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# Contemporary perspectives on laparoscopic liver resection for hepatocellular carcinoma: unravelling the potential and limitations

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## Abstract

Hepatocellular carcinoma (HCC) is a formidable global health challenge with rising incidence rates and significant morbidity and mortality. As medical technology evolves, laparoscopic liver resection has emerged as a promising alternative to traditional open surgery for HCC treatment. This manuscript provides a comprehensive review of the contemporary perspectives on laparoscopic liver resection for HCC, with a focus on elucidating its potential benefits and inherent limitations. Our review takes a close look at how laparoscopic liver resection is currently being used to treat HCC, considering its application in various stages of the disease, tumor sizes, and locations. Through a systematic analysis of existing studies and clinical trials, we highlight the main benefits of LLR, such as less blood loss, shorter hospital stays, quicker recovery times, and better cosmetic results. This review delves into the oncological safety and outcomes of laparoscopic HCC resection. Despite its promise, laparoscopic liver resection is not without limitations. The manuscript probes into the challenges associated with this approach, such as technical complexity, restricted access to certain tumor locations, and limited surgical field visualization. Furthermore, we address the critical issue of patient selection, as not all HCC patients are suitable candidates for laparoscopic resection, necessitating a personalized and multidisciplinary treatment approach.

**Keywords:** Hepatocellular carcinoma, laparoscopic liver resection, outcomes, minimally invasive liver resection, redo liver resection

## INTRODUCTION

Hepatocellular carcinoma (HCC) is a formidable global health challenge with rising incidence over the last couple of decades. HCC has become the fifth most common cancer worldwide and is a major cause of cancer-related deaths in Western countries[1,2]. HCC represents 80%-90% of primary liver cancers and the 5-year survival after diagnosis is around 10%-15%, predominantly due to delayed presentation or advanced disease at the time of presentation[2,3].

About 90% of HCC cases are linked to known risk factors, with the most common ones being chronic viral hepatitis (types B and C), excessive alcohol consumption, and exposure to dietary aflatoxin B1. Overall, one-third of cirrhotic patients will develop HCC during their lifetime[4].

Therapeutic options for HCC include locoregional treatments such as radiofrequency ablation (RFA) or transarterial chemoembolization (TACE), liver resections (open, laparoscopic, robotic, or hybrid), liver transplantation (LT), targeted therapy, and immunotherapy depending on tumor characteristics and patient's liver function. Despite recent advances in surgical treatment and surveillance improving prognosis in patients, approximately 50%-70% of patients develop recurrence within 5 years of surgery[5-7]. Liver resection (LR) remains the gold standard in the curative treatment of early-stage HCC. However, the overall prognosis remains poor for those with more advanced disease or underlying cirrhosis[2,8]. We must take into consideration factors relating to liver function and future liver remnant (FLR) alongside the presence or absence of portal hypertension while planning surgery. For patients with a generally healthy liver and minimal fibrosis, the risk of postoperative liver failure (POLF) and related complications is lower if the future liver remnant (FLR) is more than 20%[9]. However, for patients with cirrhosis or significant fibrosis, the risk of mortality, severe complications, and postoperative liver failure (POLF) rises excessively when the future liver remnant (FLR) is less than 40%[3,6,9]. Preoperative portal vein embolization (PVE) with and without hepatic vein embolization (HVE) is a useful adjunct to increase the FLR, thereby reducing the chances of the POLF. If the future liver remnant (FLR) does not grow sufficiently after PVE in a cirrhotic liver, the risk of postoperative liver failure (POLF) significantly rises, warranting it to be regarded as a relative contraindication for liver resection[1,10].

In our review of existing data, we highlight the primary benefits provided by the minimally invasive technique. However, despite its potential, laparoscopic liver resection (LLR) comes with certain limitations. This manuscript delves into the challenges associated with this approach, including technical complexity, limited access to specific tumor locations, dealing with vascular invasion, managing multifocal tumors, navigating underlying liver cirrhosis, and its pitfalls in cases with large tumors (> 5 cm). Moreover, we explore the crucial aspect of patient selection and the learning curve required for proficiency in complex LLRs. We also assess the current role of LLR in the management of HCC, considering its application across various disease stages, tumor sizes, and anatomical locations.

