

Review

Current status of laparoscopic liver resection for hepatocellular carcinoma

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Laparoscopic liver resection (LLR) is becoming widely accepted for the treatment of hepatocellular carcinoma (HCC). Laparoscopic left lateral sectionectomy and minor laparoscopic liver resection are now considered standard approaches, especially for tumors located in the anterolateral segments of the liver. Laparoscopic left lateral sectionectomy in adult donors is also gaining acceptance for child liver transplantation in many centers. Major LLRs, including left hepatectomy and right hepatectomy, have been recently attempted. Laparoscopic donor hepatectomy is becoming more popular owing to increasing demand from young living donors who appreciate its minimal invasiveness and excellent cosmetic outcomes. Several centers have performed total laparoscopic donor right hepatectomy in adult-to-adult living donor liver transplantation. Many meta-analyses have shown that LLR is better than open liver resection in terms of short-term outcomes, principally cosmetic outcomes. Although no randomized control trials have compared LLR with open liver resection, the long-term oncologic outcomes were similar for both procedures in recent case-matched studies.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor worldwide, accounting for 5.6% of all human cancers, and is the most common primary liver cancer.¹ It is also the third most common cause of cancer-related deaths worldwide.² The number of new cases is estimated to range from 500,000 to 1 million per year.¹ Up to 80–90% of HCCs develop in a cirrhotic liver.²

Liver transplantation appears to be effective treatment approach because it treats both the cancer and the underlying

liver cirrhosis. However, the scarcity of donors precludes transplantation in all patients with early HCC.² Liver resection for HCC is now considered to be a safer procedure than was previously believed owing to technical advances and improvements in postoperative patient management.^{3–6} Accordingly, in many centers, liver resection is still the first-line treatment for HCC in patients with compensated cirrhosis.⁷ Since the first laparoscopic liver wedge resection was reported in 1992, an increasing number of reports have described the feasibility, safety, and adequacy of laparoscopic hepatic procedures.^{8–11} Now, laparoscopic liver resection (LLR) is commonly performed in

Abbreviations:

HCC, hepatocellular carcinoma; LLR, laparoscopic liver resection; OLR, open liver resection; RCT, randomized controlled trial

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patients with HCC and chronic liver disease.

The indications for LLR have been changed substantially since its introduction. Initially, LLR was limited to the treatment of benign diseases. However, with increasing knowledge of this procedure, its indications have widened to include malignant disease such as HCC and liver metastasis of colorectal cancer. The extent of resection has also grown over time.¹² Major liver resection, such as right or left hemihepatectomy, has been performed more frequently in recent years.^{13,14}

Laparoscopic left lateral sectionectomy is now regarded as a standard treatment option. By contrast, it will take many years for LLR to become a standard procedure for treating all kinds of HCC.¹⁵ Extending the indications, the introduction of advanced techniques, and outcomes similar to those of open liver resection (OLR) are required for LLR to become a standard procedure in HCC.⁹

The aim of this review is to assess the current indications, advantages, and limitations of laparoscopic surgery for HCC resection. We will also discuss the feasibility of LLR and its oncologic outcomes compared to OLR. The information in this review was extracted from a literature search of Medline.

BEST INDICATIONS FOR LLR

Tumor location

Unlike laparoscopic cholecystectomy, laparoscopy is not widely accepted for liver resection because of the technical difficulty associated with parenchymal transection, hemostasis at the transection plane, the risk of air embolism, and limited

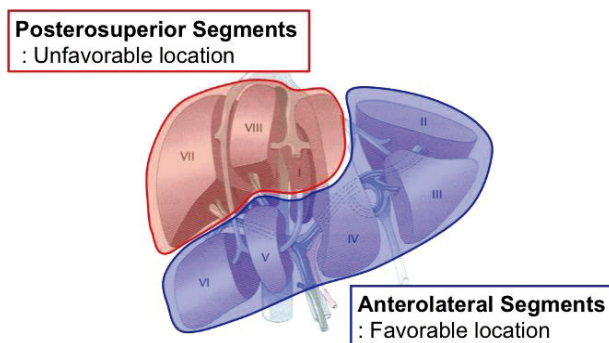


Figure 1. The peripheral area of anterolateral segments (segments 2, 5, 6, and lower part of 4) is considered to be a favorable location of tumors for laparoscopic liver resection, whereas the posterosuperior segments (segments 1, 7, 8, and upper part of 4) of the liver are unfavorable locations.

