Review Article

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Laparoscopic Liver Dissection Technique and Control of Bleeding for Hepatocellular Carcinoma

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Laparoscopic liver resection (LLR) was first reported by Reich in USA in 1991 and by Kaneko in Japan in 1993. Author personally started to perform LLR for HCC in 1998. Since the first and second International Consensus Conferences on Laparoscopic Liver Resection in 2008 and 2014, the trend of using LLR is clear and has advantages in terms of less blood loss and less complication. Laparoscopic techniques for liver resection were classified into pure laparoscopic liver resection, hand-assisted liver resection, and hybrid technique liver resection. The choice of method will depend on the tumor location and the difficulty of transection. There were several instruments for liver parenchyma dissection depending on the surgeon's experience and preference. There were 32 studies of HCC > 15 patients from each report and enrolled in this review. Totally, there were 2,511 patients of HCC, and their mean operative time was 235 minutes (ranged 140 – 420 minutes) and mean blood loss was 275.2 mL (ranged 55 – 630 mL). In addition, LLR had a better results compared with open liver resection. However, robotic approach for LLR had a similar blood loss but significantly longer operative time in the HCC patients compared with the conventional laparoscopic approach. In conclusion, laparoscopic liver resection is a procedure with significant risk and technical demand. The suggestion is for surgeons with limited experience in LLR should begin with wedge resection or minor liver resection, and then, transition to major hepatectomy with the hybrid procedures.

Key words: liver cancer, laparoscopic liver resection, operation time, bleeding control

Introduction

The success of laparoscopic cholecystectomy had been demonstrated in 1987 and enhanced the advantages of minimally invasive surgery. Since then, laparoscopic technique was adapted to liver surgery in the early 1990s for benign lesions[1] and for diagnosing the initial stages of liver cancer in 1980s.[2] Minimally invasive liver surgery has continuously developed since the first laparoscopic hepatectomy reported by Reich in America in 1991[3] and by Kaneko in Japan in 1993.[4] We had started to perform laparoscopic fenestration for giant liver cyst in 1994[1] and laparoscopic liver resection (LLR) for HCC in 1998. The procedures gradually expanded in the next couple of decades to include resections ranging from minor resection to living donor hepatectomy.[5-9] This propagation of minimally invasive surgery for LLR was due to the develop-

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ment of surgical instruments and improvement of surgical skills for liver surgical procedures.

Actually, the landmark in the rapid development of LLR was reached in 2008 during the first and second consensus meeting on laparoscopic liver surgery held in Louisville, Kentucky[10] and in Japan,[11] respectively. In addition, the European Guidelines Meeting on Laparoscopic Liver Surgery was held in Southampton in 2017 with the aim of presenting and validating clinical practice guidelines for LLR by an independent validation committee of 11 international surgeons. This meeting produced 67 guideline statements for the safe progression and dissemination of laparoscopic liver surgery.[12] Each of the statements produced a set of clinical practice guidelines for the safe development and progression of LLR. The laparoscopic approach must continue to demonstrate its potential advantages, development, and safe progression with the goal of improving patient care compared with open method. From 1998, we started to perform LLR for the patients of hepatocellular carcinoma (HCC).[5,13] LLR has additional advantages in the cirrhotic patient for tissue diagnosis in case of tumor size around 10 mm in diameter with a limited tumor resection.[5]

The challenge of LLR is mainly intraoperative bleeding during liver parenchyma transection.[14] Therefore, many reports mentioned the safety technique of LLR for liver tumor. With the improvement of laparoscopic technique and the development of new technology and instruments, LLR is feasible and safe for experienced liver surgeons.[3-5] This review presents and discusses the current status in the laparoscopic and robotic approach for LLR for the patients of HCC, especially in regards to operation time and blood loss.

Indications and LLR methods

At the beginning, diagnostic laparoscopy is considered to be a useful practice in tissue diagnosis of benign or malignant liver diseases, especially in case of tiny lesions which can be sent for pathologic diagnosis after limited resection in severe cirrhotic patients. The indications for LLR should follow the same guideline for open liver resection (OLR) pre-operative complete imaging study. Overall, the consensus recommends that patients with solitary lesions, less than 10 cm, and within peripheral segments may be amenable to LLR, and major hepatectomies or even living donor procedures should be reserved for expert liver centers for advance technique.[15,16] Criteria for exclusion from LLR were (1) proximity to the plane of transection or to major vascular or hilar structures (< 2 cm), (2) tumor diameter > 10 cm or, (3) extensive intra-abdominal adhesions at laparoscopy. The criteria listed above are general principles. However LLR for these patients with excluding criteria are currently only performed in a few expert liver centers in the world. LLR can be safely performed in selected patients even with centrally located tumors close to the liver hilum, the major hepatic veins, or the IVC that were previously considered to be contra-