## STAGING & LIVER FUNCTION ASSESSMENT

Several staging systems have been proposed to classify HCC. Five of them have been previously validated for being robustly inclusive, including the French classification, the Cancer of the Liver Italian Program (CLIP) classification, the Barcelona Clinic Liver Cancer (BCLC) staging system, the Chinese University Prognostic Index (CUPI score), and the Japan Integrated Staging (JIS). The current European Association for the Study of the Liver-European Organization for Research and Treatment of Cancer (EASL-EORTC) practice guidelines endorse the BCLC classification[2]. The BCLC staging system for HCC enables the forecasting of prognosis and the allocation of treatment, considering variables influenced by the chosen treatment, such as bilirubin level, portal hypertension, presence of ascites, and performance status.

Prognostic prediction involves factors related to tumor characteristics, including tumor size, number, nodal status, lymphovascular invasion, and the presence of satellite nodules. The BCLC classification categorizes HCC patients into five stages (0, A, B, C, and D) based on predetermined prognostic variables[11].

Liver function is typically assessed using the Child-Pugh score, and patients with Child-Pugh B or C face a heightened risk of liver failure even following a minor hepatectomy. However, although the Child-Pugh score is valuable for evaluating overall liver function, there is variability within the Child-Pugh class A group, making the score alone insufficient for accurately stratifying the risk of patients undergoing resection. Recently, a preoperative model for end-stage liver disease (MELD) has shown that scores exceeding nine are linked to lower overall survival post-LR, prompting the inclusion of the MELD score in the European Association for the Study of the Liver (EASL) guidelines for treatment allocation[2,11]. Very early HCC (BCLC stage 0) represents only 5%-10% of the diagnosed HCC patients, whereas, in Japan, the prevalence is approximately 30%, attributed to the widespread adoption of standardized surveillance programs. Recent reports indicate a 5-year survival rate ranging from 80% to 90% for very early HCCs undergoing LR[5].

For patients with early HCC (BCLC stage A), LR, LT, or local ablation are options to be considered in the algorithm and, in carefully selected cases, can reach a 50%-70% survival at the 5-year mark[5,12].

## CURRENT TRENDS IN LLR

Presently, the EASL guidelines suggest LR for cases featuring a resectable solitary nodule without macrovascular invasion and/or extrahepatic spread, irrespective of its size. In contrast, the American Association for the Study of Liver Diseases (AASLD) guidelines recommend LR for patients with Child-Pugh A cirrhosis and resectable T1 or T2 HCC. The latter is defined as solitary tumors of < 5 cm with or without vascular invasion, or multifocal tumors of < 5 cm. Meanwhile, as per The Asian Pacific Association for the Study of the Liver (APASL), all tumors lacking extrahepatic metastases are considered potentially resectable, regardless of their vascular invasion status, number, or size[2,13,14].

Recent studies investigating the role of LR in advanced stages of HCC have yielded promising outcomes[6,15]. LLR has emerged as a favorable alternative to traditional open liver surgery for HCC. The first LLR for HCC was performed nearly two decades ago, in 1995[16]. During the initial years of laparoscopic surgery, its application in LR was met with controversy, especially with respect to patient safety and oncological outcomes[17]. Advances in laparoscopic techniques, increased proficiency, and technological progress have contributed to the more widespread acceptance of laparoscopic approaches for HCC resection over the years. LLR has proven to be oncologically safe, with morbidity and mortality rates comparable to open LRs, with some studies reporting reduced morbidity[17]. Enhanced techniques, improved visualization of anatomical landmarks, and the introduction of laparoscopic cavitron ultrasonic surgical aspirators (CUSA) have facilitated the transection of deeper lesions within the hepatic parenchyma[17]. In recent years, there has been a shift in the paradigm toward minimally invasive surgical techniques, with LLR emerging as a viable and effective option, especially for treating early-stage HCC[18]. LLR is associated with comparable oncological outcomes and superior short-term results compared to open surgery[19]. Laparoscopic ultrasound is routinely used in LLR to identify anatomical landmarks and resection margins and achieve real-time mapping of vital structures during surgery[20].

