of approach, one of the 5 mm working ports is converted into a 12 mm port, once the desirable degree of hepatic mobilization is obtained. The upsized port can accommodate a vascular cartridge-loaded stapler or the laparoscopic ultrasound probe for intraoperative sonographic examination of the parenchyma.

Mobilization of the right lobe can proceed working laterally to medially and freeing up the retroperitoneal attachments and the right triangular ligament of the right lobe as shown in the video, https://www.dropbox.com/s/v247mnbo385shnt/hatzaras%20lap%20hepatectomy%20S7%202.mp4?dl=0. Gravity works to the surgeon's benefit, medializing the lobe as the dissection proceeds. Dividing fully the right triangular ligament is facilitated by additional gentle liver retraction with the right hand instrument, while a vessel-sealing device is yielded with the left hand. The right adrenal quickly comes into view, and care should be used to avoid injuring the fragile gland or its small feeding vessels (e.g. superior adrenal artery and vein). Caution is especially important in the case of a large tumor in the right lobe of the liver, which has been chronically pressing against the right adrenal gland, fusing the right adrenal with the liver capsule, and causing local venous hypertension in the small venous branches; these should be dissected carefully and clipped individually. Care should also be paid to avoiding injuring the diaphragm, which if entered, would lead to pneumothorax; if this was to occur, it can be repaired laparoscopically with heavy absorbable suture, over a suction device that will empty the air from the ipsilateral hemithorax.

Although not shown in this video, this positioning and initial hepatic mobilization allows for the inferior vena cava (IVC) to be fully exposed, if this lateral to medial dissection is continued more medially. The small direct branches from posterior of the right lobe to the IVC can be dissected, clipped and divided as needed. The IVC ligament may also be fully dissected, a vessel loop passed around it and a vascular cartridge-loaded stapler used to transect it safely. Lastly the inferior surface of the right hepatic vein can be encountered and skeletonized, and if the bare area superiorly is fully mobilized, the right hepatic vein can be encircled with a vessel loop and ligated with a vascular stapler.

To avoid the necessity of inflow control at the hilum, and outflow control at the hepatic veins, we frequently use microwave ablation to demarcate the target area of resection before transection of the parenchyma (key move#4). We aim for a 1 cm wide by 3 or 4 cm deep thermal ablation zone, which provides a safe, nearly bloodless transection zone. Alternatively, if the goal is to achieve a completely laparoscopic right hemihepatectomy, the surgeon should perform a cholecystectomy; then by using intraoperative laparoscopic ultrasound to identify the right portal bundle immediately superior and posterior the gallbladder fossa. If clearly identified, the operative surgeon can use a Glissonian approach, perform two shallow hepatotomies, each approximately half an inch long and 1 inch apart, in such a way to accommodate a vascular stapler which will ligate intrahepatically the right portal structures. Excellent demarcation of the right lobe will be seen after successful completion of this maneuver.

Once mobilization is completed we laparoscopically place "liver handles", two number one braided sutures though and through the parenchyma of the intended specimen in a figure-of eight fashion (key move#5), ensuring to avoid the tumor itself. These "liver handles" are brought through the abdominal wall from a separate lateral stab incision using a suture passer and we secure them with a hemostatic clamp. This maneuver allows easy, gentle extracorporeal intraoperative manipulation of the liver area to be resected. An alternative option of achieving this retraction in lateral lesions is to place a vessel loop around the fully mobilized right lobe, and exteriorize it from the abdominal cavity with a suture passer through a medial separate stab incision; this allows gentle upward retraction of the right liver lobe, the soon to-be-resected portion falls to the right, "opening the book" for the surgeon to deploy the vessel-sealing device and the vascular staplers. We typically use the Harmonic scalpel (Ethicon/Johnson & Johnson, Somerville, NJ) to transect the superficial portion of the parenchyma, followed by "vascular staplers" for the deeper portion. The 12 mm Hg intra-abdominal pressure in combination with the microwave ablation transection treatment renders the transection field relatively bloodless, a clear benefit of laparoscopic hepatectomy, obviating the need for transfusion. After resection and irrigation, we place a hemostatic agent on the cut surface of the liver. The combination of energy transection and vascular stapling allows the pace of the operation to be brisk, and it is typically completed in under 3 hours. The specimen can be removed through a 5–8 cm incision usually in the Pfannenstiel position. With these maneuvers, LLR can achieve the same outcome as the open approach, in the same time, with the same if not lower risk of transfusion, alas, with a much speedier recovery.

## 9. Conclusion

In the last two decades, liver surgery has become a much safer surgical procedure to be offered to patients with hepatic malignancies, including Hepatocellular Carcinoma. The laparoscopic approach to liver resection has evolved in parallel. Despite a steep learning curve, LLR can achieve excellent outcomes for well selected patients with Hepatocellular Carcinoma.

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