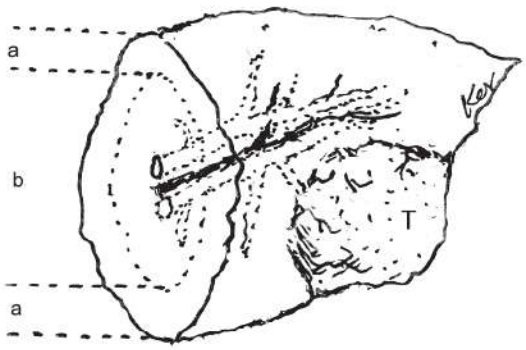

Fig. 1 Schema of the structure of liver parenchyma divided peripheral zone-a, and central zone-b. Small branch vessels or ducts supply in the zone-a, and main vessels or ducts and their branches were usually existed in the zone-b. Parenchyma transection at the zone-a could be performed with any energy devices such as Cavitron Ultrasonic Surgical Aspirator (CUSA), Microwave needle coagulator (MNC), Ultrasonic scalpel (US), and Monopolar sealer (MS), but clip or stapler should be applied on the large vessel after meticulously dissection at the zone-b.

indications for LLR reported by Yoon.[16]

Standardization of the laparoscopic surgical technical was determined in the first consensus on laparoscopic liver surgery and categorized laparoscopic techniques for liver resection into three groups: Pure laparoscopic liver resection (PLLR), Hand-assisted liver resction (HALR), and Hybrid technique liver resection (HLR).[10] HALR and the HLR technique have emerged to overcome some of the limitations faced by PLLR with the aim of expanding indications and safety of LLR.[17-19] These modalities allow surgical manipulation in a similar way to open liver resection having tactile sensation and facilitating a space for retrieving the specimen. This modality should be encouraged because of manual search for deep lesions, technical assistance during liver parenchyma transaction or vascular control and direct compression in case of bleeding. In addition, an amazing feature of HALR or HLR is that they are suitable for any type of difficult resections especially for segment VII, VIII, IVa, I, and even in living liver donation surgery.[9,20] The classical definition of minor resection is removal of one or two Couinaud segments, and major resection is defined as removal of more than three segments. In our clinical practice, most laparoscopic minor resections are left lateral sectionectomy or resections of segments II, III, IVb, V, or VI, that is, mainly the anterior and inferior segments. Therefore, the choice of method will depend on the tumor location or on the difficult part for approach. In regards to resections in the unfavorable locations, a very challenging procedure, either HALR or HLR is strongly recommended and can be cautiously applied in LLR.

Pitfall for bleeding control during parenchyma transaction

Transection of the superficial layer about 1 – 3 cm in depth of the liver parenchyma can be done with an energy device includ-