A recent meta-analysis by Kabir *et al.* demonstrated improved peri-operative outcomes and overall survival in patients undergoing LLR[21].

The Southampton Consensus Guidelines (2018) serve as the current clinical practice guidelines, designed to steer "the safe development and progression of laparoscopic liver surgery"[18]. These guidelines emphasize that most of the evidence comes from surgeons with expertise in both laparoscopic techniques and liver surgery, typically operating in high-volume centers. The guidelines acknowledge that, in skilled hands, major LLR is linked to shorter hospital stays and reduced blood loss, with oncological outcomes comparable to open LR[18,22]. A dedicated segment focusing on HCC within the practice guidelines indicates compelling consensus evidence that LLR for HCC is associated with lower blood loss, lower transfusion rates, reduced postoperative ascites, decreased instances of liver failure, and shorter hospital stays. Importantly, these advantages are achieved without a significant difference in operation time, disease-free margin, and recurrence rates compared to other treatment modalities[3,4,23]. Sposito *et al.*, in their study, employed propensity score matching explicitly for minor resections with early HCCs and reported that utilizing a laparoscopic approach emerged as the sole independent factor contributing to a decrease in the postoperative complication rate[24].

Proposed by the International Consensus Conference on Laparoscopic Liver Resections, the IWATE criteria have introduced a scoring system designed for LLR. This system categorizes difficulty into four levels (low, intermediate, advanced, and expert) based on six preoperative factors: tumor location, tumor size, proximity to major vessels, extent of hepatic resection, Hand Assisted Laparoscopic Surgery (HALS)/hybrid, and liver function. Validation studies have confirmed its correlation with both intra- and postoperative outcomes[25]. In addition, it can help to plan the resection approach based on surgeon's experience and case characteristics[25]. Presently, LLR was predominantly employed for HCCs with small tumors situated more peripherally in the liver, enabling wedge or segmental resections. Tumors located in segments 2 to 6 are considered ideal candidates for LLR compared to those in segments 7, 8, and 1, which pose challenges in terms of visualization, handling, and laparoscopic dissection, and often necessitate significant hepatic mobilization for resection. The application of laparoscopic approach for lesions in posterior segments and major resections are not universally accepted and adopted for these challenges[26].

## LARGE TUMORS (> 5 CM)

Regarding tumor sizes, except for the occasional exophytic lesions that are seemingly straightforward to resect, LLR is typically not recommended for tumors > 5 cm in diameter due to challenges in liver mobilization and tumor dissection, with associated risks of tumor rupture, seeding, and an increased likelihood of R1 margins[27]. Limitations with surgical access, coupled with proximity to major hepatic veins and other vital vascular structures, and the high risk of traction-related bleeding during dissection of these large tumors can be extremely challenging to tackle laparoscopically, especially in inexperienced hands[18]. These larger tumors also increase the risk of open conversion[27]. Additional arguments against the use of laparoscopic surgery for large tumors include the limitation posed by conventional specimen recovery bags, which are deemed too small, necessitating a relatively lengthy incision to extract the specimen. In essence, the feasibility of the procedure hinges on its safe execution in high-volume centers with expertise in undertaking such cases regularly[28]. Recently, Hong *et al.* reported favorable long-term results based on a nationwide cohort of 466 patients diagnosed with large HCCs. Their findings indicated a less favorable prognosis in subgroups characterized by low platelet counts and tumors > 10 cm in size[29]. Likewise, Thng *et al.* showed favorable long-term results for HCC. Their study identified the presence of satellite nodules and the need for blood transfusions as adverse outcome predictors associated with a poorer prognosis[30]. A recent multinational multicenter matched cohort study confirmed the safety of LLR even for tumors > 10 cm, despite the technical challenges involved[31].

## MULTIFOCAL HCC

The appropriateness of LLR in the context of multifocal HCC remains a subject of debate. Historically, individuals deemed oncologically optimal for LLR were those with a single tumor measuring < 5 cm. For multifocal, non-metastatic HCC, the conventional approach involved LT within Milan criteria[32]. For cases falling outside these criteria or deemed unsuitable for LT, treatment typically encompassed TACE or RFA[33]. Findings from the Japanese national series indicated superior outcomes in terms of overall survival for Child-Pugh A patients undergoing LLR compared to other locoregional treatments. However, it should be noted that LLR was associated with higher morbidity[34]. LLR may be an oncologically feasible treatment option for multifocal HCC, but larger datasets are required to substantiate its routine application in clinical practice.

