Laparoscopic liver resection for hepatocellular carcinoma: review of current status

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Abstract: Despite initial skepticism of laparoscopic liver resection (LLR) due to fears of uncontrolled bleeding, margin involvement resulting from a lack of palpation of laparoscopy, and a steep learning curve, LLR has progressively developed over the past two decades. Through a review of the literature, we compare perioperative and oncologic outcomes of laparoscopic and open liver resection (OLR) for hepatocellular patients, and assess current indications and limitations of laparoscopic liver surgery. Although randomized control trials have not been reported, other data indicate the safety and better short-term outcomes of LLR compared to OLR for hepatocellular carcinoma (HCC) without compromising oncologic outcomes including resection margin status and long-term survival. Moreover, LLR is associated with reduced postoperative ascites and a lower incidence of liver failure for HCC patients with liver cirrhosis (LC) and facilitates subsequent repeat surgery by reducing operation time due to minimal adhesion formation. Major hepatectomies and resections of unfavorable locations in classic indication are expected to benefit from this approach, overcoming the current limitations.

Keywords: Laparoscopy; minimally invasive; hepatectomy; hepatocellular carcinoma (HCC)

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Introduction

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver, the fifth most common cancer worldwide, and the third most common cause of cancer mortality (1). Multiple treatment options are available for HCC including surgical resection, liver transplantation, radiofrequency ablation, trans-arterial chemoembolization, and use of systemic targeted agents like sorafenib (2). The process of choice of a particular treatment modality in HCC depends on the tumor stage, patient performance status, and liver function reserve (2). Although focal ablation techniques can treat small HCCs, the only curative therapeutic options available are surgical resection and liver transplantation.

Liver transplantation is the only treatment that offers a chance of cure for HCC and the underlying liver cirrhosis (LC) simultaneously (3). However, owing to various limitations, such as donor availability and the aggressiveness of tumor recurrence from inevitable immunosuppression, liver transplantation is limited in its application. Therefore, liver resection is widely accepted as a first-line treatment for HCC with good liver function in many centers (3,4).

The first non-anatomical laparoscopic liver resection (LLR) for a benign liver tumor was performed in the early

1990s (5,6), the first anatomic LLR in 1996 (7), and the first LLR for HCC in 1995 (8). However, the adoption of LLR has been much slower than other surgical fields. Reasons include the fear of uncontrollable bleeding during parenchymal transection, complex vascular and biliary anatomy, fragile parenchyma, difficult exposure secondary to size and deep, posterior retroperitoneal attachments, lack of a dedicated instrumentation, and concern about oncological outcomes like adequate margins (9-11). Nevertheless, LLR has become a widely accepted option of curative resection for HCC by continuous progression of surgical devices, enhanced postoperative management of patients, and augmented surgical skills over the past several decades. It has also evolved to enable to perform more difficult anatomical resections (12,13).

The purpose of this review is to discuss the outcomes, and assess the current status and trend of LLR for HCC compared with open liver resection (OLR).

Benefits of laparoscopy in liver resection

LLR has universal benefits of minimal invasive surgery including reduced postoperative pain, decreased length of hospital stay and recovery, and cosmesis (14), as well as some additional theoretical benefits compared with OLR (15). These additional benefits could come mainly from magnification and pneumoperitoneum effects of laparoscopy. The main reason of bleeding during liver resection is vascular injury, in particular from the small hepatic vein. For the exposure of the intrahepatic vessels, even tiny anatomical structures within the hepatic parenchyma can be easily seen in laparoscopy. This magnification effect provides for a more accurate surgery and reduces bleeding from the hepatic vein as a result of pneumoperitoneum pressure. Although restriction on movement by remote manipulation through a trocar is a big drawback in laparoscopy, it has little effect on hepatic parenchymal transection. Hepatic parenchymal transection is mainly anterior-posterior manipulation in the cranio-caudal direction along the Cantlie line with either caviton ultrasonic surgical aspiration or clamp-crush technique in both LLR and OLR (15).