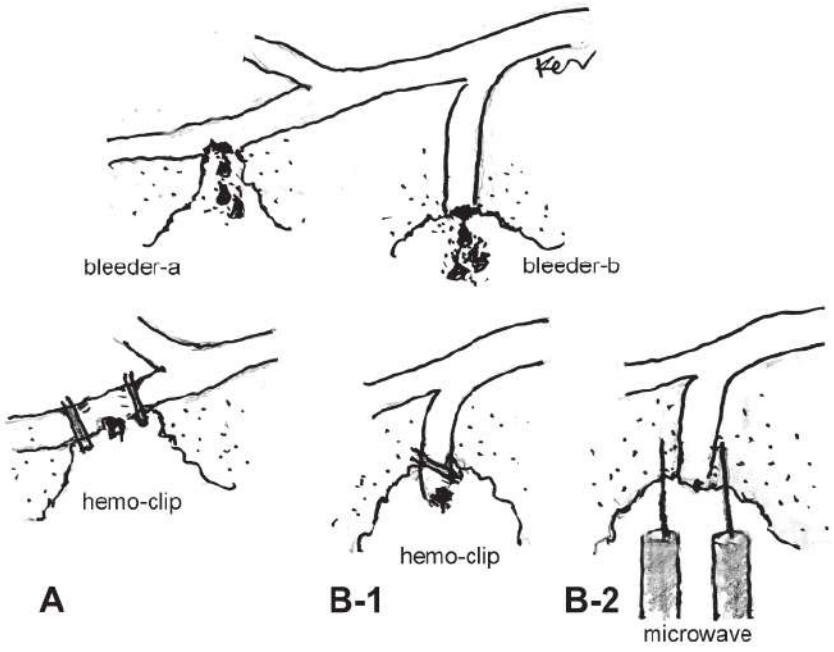

Fig. 2 Bleeding from the side hole of vessel (bleeder-a) and cut-end vessel (bleeder-b) during laparoscopic procedure. It is better to provide a space to identify the bleeder and clip the vessel proximal and distal site (A). If the bleeder due to the cut-end vessel and this bleeding vessel's direction is in front of operator view, it is better to provide a space for clipping (B-1) or with microwave needle cauterization along the bleeder (B-2).

ing Cavitron Ultrasonic Surgical Aspirator (CUSA), microwave needle coagulator (MNC), Ultrasonic scalpel (US), or Mono/bipolar sealer (MS) shown in Figure 1. Clip and stapler used for large vessel in the zone-b shown in Figure 2. Transection at the central part as shown in Figure 1 should be performed meticulously by exposing intra-parenchymal structures with an ultrasonic aspirator CUSA and clip the vessel in Figure 2 & 3. Hemostasis is usually achieved with MNC or MS for vessels of 2 mm or less, and with vessel sealing devices or clips for vessels of 3 to 6 mm. In addition, it is necessary to locate the bleeder from the side hole of the vessel (Fig. 2A) or from cut-end of vessel (Fig. 2B-1). In case of bleeder from the side hole, we can clip the bleeder after exposing an enough space to identify. If the bleeder was due to cut-end vessel and the direction of bleeding vessel is faced to your side, it was better to apply MNC or MS on the side of vessel to seal the bleeder as shown Figure 2. In case of cirrhosis, it is better to apply MNC device to cauterization along the resection line with 2 – 3 cm in depth before transection as shown in Figure 4. Locked clips or staplers are usually used for vessels of about > 7 mm. Almost all authors have reported using staplers to secure and divide major vessels such as the main hepatic veins or portal vein branches as well as the segmental Glissonian pedicles like that in open method. Multiple surgical implements are commonly chosen and mainly depended on surgeon's preference at the operation theater, Therefore, it is difficult to specify the best technique or device for laparoscopic hepatic parenchyma transection.

In case of difficulty in controlling bleeding, the pressure of pneumo-peritoneum central venous pressure (CVP), and ventilation rate and volume must be adjusted in a proper condition during operation beside the personal technical experience and instrumentation. Wakabayashi et al. had suggested to increase the pneumo-peritoneum pressure and decrease CVP appropriately, and then, this could provide a fairly good control of back-bleeding during liver transection.[21] The combination of low CVP and positive pressure pneumo-peritoneum during laparoscopic liver parenchymal transection could result in catastrophic air emboli in animal study of pig reported by Jayraman.[22] Take together of animal study and clinical experience, it was a key to establish the combination of low CVP and positive pressure pneumo-peritoneum during LLR. In addition, the role of anesthetist must be asked to reduce the tidal volume and increase the respiratory rate where

Fig. 3 Dissection liver parenchyma and extension an enough space for exposure the feeding vessel for clipping the vessel and decreasing bleeding during transection.

Fig. 4 Cauterization with MNC along the transection line to make coagulated plain in case of cirrhotic patient.

possible. In our experiences, we used to the pneumo-peritoneum pressure at the level of 8 – 12 mmHg routinely during liver LLR for prevention of carbon dioxide embolism. The energy-deviced coagulator was applied for ensuring hemostasis on the plain of liver transection surface before finishing the LLR.

Anatomic or non-anatomic resection and inflow occlusion

In the case of peripheral tumor location like zone-a in Figure 1, superficial resection can be performed non-anatomically, but care must be taken to secure an adequate resection margin due to the lack of tactile sensation during LLR. The use of intra-operative ultrasound either for accuracy of clear margins or to avoid injuries of major pedicles is recommended during LLR. Anatomic LLR is a very important concept in the treatment of HCC. HCC is usually associated with underlying impaired liver function due to chronic liver disease and cirrhosis. The techniques of anatomical liver resection could perform along the Glissonian pedicle approach have proven to be useful for limited bleeding after ligation or clipping the vessels in LLR such as Figure 5. The identification of anatomical boundary relies upon external landmarks on the liver surface made by coagulator with the aid of intra-operative ultrasound, and then selective clamping cautiously after meticulous dissection. Owing to technical development and accumulating experiences, advanced laparoscopic liver resections are being performed more often started from the non-anatomic to anatomic LLR. The lesion may be slowly completed dissected and resulting in anatomic liver resection even in case of difficult segment.