## HCC AND CIRRHOSIS

While underlying liver cirrhosis was initially viewed as a contraindication for LLR, numerous studies have explored the outcomes of LLR in cirrhotic patients. These individuals often carry the risk of postoperative hepatic decompensation and liver failure, along with challenges in managing low peri-operative platelet counts and impaired coagulation cascades. A meta-analysis encompassing 11 studies involving 1,618 patients who underwent LLR, revealed a notable 16%-26% reduction in the hazard ratio of death for patients with HCC and cirrhosis. The authors highlighted that LLR leads to overall reduced blood loss, fewer major complications, and a shorter duration of hospitalization. When considering laparoscopic liver resection (LLR) for patients with liver cirrhosis, it is essential to account for not just the oncological outcomes and technical feasibility, but also the physiological and surgical strain on both the patient and the liver, which can significantly impact the results.

Laparoscopic surgery reduces the intraoperative handling of the liver, thus allowing us to maintain the integrity of collateral vessels and abdominal wall[4]. A significant benefit of LLR in cirrhotic patients is the decreased occurrence of ascites and POLF[9]. This is attributed to the diminished disruption of portosystemic shunts, such as dilated umbilical veins, and the avoidance of electrolyte imbalances resulting from the exposure of abdominal content to atmospheric air, which happens with open LR[35]. The advantages of LLR extend even in advanced Child-Pugh B cirrhotic patients, as evidenced by a propensity score-matched study conducted across international high-volume centers, demonstrating reduced blood loss, morbidity, and major complications in the LLR group[29]. Vivarelli *et al.* in their retrospective study showed favorable outcomes by preserving the round ligament during LLR in HCC patients with portal hypertension to mitigate postoperative decompensation. Further studies and RCTs are needed prior to adopting and standardizing these surgical techniques[36].

## POSTERIOR-SUPERIOR SEGMENTS

According to the latest international consensus, LLR of posterosuperior segments is classified as a major liver resection[3,12]. This categorization is based on evidence demonstrating notably longer operative times, higher rates of open conversion, increased estimated blood loss, and extended hospital stays, in comparison to anterolateral resections. The continuous advancements in laparoscopic methods and the incorporation of innovative technologies have expanded the technical feasibility of LLR to include posterosuperior segments (I, IVa, VII, VIII) as well[37]. Patient intraoperative positioning and trocar's location in these cases are key to facilitating access to posterior segments.

There are some studies assessing the feasibility and safety of laparoscopic isolated caudate resection, confirming that it is associated with low blood loss, minimal transfusion requirement, reasonable operative times, and safe oncological margins and outcomes[35,38]. More recently, Cassese *et al.* have summarized the treatment strategy for operable non-metastatic HCC using minimally invasive surgery in their review[39].

## REDO SURGERY FOR RECURRENCE & CONVERSION TO OPEN

HCC carries a significant recurrence risk following both LR and LT. Consequently, the prevalence of redo-LLR has risen due to the widespread adoption of minimally invasive techniques. Additionally, LLR helps diminish the likelihood of severe adhesions, making liver mobilization easier and decreasing bleeding. A study by Kanazawa *et al.* revealed that the operative time for redo-LLR following a prior LLR was notably shorter compared to that following open LR[40]. Belli *et al.* documented reduced postoperative complications, lower incidents of bleeding, and shorter hospital stays following redo-LLR compared to redo-open LR[41]. There has been a growing inclination toward employing a laparoscopic approach for redo resections after LT, further expanding the boundaries of LLR[42]. Morise *et al.* published findings from an international multi-institutional study based on propensity scores for redo-LLR in HCC, demonstrating decreased blood loss and shorter hospital stays for the laparoscopic group. This was observed even when LLR was the preferred technique for patients with favorable tumor characteristics[43].

