REVIEW ARTICLE

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Developments and perspectives of laparoscopic liver resection in the treatment of hepatocellular carcinoma

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Abstract

Laparoscopic liver resection (LLR) was introduced in the early 1990s, initially for partial resection of the anterolateral segments, from where it has expanded in a stepwise fashion. Movement restriction makes bleeding control demanding. Managing pneumoperitoneum pressure with inflow control can inhibit venous bleeding and create a dry surgical field for easier hemostasis. Since the lack of overview leads to disorientation, simulation and navigation with imaging studies have become important. Improved direct access to the liver inside the rib cage can be obtained in LLR, reducing destruction of the associated structures and decreasing the risk of refractory ascites and liver failure, especially in patients with a cirrhotic liver. Although LLR can be performed as bridging therapy to transplantation for severe cirrhosis, its impact on expanding the indications of liver resection (LR) and the consequent survival benefits must be evaluated. For repeat LR, LLR is advantageous by producing fewer adhesions and reducing the need for adhesiolysis. The laparoscopic approach facilitates better access in a small operative field between adhesions. Further evaluations are needed for repeat anatomical resection, since alterations of the anatomy and surrounding scars and adhesions of major vessels have a larger impact.

Keywords Laparoscopic liver resection · Liver cancer · History · Technique · Concept · Approach · Posture · Simulation · Hepatocellular carcinoma · Liver cirrhosis · Repeat resection

Developments and current status of laparoscopic liver resection

The concept of diagnostic laparoscopy was introduced in the 1960s. New technologies for pneumoperitoneum and the charge-coupled device (CCD) camera, which magnifies and projects laparoscopic images onto monitors, led to the first laparoscopic cholecystectomy in the current style in 1987 [1]. Because of the clinical experience of less pain and rapid recovery, in addition to its cosmetic advantages, the procedure gained immediate acceptance [2, 3]. Thereafter, the field of laparoscopic surgery has expanded rapidly to include even more technically demanding abdominal surgery.

The early 1990s witnessed the inception of laparoscopic liver resection (LLR), with initial reports of partial resections [4–6] published in 1991 and 1992. LLR began as partial resection of the anterolateral segments, which are easy to access with the laparoscope and comprise segments 2, 3, 5 and 6, and the caudal part of 4. These were followed by reports of left lateral sectionectomy (LLS) [7, 8] in 1996. The procedure was then expanded to hemi-hepatectomy [9–12], followed by medial, anterior and posterior sectionectomies [13–15]. The laparoscopic approach to the liver involves maneuvering the laparoscope and forceps into the subphrenic rib cage, where the liver is protected inside, from the caudal direction ("caudal approach", Fig. 1b [15–17]). Through the development of devices and techniques for hemostasis, the inter-lobar or -segmental planes (flat planes aligned in the direction from the caudal edge to the cranial edge of the liver) were now able to be handled via a laparoscopic-specific approach. Thereafter, LLR was expanded to segmentectomy and partial resection of the posterosuperior segments (segments 7, 8, 1) [18–22], using additional techniques, such as intercostal ports ("Lateral approach", Fig. 1c [19]), thracoscopic approach [20] and position changes [21]. The lateral approach using intercostal ports has been widely adapted for resections of segment 7 and sometimes 8, in addition to the caudal approach [19].