ability to explore the deeper regions of the liver.¹⁶ Therefore, LLR has been reserved for patients who require limited resection of tumors located on the left side of the liver. The recent improvements in laparoscopic techniques and the introduction of new technologies mean that LLR is technically feasible and safe for tumors on the right side of the liver.¹⁷ The first international position statement on LLR published in 2008 stated that the best indications for LLR were patients with solitary lesions, ≤ 5 cm in diameter, located in the peripheral liver segments (i.e. segments 2–6; Fig. 1). Laparoscopic left lateral sectionectomy should be considered as the standard of care, but major hepatectomy, such as right hepatectomy, should be reserved for experienced surgeons.¹⁵

Improved laparoscopic techniques, better visualization of the operative field using a flexible laparoscope, and routine use of a laparoscopic cavitron ultrasonic surgical aspirator for transecting the deeper portion of the liver parenchyma have allowed laparoscopic left lateral sectionectomy to be performed more widely.¹⁸⁻²⁰ LLR for HCC located in the posterosuperior segments in selected patients was reported to be safe and feasible, and offered comparable oncologic outcomes to those of OLR. Other benefits of LLR include reduced blood loss, fewer complications, and shorter postoperative hospital stay compared with open resection.²¹

Presence of cirrhosis

Cirrhosis precedes HCC in approximately 80%–90% of cases worldwide.²² Asian countries, especially, have a disproportionately high prevalence of HCC, mainly because hepatitis B and C viruses are endemic in these countries,²³ and chronic infection is associated with high risk of liver cirrhosis and HCC.²⁴ When considering liver resection in patients with liver cirrhosis, it is important to consider the degree of surgical stress placed on the patient and the liver, as well as the oncological outcomes.⁸ Decompensated cirrhosis is generally considered to be a contraindication to liver resection and thereby LLR.²⁵ Uncontrolled portal hypertension, including esophageal varices and low platelet count, is also usually considered as an exclusion criterion for LLR.²⁶ Anatomical liver resection is preferred for HCC because of its tendency to invade the portal veins and spread along the intrasegmental branches.²⁷

Major advantages of laparoscopy are the rapid recovery of patients and the shorter hospital stay compared with open surgery, as previously reported for LLR of HCC.^{28,29} These advan-

tages are related to less postoperative pain, early ambulation, early return of oral feeding, and lower incidence of postoperative complications after LLR. Another important advantage of LLR in cirrhotic patients is the lower incidence of postoperative liver failure and ascites. This may be due to the reduced invasiveness of laparoscopy, which helps to preserve the abdominal musculature by avoiding large abdominal incisions, preserve the parietal circulation, and minimize liver manipulation.⁸

RECOMMENDATIONS OF THE FIRST AND SECOND CONSENSUS MEETINGS FOR LLR

Because the potential applications for LLR have expanded considerably in the last 15 years,^{28,30,31} a first International Consensus Conference on LLR was convened in Louisville, Kentucky, in 2008.¹⁵ The experts discussed achievements and recommendations for this approach.¹⁵ This consensus statement defined the current international position on laparoscopic liver surgery as “a safe and effective approach for the management of surgical liver disease in the hands of trained surgeons with experience in hepatobiliary and laparoscopic surgery.” It also stated that the best indications for LLR were patients with solitary lesions, ≤ 5 cm in diameter, located in the peripheral liver segments (i.e. segments 2–6) and that laparoscopic left lateral sectionectomy should be considered as the standard of care. If local resection of HCC is performed, it should involve anatomical segmental resection, if possible, considering the overall function of the liver. This is because this procedure is associated with lower local recurrence rates and should be used instead of tumorectomy. Since then, LLR has been introduced to middle-tier centers as well as high-volume and/or specialized centers.³² Moreover, the number of HCC cases treated by LLR has increased over the last 5 years, especially in Asia and Europe.³³