Outcomes of LLR for HCC patients

A literature search to evaluate the outcomes of LLR compared with OLR was performed using PubMed. English language articles were selected using the following combinations of keywords: (laparoscopic or laparoscopy) and (liver resection or hepatic resection or hepatectomy) and (hepatocellular carcinoma). The final search was completed by August 2016. All titles and abstracts were screened and those related to LLR for HCC were retrieved. The PubMed search identified a total of 580 articles. Of these, 41 comparative studies (16-36) for LLR for HCC (37-56) and 11 meta-analyses (20,57-66) for HCC were identified. We excluded the articles included the data of other malignant or benign diseases. Lastly, we selected 36 comparative studies (16-35) between LLR and OLR for HCC (36-51) and 9 meta-analyses (20,57,59-65) for HCC. Studies listed in table in present study are restricted to 23 comparative studies (16-23,25,27-33,36-38,40-42,44) including more than 30 patients in each arm published since 2010.

Operative outcomes

Operation time

Most comparative studies between LLR and OLR showed heterogeneous results. Some studies reported longer operative time in the LLR group (19,20,23,27,41,50), while others described shorter operative time in the LLR group (16,22,32,33,39,43,46). The reason the operation time varied so markedly was that it can be affected by the type of resection and surgeon's experience. In addition, surgical techniques are not standardized yet. However, seven of nine meta-analyses (57,59-63) demonstrated that operation time was not significantly different between both groups.

Open conversion rate

There is universal acceptance that conversion should not be considered as a complication (14). However, open conversion is usually considered a criterion of quality in laparoscopic surgery (67). Selected literatures in this study reported widely variant conversion rates for LLR of 0% to 34.2% (*Table 1*). The main reasons for conversions are bleeding and technical problems including difficult exposure, insufficient or poor quality view, fragile tumor with risk rupture, and uncertainty about the distance between the tumor and the transection plane (66). In case of bleeding, we should also consider that the process of conversion might lead to the further bleeding or hemodynamically unstable situation, so that efforts should be made to control the bleeding before converting in

Table 1 Operative outcomes in comparative studies of laparoscopic and open liver resection for hepatocellular carcinoma (including more than 30 patients published since 2010)

Study	Patients, n		LC patients, %		Mean [median] OP time, min			Open conversion, %	Mean [median] blood loss, mL			Transfusion, % of pts		
	LLR	OLR	LLR	OLR	LLR	OLR	P value		LLR	OLR	P value	LLR	OLR	P value
Cheung *et al.* (16), 2016	110	330	70.9	75.8	[185]	[255]	<0.001	5.4	[150]	[410]	<0.001	2.7	5.8	NS
Sposito *et al.* (17), 2016	43	43	100	100	[199]	[199]	NS	4.6	–	–	–	–	–	–
Ahn *et al.* (18), 2016	32	93	75.0	66.6	321.2	348.4	NS	6.3	–	–	–	6.3	19.3	NS
Komatsu *et al.* (19), 2016	38	38	57.9	50	365	300	<0.001	34.2	100	80	NS	5.2	2.6	NS
Leong *et al.* (20), 2015	42	100	59.5	35.5	250.4	349.9	<0.001	11.9	495.8	1,085	<0.001	9.5	39.1	<0.001
Martin *et al.* (21), 2015	100	254	40.0	60.0	–	–	–	–	336	637	NS	1.2	1.9	NS
Yoon *et al.* (22), 2015	58	174	–	–	[207]	[255]	0.00	0	–	–	–	3.4	7.5	0.04
Luo *et al.* (23), 2015	53	53	–	–	[180]	[150]	0.025	–	[210]	[290]	0.012	–	–	–
Meguro *et al.* (25), 2015	35	35	48.5	48.5	277	290	NS	–	150	310	0.002	2.9	11.4	NS
Takahara *et al.* (27), 2015	387	387	61.7	59.6	294.4	271	0.025	6.5*	[158]	[400]	<0.001	7.2	9.8	NS
Han *et al.* (28), 2015	88	88	62.5	59.1	[305]	[285]	NS	9.1	[500]	[525]	NS	20.0	26.1	NS
Yamashita *et al.* (29), 2015	63	99	–	–	299.5	287.4	NS	–	455.7	436.6	NS	6.0	2.0	NS
Ahn *et al.* (30), 2014	51	51	68.6	66.7	210.7	202	NS	–	350	355.2	NS	5.9	9.8	NS
Lee *et al.* (31), 2015	43	86	43.9	38.8	[170]	[197]	NS	13.9	[300]	[700]	0.004	–	–	–
Memeo *et al.* (32), 2014	45	45	100	100	[140]	[180]	0.02	0	[200]	[200]	NS	0	0	NS
Kim *et al.* (33), 2014	70	76	–	–	215.5	282.3	0.001	8.6	215.5	282.3	0.001	24.2	40.7	0.001
Ai *et al.* (36), 2013	97	178	80.4	80.3	245	225	NS	9.2	460	454	NS	4.6	2.8	NS
Cheung *et al.* (37), 2013	32	64	87.5	79.7	232.5	204.5	NS	0	[150]	[300]	0.001	0	4.7	NS
Hu *et al.* (38), 2011	30	30	–	–	180	170	NS	0	520	480	NS	–	–	–
Ker *et al.* (40), 2011	139	1,147	–	–	156.3	190.9	NS	4.3	138.9	1,147.4	<0.001	6.9	50.9	<0.001
Lee *et al.* (41), 2011	33	50	84.8	64.0	[225]	[195]	0.019	18.2	[150]	[240]	NS	6.1	10.0	NS
Truant *et al.* (42), 2011	36	53	–	–	193.4	215.8	NS	19.4	452.2	447.2	NS	2.8	3.8	NS
Tranchart *et al.* (44), 2010	42	42	73.8	81.0	233.1	221.8	NS	4.7	364.3	723.7	<0.0001	9.5	16.7	NS