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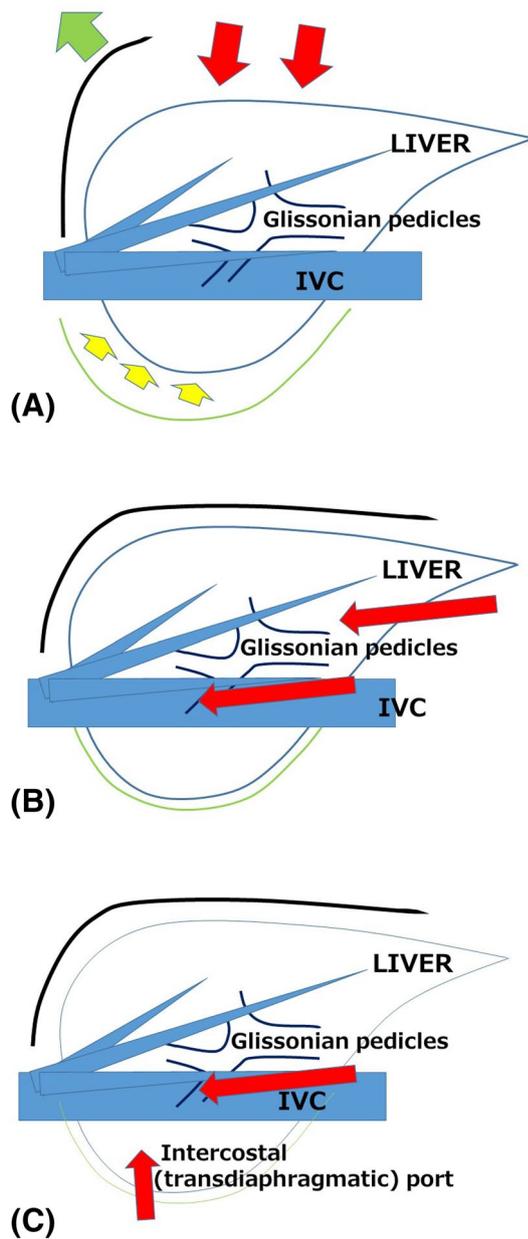
Fig. 1 Schema of open liver resection (**a**), usual laparoscopic liver resection (caudal approach, **b**) and laparoscopic liver resection with intercostal ports (lateral approach, **c**). Red arrows indicate the directions of view and manipulation in each approach. **a** In the open approach, the subphrenic rib cage containing the liver is opened with a large subcostal incision, then instruments are used to lift the costal arch, and the liver is dissected and mobilized (lifted) from the retroperitoneum. **b** In the usual laparoscopic caudal approach, the laparoscope and forceps are inserted into the subphrenic rib cage from the caudal direction, and surgery is performed with minimal alteration and destruction of the associated structures. **c** In the laparoscopic lateral approach, the intercostal (transdiaphragmatic) ports combined with total mobilization of the liver from the retroperitoneum can allow the direct lateral approach into the cage and to the posterosuperior tumors. (Modification from Morise Z, Wakabayashi G. First quarter century of laparoscopic liver resection. World J Gastroenterol. 2017;23(20):3581–3588. [27])

Nowadays, parenchymal-preserving limited and modified (extended and/or combining limited) anatomical resections [23–26], using simulation and navigation with precise imaging studies, are advocated. This expansion of LLR procedures in a stepwise fashion is the result of advances in both instrumental technology and technical skill with conceptual changes (Table 1).

Two international consensus conferences (ICCLLR) were held during this period: in 2008 in Louisville, KY, United States [28] and in 2014 in Morioka, Japan [29], providing up-to-date summaries of the status and perspective of LLR. The reservations about LLR-specific complications, including gas embolism [30], were eased by cautious application of the procedures and evidence that the long-term outcomes of LLR were similar to those of open liver resection (OLR) in selected patients. The advantages and disadvantages of LLR were also recognized during this period. Movement restriction in laparoscopic surgery makes bleeding control during transection demanding and reconstruction of the vessels difficult. Bleeding control during transection has been established by compression with or without hemostatic material, as in the open procedure, using clipping, suturing, temporary clamp for vessels, and various energy devices such as bipolar and monopolar coagulation [31]. The control of pneumoperitoneum pressure, airway pressure (sometimes via a brief pause in artificial ventilation) and central venous pressure, accompanied by inflow control [16, 32], can be used to inhibit venous bleeding and achieve a dry and clear surgical field to allow a clear view of the bleeding points. However, procedures involving vessel resections and reconstructions, such as resection of hilar cholangiocarcinoma, are not yet common [33]. Although the lack of a three-dimensional (3D) view was partially overcome by the development of the 3D laparoscope [34], the lack of overview in the operative field (a trade-off for the local fine magnified view) combined with the lack of tactile sensation can result in disorientation of the operator on the perspective of the organs, tumors, and intrahepatic structures. Therefore, intraoperative laparoscopic ultrasonography, preoperative simulation, and intraoperative navigation using preoperative precise imaging studies, and intraoperative imaging study of near-infrared fluorescence scans with indocyanine green have become important and are being developed further [35, 36]. Based on the development of these imaging techniques, parenchymal-preserving limited anatomical resection and modified anatomical resection are advocated [23–26].