Pringle's maneuver is a useful method to reduce blood loss and decrease operation time in open liver resection or LLR.[23,24] Pringle's maneuver under laparoscopic approach was not easy due to the narrow space for encircling the portal triad to achieve adequate hepatic inflow control between hepatoduodenal ligament and inferior vena cava. The additional innovative equipments were used for controlling the hepatic inflow occlusion such as Endo Retract Maxi,[25] hanging maneuver method[26] and six-loop tube[24] for anatomic or non-anatomic LLR. Operation time and blood loss reported from the 32 literatures and the instruments their used for LLR were listed in Table 1.

Discussion

LLR has been becoming a common surgical procedure for treatment of both benign and malignant liver tumors, especially in the past decade. Proportion of liver resections performed by laparoscopy had a slight but progressive increase through the 3 periods reported by Vigano et al.,[57] it passed from 17.5% in 1996 – 1999 to 22.4% in 2000 – 2003, and to 24.2% in 2004 – 2008. A national survey from Japan showed that the percentage of total liver resection with LLR procedure was found to be 9.9%

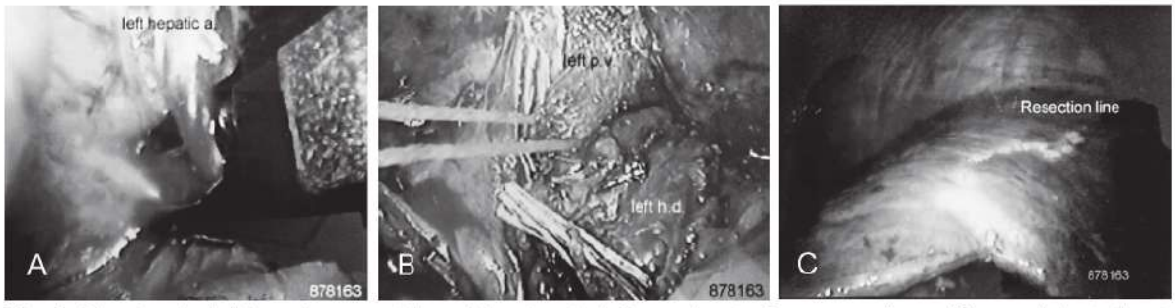

Fig. 5 Clipping the left hepatic artery (A), and ligation the left portal vein (B) were performed first, and the ischemic demarcation was found and produced a resection boundary marked by coagulator (C) for left hepatectomy.

Table 1. Operation time, blood loss and parenchyma transection instruments, used in LLR of HCC patients (original report and n >15 patients).

	Author	N HCC/total	Operation time (min) mean	Blood loss (mL) mean	Instruments for transection				Remarks
					UltraS	CUSA	MNC	Mono/ bipolar	
1	Belli[27] Italy 2004	16	152	280	v			v	One mortality
2	Kaneko[28] Japan 2005	40			v	v	v	v	
3	Belli[29] Italy 2009	15		300	v	v		v	Redo & Pringle
4	Lai EC[23] Hong Kong 2009	25	150	200	v	v		v	Pringle
5	Bryant[30] France 2009	64/166	180	200	v	v			Pringle
6	Inagaki[31] Japan 2009	36/52	214	393				v	
7	Santambrogio[32] Italy 2009	22	199	183				v	
8	Nitta[33] Japan 2010	15/47	317	631				v	Major
9	Ker[34] Taiwan 2011	116	156.3	138		v	v	v	Minor & Major
10	Casaccia[35] Italy 2011	22	300	55	v	v		v	
11	Chao[24] Taiwan 2012	18/20	33*	102	v	v		v	Pringle Minor
12	Shetty[36] Korea 2012	24	205	500	v	v		v	Single port
13	Honda[37] Japan 2013	21/69	361	216	v	v		v	Pringle
14	Lai[38] Hong Kong 2013	41	202.7	373.4					Robotic
15	Memeo[39] France 2014	45	140		v	v		v	
16	Wu[40] Taiwan 2014	41/69 #38/52	227 #380	173 #227					Robotic
17	Xiang[41] China 2015	126	195	253.8	v			v	Inflow occlusion