*, included conversion to laparoscopy-assisted method. LC, liver cirrhosis; OP, operation; LLR, laparoscopic liver resection; OLR, open liver resection.

certain circumstances (14). This is because surgeons with validated laparoscopic skill can control the bleeding more easily under magnified visualization of laparoscopy.

Open conversion also can be affected by types of resection and aspects of surgeon's expertise like operation time. Nomi *et al.* (68) analyzed a learning curve using a cumulative sum technique in 173 patients that underwent major LLR. The learning curve comprised three phases: phase 1 (45 initial patients), phase 2 (30 intermediate patients), and phase 3 (the subsequent 98 patients). The learning curve adjusted for the risk factors of conversion demonstrated that the rate of conversion to open surgery decreased in later years (18, 20 and 6% in phases 1, 2, and 3 respectively). Previous abdominal surgery, resection of adjacent organs, blood loss greater than 500 mL, intraoperative transfusion, and vascular clamping were associated with a significantly higher risk of conversion (68).

HCC often occurs in the background of a chronic liver disease. Several studies on LLR for HCC patients with LC reported conversion rates ranging from 2% to 19.4% (35,37,42,46,69-71). Cirrhotic patients seemed not to show higher conversion rate in LLR.

Two representative comparative studies between LLR with LC and without LC showed no significant difference in association with conversion rate and LC (69,70). Shehta *et al.* (70) reported that open conversion occurred in 13 cases (9.1%) of the LC group (N=141) and 10 cases (11%) of the non-LC group (N=91) (P=0.824). Worhunsky *et al.* (69) reported that conversion to open surgery occurred in one case (2%) of the LC group (N=48) and 2 cases (2%) of the non-LC group (N=119) (P=1.0). However, conversion to hand-assisted laparoscopy occurred in 4 cases (8%) of the LC group and one case (1%) of the non-LC group (P=0.024).

Blood loss, transfusion

Major blood loss during liver resection has a direct effect on postoperative course and negatively affects oncological outcomes. Perioperative blood transfusions are associated with a higher rate of recurrence and lower survival after surgical treatment of malignant diseases, especially HCC (72). Many cases of bleeding during parenchymal transection in LLR are related to hepatic vein injuries. The positive pressure of pneumoperitoneum, magnified vision of operative field of laparoscopy, and the development of new transection devices has resulted in reduced blood loss, less intraoperative bleeding, and lower rates of blood transfusion. Most comparative studies and meta-analyses series that were presently selected demonstrated significantly less intraoperative blood loss and blood transfusion requirement compared with OLR (*Table 1*).

Postoperative outcomes

Hospital stay

Length of hospital stay ranged from 4 to 16.2 days, with comparative studies consistently showing shorter length of hospital stay compared with OLR (*Table 2*). Most meta-analysis showed significantly shorter length of hospital stay in LLR (*Table 3*). However, the variability of hospital stays may be due to a culture and health insurance system bias.