The specific advantage of LLR, other than the established benefits of all laparoscopic surgery, includes improved direct access to the liver while it is protected inside the rib cage under the laparoscopic-specific view via the caudal approach (Fig. 1b [15–17]). In the open procedure, the liver is resected after opening the cage through a long subcostal incision, then mobilizing it from the retroperitoneum and picking it

Table 1 Development of laparoscopic liver resection over the first 25 years (Modification from Morise Z, Wakabayashi G. World J Gastroenterol. 2017;23(20):3581–3588. [27])

Year	Procedure [Ref]	Related developments (technological, technical, conceptual)
1991	First report of LLR [4–6] (partial resection in AL)	
1996	LLS [7, 8]	
1997	Hemi-hepatectomy [9–12]	
		Energy devices [30]
		(coagulating, sealing, shearing)
		CUSA
		HALS and hybrid procedures
		Inflow control [16]
2000s–2010s	Sectionectomy (right posterior, right anterior, left medial)	
		Glissonian approach (extra-, intrahepatic [13, 14])
		Caudal approach [15–17]
		Postural change [15]
	Segmentectomy and partial resection of segments 7, 8, 1	
		Postural change [15, 21]
		Caudal approach [15–17]
		Lateral approach (intercostal port) [19]
		Thoracoscopic approach [20]
	Limited and modified (extended and/or combining limited) anatomical resection [23–26]	
		Simulation and navigation [34, 35]
		Three-dimensional laparoscope [33]

Ref Reference number in the References section, *LLR* Laparoscopic liver resection, *AL* Anterolateral segments, *LLS* Left lateral sectionectomy, *CUSA* Cavitron ultrasonic surgical aspirator, *HALS* Hand-assisted laparoscopic surgery, *hybrid* Laparoscopic-assisted LLR

up. These manipulations can damage the liver and associated structures by compression and destruction, in addition to the damage caused by the liver resection itself. The laparoscopic approach allows direct access to the surgical field in the rib cage by maneuvering the laparoscope and forceps without destroying the surrounding environment, such as collateral vessels in patients with liver cirrhosis, and with less compression damage on the liver parenchyma [16, 37]. These careful maneuvers reduce the risk of postoperative ascites and liver failure in patients undergoing LLR of a cirrhotic liver [37]. The pneumoperitoneum pressure during laparoscopic surgery also minimizes blood loss from the hepatic vein, concomitantly with inflow control [16]. This creates a dry surgical field, with clear visualization of the detailed internal structures of the liver under a magnified view.

After the second ICCLLR in Morioka (2014), two important studies were published: one on hepatocellular carcinoma (HCC) and one on colorectal liver metastases, using propensity score analyses of data on about 5000 patients. Both showed the short-term benefits of LLR and similar long-term results to the open procedure [38, 39]. In the context of these advantages, several endeavors have been made to promote the adoption of LLR in clinical practice. To ensure the safe and consistent extended application of the procedure, the learning curve of LLR has been analyzed [40, 41]

and a difficulty scoring system [42] (calculated according to tumor condition, resection style, and liver condition) proposed for the appropriate selection of patients according to the surgeon's skill set [29].

Treatment for HCC in patients with chronic liver disease

The treatment options for HCC include liver resection (LR) [43], liver transplantation (LT) [44], transarterial chemoembolization, and local ablation therapy [45]. LR, LT, and local ablation therapy (only for small tumors) provide the best hope for cure [45–48]. However, most patients with HCC have underlying chronic liver disease (CLD) and are thus at high risk of post-treatment complications and metachronous multicentric recurrent lesions from the preneoplastic background. Currently, the choice of LR, LT, local ablation therapy, or transarterial chemoembolization is made for each patient depending on the tumor condition and their liver function [49]. However, a large number of HCC patients are not able to undergo any such treatment because of poor liver function and/or complicated tumor conditions. This is especially true after repeated treatments for recurrent disease.