18	Chan[42] Hong Kong 2016	26/49	420	600	v	v		v	Major
19	Chen[43] China 2017	225	222.4	156	v	v		v	Inflow occlusion
20	Chen[44] Taiwan 2017	34	402	182				v	Robotic Inflow occulusion
21	Di Sandro[45] Italy 2018	75	165	150	v	v		v	Minor
22	Ei-Gendi[46] Egypt 2018	25	120.3	250	v			v	Pringle Habit 4X
23	Lee[47] Taiwan 2018	18	287	217.2	v			v	Inflow occlusion
24	Liu[48] Taiwan 2018	135	LigaSur 199.4 CUSA 233.7	LigaSur 200.6 CUSA 409	v	v			Pringle Minor
25	Peng[49] China 2019	92	$LHIOA 157	$LHIOA 60	v			v	Inflow occlusion
26	Aldrighetti[50] Italy 2019	362/1032	175	210	v	v		v	Pringle
27	Tsai[51] Taiwan 2019	153	175.1	363.1	v	v		v	
28	Wu X[52] China 2019	86		150					
29	Zeng[53] China 2019	38	373.5	679.4	v	v		v	
30	Lee[54] Korea 2020	268	302.5	221.8					Robotic
31	Sucandy[55] USA 2020	22/80	233	150					Robotic
32	Yoon[56] Korea 2020	217/651	234.2	225.7	v	v		v	Pringle manuver
	Total	**2511	*235	275.1	22	18	2		

UltraS: ultrasonic Scapel; CUSA: Cavitron Ultrasonic Surgical Aspirator; MNC: microwave needle coagulator; Pringle: Pringle maneuver; Robotic: robotic LR; Minor: minor LLR; Major: major LLR
*excluded the list number 11 due to transection time not operation time
$ laparoscopic hepatic inflow occlusion apparatus (LHIOA); # robotic liver resection
**HCC patient number only

in 2011 and increasing to 24.8% in 2017.[58] In general, since the first and second International Consensus Conferences on Laparoscopic Liver Resection in 2008 and 2014, the trend of use of LLR is clear and has advantages in terms of less blood loss, less complication and shorten hospital stays.[10,11] However, LLR surgery requires experienced surgeons in open hepatic resection surgery, minimally invasive surgery, and laparoscopic ultrasonography. We believe that indications for laparoscopic liver resection should be broadened due to the increasing development of available instruments. Resections of liver segments I, VII, VIII and major liver resections such as right hepatectomy, left hepatectomy, extended right, or left hepatectomy should be reserved for significant experience in laparoscopic liver surgery. A hand-assisted laparoscopic liver resection or laparoscopic-assisted hybrid approach should be considered for these major difficult resections where possible. In concern of a posterior tumor in the right lobe for resection or a bulky right lobe for a right hemi-hepatectomy, hand-assisted LLR are used selectively in right-sided resections where mobilization is difficult. A multi-institutional review on laparoscopic major hepatectomy by Dagher et al.[59] showed that hand-assisted laparoscopic (n = 119, 56.7%) was choose more than pure laparoscopic (n = 91, 43.3%) for liver resection. Their operative time were 230.2 ± 86.4 minutes and 299.9 ± 112.3 minutes ($p < 0.0001$) respectively between the two groups. In the case of high difficulty for dissection or control bleeding, conversion to an open procedure should not be deemed a failure. Conversion to open resection should be encouraged if adequate resection margins cannot be obtained.

Operative time and blood loss were compared between the patients with different type of methods and instruments. In this review, we enrolled 32 studies of HCC > 15 patients for each report listed in the Table 1. There were a total of 2,511 patients of HCC and their mean operative time was 235 minutes with range 140 – 420 minutes and mean blood loss was 275.2 mL with range 55 – 630 mL. A study by Tozzi F showed that operative blood loss was reduced in 58 patients undergoing laparoscopic liver resection compared with 58 patients undergoing open resection (480 vs. 550 mL, $p = 0.577$).[60] Their mean operation time was 156.3 minutes and 190.9 minutes for LLR and traditional liver resection respectively. The necessity for blood transfusion was also found in 6.9% and 50.9% for LLR and traditional liver resection in our previous report.[34] When surgeons become more adroit in this field of hepatobiliary surgery, LLR may become a less time-consuming operation. Cannon et al. found that, the operative time was decreased from 3 hours for their first 100 patients and down to about 2 hours for the latest 100 patients.[61] Without question, the trend consistently showed that operative times and blood lost significantly decreased by increasing experiences.