Complication rate

A large study of LLR including malignant and benign indications (73) demonstrated that the overall morbidity was 0% to 50%. Of 2,804 patients, 295 complications were reported (10.5%). Postoperative bile leak was reported in 1.5% of the cases; other liver-related complications included transient liver failure/ascites (1%). Most common surgery-related complication was trocar site bleeding, and the most common general complication was pleural effusion. Complications tended to occur more frequently after LLR for HCC (50%) compared with LLR for colorectal metastasis (11%, P=0.02), likely due to underlying liver disease and the potential for postoperative liver failure. A recent multi-institutional Japanese study of LLR for HCC (27) demonstrated that common complications were ascites and bile leak, with a complication rate of 6.72%.

The literatures (16-35) in this study (36-51) reported complication rates ranging from 0% to 44.0%; 12 out of the 36 comparative studies (17,19,22,26,27,29,32,35,36,40,41) showed significantly lower complication rate in LLR. Most meta-analyses showed significantly lower complication rate in LLR (*Table 3*). Among the aforementioned 36 comparative studies, 18 (20,23,25-27,29,30,32-37,40,42-44,50) analyzed postoperative ascites development; 7 of them (29,32,34-36,40,44) showed significantly reduced incidence of ascites. These results were validated by 4 meta-analyses (59,61,63,64), which showed significant reduction in the incidences of postoperative ascites and liver failure. In addition, recent systematic review that was prepared to create recommendations before the 2nd International Consensus Conference on Laparoscopic

Table 2 Postoperative outcomes in comparative studies of laparoscopic and open liver resection for hepatocellular carcinoma (including more than 30 patients published since 2010)

Study	Mean [median] hospital stay, d			Complication rate, %			Postop. ascites, %			Postop. liver failure, %		
	LLR	OLR	P value	LLR	OLR	P value	LLR	OLR	P value	LLR	OLR	P value
Cheung *et al.* (16), 2016	[4]	[7]	<0.001	9.1	15.2	NS	–	–	–	–	–	–
Sposito *et al.* (17), 2016	[5]	[8]	<0.001	18	49	0.004	–	–	–	–	–	–
Ahn *et al.* (18), 2016	7.2	12.2	0.045	18.8	25.8	NS	–	–	–	–	–	–
Komatsu *et al.* (19), 2016	7.5	10	NS	31.6	60.5	0.011	–	–	–	–	–	–
Leong *et al.* (20), 2015	7.5	11.4	<0.001	38.1	45.5	NS	2.4	3.6	NS	4.8	0.9	NS
Martin *et al.* (21), 2015	6.2	9.14	0.002	44.0	56.9	NS	–	–	–	–	–	–
Yoon *et al.* (22), 2015	[9.2]	[15]	0.00	8.6	22.9	0.02	–	–	–	–	–	–
Luo *et al.* (23), 2015	[10]	[12]	0.015	30.1	35.8	NS	5.6	5.6	NS	1.8	3.7	NS
Meguro *et al.* (25), 2015	NA	NA	–	18.3	16.5	NS	10.0	8.3	NS	4.5	3.3	NS
Takahara *et al.* (27), 2015	[13]	[16]	<0.001	6.72	12.99	0.003	1.8	3.7	NS	0.5	1.8	NS
Han *et al.* (28), 2015	[8]	[10]	<0.001	12.5	12.5	NS	–	–	–	3.4	8.9	0.041
Yamashita *et al.* (29), 2015	16.2	10.3	0.0008	10.0	26.0	0.0459	0	7.0	0.0077	–	–	–
Ahn *et al.* (30), 2014	8.2	12.3	0.004	5.9	9.8	NS	1.9	3.9	–	–	–	–
Lee *et al.* (31), 2015	[5]	[7]	<0.001	23.3	39.5	NS	–	–	–	–	–	–
Memeo *et al.* (32), 2014	[7]	[12]	<0.0001	20	45	0.01	2	18	0.01	2	11	0.09
Kim *et al.* (33), 2014	12	17.1	NS	7.1	14.4	NS	0	17.2	0.025	–	–	–
Ai *et al.* (36), 2013	8.2	13.5	0.028	11	28	0.01	0	2.2	0.003	–	–	–
Cheung *et al.* (37), 2013	[4]	[7]	<0.001	6.3	18.8	NS	0	1.6	NS	–	–	–
Hu *et al.* (38), 2011	13	20	<0.01	13.3	10	NS	–	–	–	0	0	-
Ker *et al.* (40), 2011	6.2	12.4	0.001	6	30.2	<0.001	1.7	12.5	0.002	–	–	–
Lee *et al.* (41), 2011	[5]	[7]	<0.0005	6	24	0.033	–	–	–	–	–	–
Truant *et al.* (42), 2011	6.5	9.5	0.003	25	35.8	NS	13.9	22.6	NS	–	–	–
Tranchart *et al.* (44), 2010	6.7	9.6	<0.0001	21.4	40.5	NS	7.1	26.1	0.03	–	–	–