Six years later, the second International Consensus Conference on LLR was held to evaluate the current status of LLR and to develop recommendations and guidelines. This goal was achieved through analysis of the available literature and expert presentations, which including videos presented to an independent jury. The organizing committee invited 43 respected surgeons from 18 countries. The expert panel comprised 34 members, with demonstrated experience in LLR, and the jury contained 9 members. The expert panel provided evidence and developed recommendations. The organizing committee pre-

pared 17 questions in 2 categories—benefits and risks, and techniques of LLR. Each question was assigned to a working group of 3–7 members of the expert panel who were selected based on their scientific and clinical activities. The jury concluded that minor LLRs had become standard practice (IDEAL 3) and that major liver resections were innovative procedures in the exploratory phase (IDEAL 2b). Continued cautious introduction of major LLRs was recommended. All of the evidence available for scrutiny was considered to be of low quality by GRADE, which prompted the recommendation for higher quality evaluative studies. The expert panel developed recommendations regarding preoperative evaluation, bleeding control, transection methods, anatomical approaches, and equipment. Both the expert panel and jury recognized the need for a formal structure of education for surgeons interested in performing major LLR because of the steep learning curve.³⁴

RETROSPECTIVE COMPARISON OF OUTCOMES BETWEEN LAPAROSCOPIC AND OPEN LIVER RESECTION

Over the past decade, LLR has progressed internationally following advances in technology and the increasing experience of liver surgeons. Indeed, more than 9,000 procedures were reported in the English literature.³⁵ With the proper selection of patients, LLR is considered as a safe technique, with mortality and morbidity rates of 0% and 15%, respectively.³⁶ Since the first case was reported, an increasing number of case-series have been published especially from the beginning of new millennium.³⁷ LLR was initially performed for low-risk operations, including the excision of benign hepatic lesions. The techniques have gradually become incorporated into the practices of most liver centers, and LLR is now widely accepted for the management of benign and malignant liver tumors.³⁸ In a global survey of the current practices of liver surgery, Yoshihiro et al. reported that 88% of the participating centers had incorporated laparoscopic approaches into liver surgery.³³

To our knowledge, no randomized controlled trials (RCT) have compared the outcomes between LLR and OLR. However, several retrospective case-cohort matched studies have compared these two procedures. The majority of studies showed that LLR has major benefits compared with OLR. LLR was associated with less intraoperative blood loss, less postoperative pain medication requirement, earlier return of oral feeding,

Table 1. Previous studies comparing the outcomes of laparoscopic liver resection versus open resection.

Author	Type	Blood loss	Transfusion	Operative time	Hospital stay	Complications	Resection margin
Zhou et al. [40] (2011)	Meta-analysis 21 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD
Rao et al. [41] (2011)	Systematic review 10 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD
Fancellu et al. [42] (2011)	Meta-analysis 9 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD
Li et al. [43] (2012)	Meta-analysis 10 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD
Xiong et al. [44] (2012)	Meta-analysis 16 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD
Yin et al. [45] (2013)	Meta-analysis 15 studies	LLR < OLR	LLR < OLR	NSD	LLR < OLR	LLR < OLR	NSD

LLR, laparoscopic liver resection; OLR, open liver resection; NSD, no significant difference.

Table 2. Recent studies on long-term outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma

Study	Type	1 year survival	3 year survival	5 year survival	1 year DFS	3 year DFS	5 year DFS	Overall and DFS
Lee et al. [50] (2011)	Case matched	L - 86.9% O - 98%	L - 81.8% O - 80.6%	L - 76% O - 76.1%	L - 78.8% O - 69.2%	L - 51% O - 55.9%	L - 45.3% O - 55.9%	NSD
Parks et al. [51] (2014)	Meta-analysis	L - 92% O - 91.3%	L - 77.7% O - 76.5%	L - 61.9% O - 56.5%	NA	NA	NA	NA
Cheung et al. [52] (2013)	Retrospective	L - 96.6% O - 95.2%	L - 87.5% O - 72.9%	L - 76.6% O - 57%	L - 87.3% O - 63.5%	L - 72.6% O - 50%	L - 54.5% O - 44.3%	NA
Kim et al. [53] (2014)	Case matched with PSM	L - 100% O - 96.5%	L - 100% O - 92.2%	L - 92.2% O - 87.7%	L - 81.7% O - 78.6%	L - 61.7% O - 60.9%	L - 54% O - 40.1%	NSD
Han et al. [54] (2015)	Case matched with PSM	L - 91.6% O - 93.1%	L - 87.5% O - 87.8%	L - 76.4% O - 73.2%	L - 69.7% O - 74.7%	L - 52% O - 49.5%	L - 44.2% O - 41.2%	NSD
Takahara et al. [46] (2015)	Case matched with PSM	L - 95.8% O - 95.8%	L - 86.2% O - 84%	L - 76.8% O - 70.9%	L - 83.7% O - 79.6%	L - 58.3% O - 50.4%	L - 40.7% O - 39.3%	NSD