LLR can be converted to laparotomy due to anatomical and technical reasons or to ensure patient safety. Although most studies indicate a conversion rate of around 4%-8%[44], some have reported higher conversion rates of around 15%-17%[44]. Excessive bleeding stands out as the most common reason for conversion, with additional factors such as adhesions, gas embolism, poor visualization, anatomic disorientation, or proximity to large vessels contributing toward the decision to convert to open LR[1,5,15,23,40,44]. A multivariate analysis revealed that the resection of posterior-superior segments and major hepatectomy were independent factors associated with conversion, distinguishing them from minor hepatectomy[18,22].

## FLUORESCENCE-GUIDED SURGERY

In laparoscopic and robotic LRs, palpation of the tumor is not possible. Intraoperative ultrasound might not identify small tumors, whereas fluoroscopic imaging enables the identification of subcapsular liver tumors through the accumulation of indocyanine green (ICG) in dysplastic nodules, thereby increasing the accuracy and the easiness of minimally invasive resections[45]. In HCC, fluorescence-guided surgery serves various purposes, including selective Glissonian clamping by injecting ICG into the segmental portal vein. In these cases, clear demarcation of segments can assist in identifying the segment to be resected[46]. In a recent propensity score matching study by Jianxi *et al.*, comparing ICG-guided laparoscopic hepatectomy to conventional laparoscopic hepatectomy in HCC patients, the procedure was found to be safe and effective, with low postoperative complications and similar overall survival, but longer procedure times[47].

## ROBOTIC SURGERY

Robotic surgery, an integral component of Minimally Invasive Surgery (MIS), has already seen widespread adoption across high-volume experienced centers for liver resection. Its unique 3D vision and multiple working arms and manoeuvrability contribute to a potentially shorter learning curve and overcome limitations of LLR, such as access to posterior segments and caudate lobe resections. A systematic review conducted by Magistri *et al*. demonstrated that the robotic approach can yield comparable oncological outcomes, specifically in terms of achieving R0 margins and ensuring disease-free survival, compared to the effectiveness of laparoscopic and open approaches[48]. Similar findings were observed in the largest Western study by Di Benedetto *et al.*, which compared robotic and open approaches for hepatocellular carcinoma (HCC)[49]. However, factors such as high present costs, availability, training & learning curve, non-availability of proctorship, and absence of a robotic CUSA for parenchymal transection are some of the limitations. It also highlights the need for the standardization of robotic procedures.

## ANATOMICAL *VS.* NON-ANATOMICAL LIVER SURGERY

High surgical complexity and steep learning curve associated with performing laparoscopic anatomical liver resection delayed its widespread adoption after being first introduced in 1980. The main challenges initially encountered were bleeding and longer operative times[50]. Ultrasound-guided glissonian approach for anatomical resections has enabled in more recent times to perform these surgeries safely with similar outcomes compared with non-anatomical approach[50]. Underlying liver disease and post-resection FLR independently guide surgeons between the two approaches in minimally invasive liver surgery for operable HCC.

## SUMMARY & FUTURE PERSPECTIVES

The decision to employ laparoscopic surgery for HCC should be individualized, considering various factors such as the patient's overall fitness, tumor characteristics, liver function, future liver remnant, and the risk of postoperative liver failure. Additionally, the surgeon's proficiency in executing complex laparoscopic liver resections is a crucial consideration. It is now advisable to recommend laparoscopic resections for HCC in high-volume hepatobiliary centers. In the initial stages, clinical practice should adopt a gradual approach, commencing with minor liver resections in anterolateral segments and progressing to major liver resections and resections of lesions situated in posterosuperior segments. The latter poses greater difficulty due to the orientation of the transection planes and the longer learning curve needed to attain proficiency in performing complex LLR safely.

## DECLARATIONS

### Authors' contributions

Conceptualized the article, defined the literature review, and prepared the final draft of the manuscript: Hakeem AR

Performed the literature review and wrote the article: Suresh N, Ng KC, Blanco-Colino R

Contributed equally to the manuscript writing and agreed with the final version of the manuscript: Suresh N, Ng KC, Blanco-Colino R, Hakeem AR

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### Consent for publication

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