LLR, laparoscopic liver resection; OLR, open liver resection.

Table 3 Meta-analyses of laparoscopic and open liver resection for hepatocellular carcinoma

Study	No. of studies	Patients, n		Operation time	Blood loss	Transfusion	Hospital stay	Cx	Ascites	Liver failure	Resection margin	Overall survival	Recurrence-free survival
		LLR	OLR										
Chen *et al.* (57), 2015	7	281	547	NSD	LLR	LLR	LLR	LLR	NA	NA	LLR	NSD	NSD
Leong *et al.* (20), 2015	18	641	1,013	NA	NA	NA	LLR	LLR	NA	NA	NA	NA	NA
Morise *et al.* (58), 2015	21	758	1,255	NA	NA	NA	NA	NA	LLR	LLR	NA	NA	NA
Twaij *et al.* (59), 2014	4	150	270	NSD	LLR	LLR	LLR	LLR	NA	NA	LLR	NSD	NSD
Yin *et al.* (60), 2013	15	485	753	NSD	LLR	LLR	LLR	LLR	NA	NA	NSD	NSD	NSD
Xiong *et al.* (61), 2012	9	234	316	NSD	LLR	LLR	LLR	LLR	LLR	LLR	NSD	NA	NSD
Li *et al.* (62), 2012	10	244	383	NSD	LLR	LLR	LLR	LLR	NA	NA	NSD	NA	NSD
Fancellu *et al.* (63), 2011	9	227	363	NSD	LLR	LLR	LLR	LLR	LLR	LLR	LLR	NSD	NSD
Zhou *et al.* (64), 2011	10	213	281	NSD	LLR	LLR	LLR	LLR	LLR	NSD	NSD	NSD	NSD

Cx, complications; NSD, no significant difference; NA, not available; LLR, laparoscopic liver resection; OLR, open liver resection.

Liver Resection also showed significant lower incidences in both postoperative ascites and postoperative liver failure development (74).

Mortality

Thirty-day postoperative mortality or in-hospital mortality rates ranged from 0% to 4.5% in the comparative studies. On the contrary, reported mortality rate for OLR was in the range of 0% to 7.5%. A world review (73) reported an overall mortality was 9 of 2,804 patients (0.3%). A French survey (75) in 351 patients found the 30-day postoperative mortality rate was 2%. The largest systematic review to date reported 37 deaths out of 9,627 total LLRs, giving a mortality rate of 0.39%. From the meta-analysis comparing case-matched LLR to OLR, there was no increased mortality (76).

Oncologic outcomes

Resection margin

In the initial application period of laparoscopic liver surgery, the oncologic efficacy of LLR was much debated. Many surgeons were indifferent because of the vague fear of margin involvement due to lack of palpation of laparoscopy and trocar site tumor seeding. Since then, several retrospective comparative studies (46,47) have shown that surgical margins are comparable irrespective of whether the operation was performed by laparoscopy or laparotomy (77). Most of the presently identified comparative studies (16,19-21,24,25-28,34,36,39,41,43,46,47,50,51) indicated similar rates of positive resection margin after LLR when compared with OLR, and 4 of the searched meta-analyses demonstrated no significant positive resection margin rates in LLR (60-62,64); 3 of the meta-analyses also demonstrated significant wider resection margin (57,59,63) (*Table 3*). Presently, there was no reported port-site recurrence of HCC. But, one case of subcutaneous seeding of HCC in the laparotomy wound following laparoscopy-assisted partial hepatectomy was reported in 2011 (78). In LLR for colorectal cancer liver metastasis, one port-site metastasis was reported (79).