When considering LR for HCC patients with CLD, not only the oncological therapeutic effects, but also the residual liver function and the degree of invasive surgical stress, especially to the diseased liver, should be taken into account. Patients with CLD have various symptoms [50] and a high risk of morbidity and mortality following anesthesia and surgery depending on the Child–Pugh (CP) class of their liver disease [51, 52]. For severe CLD patients, even limited LR can lead to refractory ascites, which may be fatal [53, 54]. Liver function assessment and a good understanding of the segmental liver anatomy through more accurate imaging studies, as well as surgical technical progress, are the most important factors that have reduced the mortality rate of HCC over the past decades. The expected 5-year survival after LR is now 38%–61%, depending on the stage of the disease [55]. Despite these advances, less than 30% of HCC patients are eligible for LR [56, 57]. Emerging evidence of the value of LLR [28, 29] may lead to the expansion of LR indication in the therapeutic system for HCC patients with CLD.

Impact of LLR on liver function

Patients who undergo LR are exposed to three different stresses: general whole-body surgical stress; reduced liver function, resulting from the reduced liver volume after resection; and surgery-induced injury to the environment surrounding the liver (caused by disruption of the collateral blood and lymphatic flow following laparotomy and mobilization) and residual liver parenchyma caused by parenchymal injury from compression [37]. Reduction of the third stress by the laparoscopic-specific "caudal approach [15–17]" in LLR (Fig. 1b), especially for HCC in patients with CLD, decreases the risk of refractory ascites, leading to a smoother recovery without liver failure [37, 38].

The impact of LLR on this depends on the severity of the CLD; the operative technique, including the extent of dissection of the peritoneal attachments and adhesions; and the extent of resection. Our previous study evaluated the short-term outcomes of liver surface small LLR for patients with severe CLD (Child–Pugh B or C and indocyanine green retention rate at 15 min (ICGR15) ≥ 40%), vs. those for patients with mild–moderate CLD [58]. Although the study was a small, retrospective unmatched study, it revealed comparable perioperative outcomes of the patients with severe CLD to those with mild-to-moderate CLD. These operations were performed with direct access to the surface tumors and minimum dissection of attachments and adhesions, even without inflow control and not touching any associated structures around the tumors. Only a laparoscopic approach can make possible this setting of resection with comparable outcomes to those of patients with less severe CLD. This is an important difference from OLR. As

an essential limitation, there cannot be objective data from a large number of patients with severe CLD undergoing LR. However, there is still a theoretical possibility that the indication for LR in patients with severe CLD can be expanded by the laparoscopic approach. The survival rate after transarterial chemoembolization for a small tumor is reportedly lower than that after LR [59] and a risk of tumor rupture and seeding has been reported in association with radiofrequency ablation for surface tumors [60]. Therefore, patients with surface small tumor outside the bare area, who do not need dissection of peritoneal attachments on the surface or major vessels on the bottom during transection, could benefit theoretically from LLR. However, the survival advantages of HCC treatments for patients with severe CLD (Child–Pugh C) have not been proven [61]. The median overall survival of our 12 patients who underwent LLR with an ICGR15 value of 40% or more and Child–Pugh B/C was 28.5 months [62]. Two of these patients underwent LT after LLR and one of them survived for more than 5 years after LLR. The other died of an accident unrelated to liver disease 36 months after LLR. Although LLR could be a bridging therapy to LT for HCC patients with severe CLD, the impact of LLR on the indications for LR and the consequent survival benefits should be evaluated further through a randomized control study comparing the overall survival of patients without any treatments vs. those treated with LLR and OLR. However, the population of patients with severe CLD who undergo treatments for small surface HCC would be limited. In association with Ghent University in Belgium as a center, we are now collecting data to analyze on Child–Pugh B/C patients who underwent LR from the institutes around the world. Thereafter, we need to conduct a prospective registry study to evaluate and discuss the selection criteria for LT and LR for these patients. Furthermore, we speculate that LLR would cause less deterioration of liver function postoperatively because there is less damage [63]. This should also be evaluated further.