The suggestion for surgeons with limited experience in LLR is they should begin with minor hepatectomy, or minor non-anatomic hepatectomy, and transition to major hepatectomy with the hybrid procedures from our opinion. In a risk-adjusted Cumulative Sum analysis showed that the learning curve for LLR of 58 cases for each three consecutive periods (1996 – 1999, 2000 – 2003, and 2004 – 2008) were compared and significant improvements were seen in conversion rates (15.5%, 10.3% and 3.4%, $p < 0.005$), operative time (210, 180 and 150 minutes, $p < 0.05$), and operative blood loss (300, 200 and 200 mL, $p < 0.05$).[57] In this review which included 32 reports of 2,511 HCC patients, these patients number were increasing from 233, 492 to 1,786 reported in the divided 3-period 2004 – 2010, 2011 – 2015 and 2016 – 2020 as shown in Table 2. The differences of operation time and blood loss were not significant, but it was clear that more difficult LLR were performed without increasing operation time or blood lost in recent years.

A pre-operative index of difficulty for evaluation for LLR was assessed and there were two different difficulty scores developed in the setting of laparoscopic resections; by Ban et al.[62] and by Kawaguchi et al.[63] These two scoring methods were used either to count the type of procedures or to categorize it into three levels of surgical difficulty. Usually, the stratification was built based on intra-operative outcomes including operative time, blood loss, and conversion rate.[63] The learning curve as evaluated by the cumulative sum analysis showed its first reverse for improving surgical results after 22 cases, and the second reverse for difficult LLR needed an additional 40 cases of experience.[64] Another cumulative sum analysis showed that operative time improved after the 25th LLR.[42] Lee et al.[65] had compared patients with lesions located in the anterio-lateral segments (AL group, n = 44) to posterior-superior segments (PS group, n = 25) undergoing LLR for HCC. The operation time (355 minutes vs. 212 minutes, $p < 0.005$) and blood loss (600 mL vs. 410 mL, $p < 0.001$) were significantly greater in the PS group than in the AL group. Therefore, laparoscopic approach for the lesion located in postero-superior segment is technically demanded with the possibility of significant bleeding or time consuming for liver parenchyma transection and recommended to be performed by very experienced surgeons.

Nowadays, the advances in technology have led to a development of robotic surgery being widely adopted in LLR. The robotic liver resection through its 3D imaging and advanced-mobility instruments may accommodate for LLR in difficult patients. In an analysis of minor liver resection for HCC, when robotic approach compared with the conventional laparoscopic approach, the robotic group had similar blood loss (mean, 373.4 mL vs. 347.7 mL) and significantly longer operative time (202.7 minutes vs. 133.4 minutes).[38] Another report of total of 80 patients underwent robotic hepatectomy, operative time was 233 minutes (267.2 ± 109.6), and blood loss was 150 mL (265.7 ± 319.9).[55] Notably, this robotic laparoscopic technique can be very helpful when performing hilar dissection, transection of hepatic parenchyma tissue and control of liver outflow, and when dealing with posteriorly located hepatic lesions. Robotic surgery is completely different from traditional surgery and many adjustments need to be inspected including robotic port placement, development of more advanced surgical instruments and training of table-side surgeons, while hospital costs should always be taken into consideration. Without question, robotic approach is safe and feasible, and even widely adopted in the field of hepato-bilio-pancreatic surgery.

In conclusion, the majority of the LLR usually begins with wedge resection or left lateral segmentectomy. In the case of left or right major hepatectomy which are more challenging and technically demanded, those difficult cases should be attempted only by highly skilled and experienced surgeons. In order to have a safe transection in a difficult segments, Pringle's maneuver or isolated inflow control procedures should be performed and keep in

Table 2. Accumulated mean operation time and blood loss in LLR for HCC reported from enrolled literatures of Table 1.

Variant	2004 – 2010	2011 – 2015	2016 – 2020 May	*p* value
Number of reference	8	9	15	-
Number of HCC	233	492	1786	-
Operation time (min)	202.0 ± 61.8	223.3 ± 73.6	247.6 ± 95.7	0.523
Blood loss (mL)	312.4 ± 158.8	226.4 ± 147.8	254.4 ± 170.2	0.585

main always. In the face of difficulty in LLR, it is better to change into hand-port assisted or hybrid approach for safe approach or easier bleeding control during transection. LLR for HCC was increasing gradually and was considered a safe and feasible procedure due to the developments of advanced instruments for LLR even in every difficult cases which were recognized as mission impossible in the past.

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