In a European multicenter study regarding LLR for malignancies, the rate of obtaining surgical margins less than 1 cm decreased from 60% to 20% when laparoscopic ultrasound was used (80). A widespread use of intraoperative ultrasound can help to overcome the lack of tactile feedback in laparoscopy as well as aiding the surgical plane in order to obtain clear surgical margins. In addition to identifying occult unknown lesions (72,81). The optimal extent of the margin of liver resection for HCC remains controversial despite extensive studies. In a randomized trial comparing a wide 2 cm margin with a narrow margin aiming for 1 cm in partial hepatectomy, improved survival outcomes were observed in the wide margin group. However, it is accepted that a 1 cm surgical margin is adequate for the majority of patients with HCC. On the other hand, other authors found that a minimal resection margin (surgical margin less than 1 mm) did not negatively affect postoperative recurrence free survival (82,83).

In order to minimize the risk of local recurrence and maximize the overall survival change, a surgical strategy that supports the preference for anatomical and adequate resection with free margins should be adopted whenever possible (83).

Overall survival and disease-free survival

Most comparative studies indicated no significantly different overall survival and disease-free survival in LLR compared to the OLR (*Table 4*). Although involved studies in meta-analyses are all non-randomized trials and including mainly minor LLR, and had a limitation of data heterogeneity, most meta-analyses demonstrated no statistical difference in overall survival and disease-free survival between two cohorts (*Table 3*). The long-term oncological outcomes of LLR for HCC did not show favorable results. However, LLR also does not compromise oncological principles as a treatment modality for HCC.

Role of Laparoscopy in Repeated Operation for Recurrent HCC

Recurrence is still a major problem after surgical resection. It occurs in the liver in around 50–80% of the cases as a consequence of metastatic spread from the tumor removed or "*de novo*" occurrence due to underlying liver disease (83,84). Several less invasive treatments, such as percutaneous ablation and chemoembolization, can be safely proposed with good long-term results and low morbidity and mortality if the remnant liver preserves adequate liver function in case of recurrence (85). However, surgical removal using either salvage liver transplantation or repeat liver resection is still believed to be the most effective therapy that is potentially curative for recurrent HCC (83,86).

Liver resection

Although not properly addressed in a prospective trial, repeated liver resection in patients with solitary liver recurrence resulted in better survival than palliative treatment (37–86% in 5 years) (83,87). The resectability rate varies and depends on the extent of primary resection and the functional status of the remnant liver (83,88). Repeated liver resection is difficult because of modification of the anatomy and vascular-rich adhesions between the abdominal wall at the original large surgical scar and the resected portion of the liver. Generally, because of complexity of postoperative adhesion, laparoscopic surgery is not recommended for repeat surgery.

Kanazawa *et al.* (89) reported their results of 20 cases of laparoscopic resection and 20 cases of open resection for 40 recurrent HCC patients. Laparoscopy was associated with significantly less intraoperative blood loss, lower incidence of postoperative complications, shorter hospital stay, and lower incidence rates of surgical site infection and ascites. In addition, Zhang *et al.* (90) reported that regarding operation time, the postoperative time until the patient could walk, postoperative pain, laparoscopic resection were superior to open surgery in a prospective study of 64 patients, all of whom had undergone open surgery once before and who had been diagnosed with recurrent HCC. This may be due to a reduced need for adhesiolysis because of the specific view and caudal approach of LLR (15,91). Moreover, once pneumoperitoneum was established under laparoscopic guidance, the increase in pressure increased the tension of adhesions, which, together with a large laparoscopic operating field, facilitated the separation of the adhesion. This is why the laparoscopic reoperation has a shorter operation time compared with open surgery (90).

Salvage liver transplantation

Salvage LT is also a good potential curative treatment option in recurred HCC patients after initial liver resection (92). Traditionally, surgical resection has been conducted by laparotomy in most salvage LT, but this approach usually leads to strong post-operative intra-abdominal adhesions in a contest of portal hypertension and, as possible consequence, increases LT difficulty with particular consideration to the operative time and blood transfusions (85). Laurent *et al.* (93) reported the first single center series of 24 LTs following laparoscopic and open resection for cirrhotic patients affected by HCC, showing reduced

Table 4 Oncologic outcomes in comparative studies of laparoscopic and open liver resection for hepatocellular carcinoma (including more than 30 patients published since 2010)