Repeat LLR

Treatment of recurrence is another major issue for patients with HCC and CLD, as the CLD background harbors potential for multicentric metachronous lesions. Modifications of the anatomy and the formation of adhesions increase the difficulty of repeat LR. Laparoscopic surgery makes subsequent procedures easier through the minimization of adhesion formation [64]. Furthermore, LLR allows for better visibility and manipulation in a small operative field between adhesions when repeat LR is needed [65]. Several studies have compared LLR and OLR in the setting of repeat LR for HCC in patients with CLD [66, 67]. Although the operation time for repeat LLR in patients who underwent LLR as their initial surgery was significantly shorter than that in

Table 2 Summary of the present status of laparoscopic liver resection

Disadvantages

1. Movement restriction makes bleeding control demanding and reconstruction difficult

    Bleeding is controlled during transection using compression, clipping, suturing, temporary clamping, and various energy devices [16]

    Pneumoperitoneum pressure, airway pressure, and central venous pressure are managed with inflow control, which decreases venous bleeding and achieves a dry surgical field for easy hemostasis [16, 32]

    Procedures with vessel reconstructions such as the resection of hilar cholangiocarcinoma are not yet common [33]

2. The lack of overview in the operative field combined with the lack of tactile sensation can easily lead to disorientation of the operator

    Imaging studies and simulation and/or navigation have become more important [35, 36]

Advantages

1. Pneumoperitoneum pressure during laparoscopic surgery can reduce venous bleeding

2. The laparoscope provides a local fine magnified view

    By (1), a dry surgical field is created for easy hemostasis. (1) and (2) allow clear visualization of the bleeding points and detailed internal structures [16, 32]

3. Direct access to the liver inside the rib cage can be obtained (caudal approach [15–17])

    It allows for liver resection without destruction of the surrounding environment and with less compression damage to the liver [16, 37]

    A) These advantages decrease the risk of refractory ascites and liver failure, especially in HCC patients with CLD and collateral vessels [37]

    B) Liver surface small LLR can be applied as bridging therapy to LT for patients with severe CLD [58, 62]

    C) LLR is advantageous for repeat LR not only because it results in fewer adhesions but also because it reduces the need for adhesiolysis [65, 67]

    D) Repeat LLR is speculated to cause less liver function deterioration after LR [63]

  Expectation for HCC Treatment

    LLR may prolong the overall survival of HCC patients with CLD as a powerful local therapy which can be applied repeatedly with minimal deterioration of liver function

Future topics for evaluation

1. The impact of LLR on the expansion of LR indications and the consequent survival benefits, especially for patients with severe CLD

2. The outcome of repeat anatomical resections (or resections with exposure of major vessels) after previous anatomical resections

LLR Laparoscopic liver resection, *HCC* Hepatocellular carcinoma, *CLD* Chronic liver disease, *LT* Liver transplantation, *LR* Liver resection

patients who underwent initial OLR, repeat LLR was also associated with less blood loss, reduced transfusion rates, fewer postoperative complications, and a shorter hospital stay, than repeat OLR, regardless of the initial approach [66, 67]. Thus, LLR is advantageous not only for causing fewer adhesions as a preceding operation, but also for reducing the need for adhesiolysis in repeat LR. The laparoscopic view and manipulation through the "caudal approach" (Fig. 1b [15–17]) facilitates better access in a small operative field between adhesions and decreases the need for adhesiolysis. This could be explained as similar to the aforementioned advantages of LLR in CLD patients. On the other hand, LLR has its specific disadvantages, including the risk of operator disorientation from the lack of tactile sensation and limited overview of the whole operative field. Simulation and navigation from pre- and intraoperative imaging studies and well-planned small anatomical resection, to secure tumor localization in the resected area and a tumor-free resected margin, are used to overcome this disadvantage [63]. Although reports of repeat LLR generally mentioned that it is related to better short-term outcomes [65], most reported cases of repeat LLR are of minor repeat resection.

The impact of anatomical alterations to the liver parenchyma and intrahepatic structures from the previous LR could be relatively small in such cases. Among our 33 repeat and 12 three or more-times repeat LLRs, there were three anatomical resections or resections exposing the major vessels after previous anatomical resection complicated by postoperative bile leakage and a longer postoperative hospital stay. Since alterations of the anatomy and scars/adhesions surrounding the major vessel structures would have a big impact on anatomical resection or resections exposing major vessels in repeat LLR, further experience and evaluations of repeat LLR cases are needed.

Conclusion

From its inception in the early 1990s, LLR procedures have developed in a stepwise fashion based on technological and technical advances with conceptual changes (Table 1). Since then, specific advantages and disadvantages of LLR have been revealed (Table 2). LLR may prolong the overall survival of HCC patients with CLD as a powerful local therapy

which can be applied repeatedly with minimal impairment of liver function. The impact of LLR on expanding the indications for LR and the consequent survival benefits should be evaluated further.

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