DFS, disease free survival; PSM, propensity score matching; L, laparoscopic liver resection; O, open liver resection; NSD, no significant difference; NA, not analyzed.

and shorter hospital stay compared with OLR. In addition, from a financial standpoint, although the minimally invasive LLR approach was associated with higher operating room costs in some studies, the total hospital costs were either offset or improved by LLR because of the shorter hospital stay. In addition, LLR did not compromise oncological measures such as margin status, disease-free survival, or overall survival, but did improve short-term perioperative outcomes.³⁹

A systematic review published in 2012 compared LLR with OLR.⁴¹ The data analysis suggested that LLR was associated with improvements in most of the perioperative factors, including blood loss, the number of patients requiring transfusion, and the use of portal triad clamping. By contrast, the operation

time was shorter with OLR than with LLR. LLR was also associated with shorter hospital stay and earlier return of oral feeding. However, all of these significant results were associated with significant heterogeneity in the evaluated studies. There were no differences between the two groups in terms of adverse outcomes in the early postoperative period. Nevertheless, a significant finding was the lower number of positive resection margins in the LLR group than in the OLR group. This finding was not associated with significant heterogeneity. The other variables associated with oncological clearance were not significantly different between LLR and OLR. Another important result was that LLR was associated with a significant reduction in overall morbidity compared with OLR.

In the last 5 years, several meta-analyses of studies comparing LLR and OLR for malignant lesions have been published (Table 1). All of these meta-analyses concluded that LLR is superior to OLR in terms of perioperative outcomes. The operation time was not significantly different between LLR and OLR, even though operation time was shorter for OLR in prior studies. The absence of a difference in the meta-analyses could be explained by recent advances in surgical instruments, accumulated experience, and overcoming the learning curve. Furthermore, no technique compromised the oncological outcomes.⁴⁰⁻⁴⁵ Unfortunately, it is impossible to reach a convincing conclusion regarding the benefits and risks of LLR over OLR in the absence of RCTs.⁴⁶ However, Abraham et al. recently reported that a meta-analysis of well-designed non-randomized controlled trials of surgical procedures is probably as reliable as a meta-analysis of RCTs.⁴⁷

RECENT PUBLICATIONS OF CASE-MATCHED STUDIES FOR COMPARING LONG-TERM OUTCOMES OF LAPAROSCOPIC VERSUS OPEN LIVER RESECTION

LLR not only achieve equivalent short-term postoperative outcomes but also provide favorable long-term survival prognosis to OLR. Several studies have reported that LLR is less invasive and is associated with similar disease-free survival and overall survival rates to OLR in patients with HCC.^{48,49} However, we still lack data on the long-term oncological outcomes of LLR particularly in patients with HCC. To date, there have been no prospective RCT comparing the outcomes between LLR and OLR. However, many meta-analyses, retrospective studies, and case-matched studies with propensity score matching comparing the long-term outcomes of LLR and OLR in patients with HCC have been published in recent years (Table 2). These studies showed that the survival rates at 1, 3, and 5 years were similar between patients undergoing LLR and patients undergoing OLR for HCC, as were the overall recurrence rate, mortality rate, overall survival rate, and disease-free survival time.^{46,50-54} One study determined the long-term survival of patients with HCC in reference to the stage of the disease. Survival was not significantly different between patients with stage I and stage II HCC.

CONCLUSION

LLR is now considered as a standard procedure in the management of HCC in some settings, and it is increasingly being performed worldwide. The short- and long-term outcomes of LLR were comparable to those of OLR.

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Conflicts of Interest

The authors have no conflicts to disclose.

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