Study	Positive resection margin, %			Overall survival (5-year, %)			Recurrence-free survival (5-year, %)		
	LLR	OLR	P value	LLR	OLR	P value	LLR	OLR	P value
Cheung *et al.* (16), 2016	0.9	3.9	NS	69.4	56.1	NS	54.2	40.1	0.045
Sposito *et al.* (17), 2016	–	–	–	38	46	ns	25	11	NS
Ahn *et al.* (18), 2016	0	0	–	91.8	90.3	ns	40.9	47.2	NS
Komatsu *et al.* (19), 2016	15.8	15.8	NS	73.4 (3-yr)	69.2 (3-yr)	ns	29.7 (3-yr)	50.3 (3-yr)	NS
Leong *et al.* (20), 2015	2.4	7.3	NS	80.5	83.8	ns	52.5	38.2	0.035
Martin *et al.* (21), 2015	0	6.8	NS	60.7 (3-yr)	41.8 (3-yr)	ns	20	26.2	NS
Yoon *et al.* (22), 2015	0	1.7	0.03	86.0 (4-yr)	84 (4-yr)	ns	56.0 (4-yr)	62.0 (4-yr)	NS
Luo *et al.* (23), 2015	–	–	–	–	–	–	–	–	–
Meguro *et al.* (25), 2015	5.7	14.3	NS	82.1	61.8	ns	43.8	37.2	NS
Takahara *et al.* (27), 2015	4.7	4.4	NS	76.8	70.9	ns	40.7	39.3	NS
Han *et al.* (28), 2015	1.1	5.4	NS	76.4	73.2	ns	44.2	41.2	NS
Yamashita *et al.* (29), 2015	–	–	–	78	77	ns	33	41	NS
Ahn *et al.* (30), 2014	0	0	–	80.1	5.7	ns	67.8	54.8	NS
Lee *et al.* (31), 2015	0	0	–	89.7	87.3	ns	53.5	58.6	NS
Memeo *et al.* (32), 2014	5.0	15.0	0.03	59	44	ns	19	23	NS
Kim *et al.* (33), 2014	–	–	–	60.3	57.7	ns	51.0	54.3	NS
Ai *et al.* (36), 2013	20.6	22.5	NS	86 (3-yr)	88 (3-yr)	ns	66 (3-yr)	67 (3-yr)	NS
Cheung *et al.* (37), 2013	–	–	–	76.6	57.0	NS	54.5	44.3	NS
Hu *et al.* (38), 2011	–	–	–	50.0	53.3	NS	–	–	–
Ker *et al.* (40), 2011	–	–	–	62.2	71.8	NS	–	–	–
Lee *et al.* (41), 2011	3.0	2.0	NS	76.0	76.1	NS	45.3	55.9	NS
Truant *et al.* (42), 2011	–	–	–	70	46	NS	35.5	33.6	NS
Tranchart *et al.* (44), 2010	–	–	–	59.5	47.4	NS	45.6	37.2	NS

LLR, laparoscopic liver resection; OLR, open liver resection.

operative time, blood loss and transfusion requirements in the laparoscopic group compared to the open group. LT after a previous laparotomy was often more challenging and was associated with longer operation times and a higher blood loss. The main consideration on their series was that during transplantation the hepatectomy phase was easier in the patients operated by laparoscopy, where the absence of adhesions gave immediate access to the liver in all cases. In contrast, nearly all patients operated by laparotomy required dissection of long hemorrhagic adhesions before the beginning of hepatectomy, and globally the laparoscopic group had a shorter median operation time of 60 minutes with significant lower role of blood transfusions. Recently, Felli *et al.* (85) also reported salvage LT after LLR for HCC was comparable to open surgery in terms of operative time, oncological radicality, morbidity and mortality, with the advantages of laparoscopic surgery. Although prospective studies has not yet been reported, subsequent salvage LT following LLR has advantages over following OLR that minimal dissection in LLR are less adhesion, minimal manipulation in liver hilum, and decreased blood loss (83,93,94).

Role of LLR for HCC with cirrhotic patients

Use of LLR initially involved benign disease having malignant potential, such as hepatocellular adenoma and intrahepatic stones, because it did not need to be considered oncologic safety. LLR was extended and became widely adopted in treatment of HCC. Most patients with HCC have underlying chronic liver disease, and a liver resection in the setting of cirrhosis adds an extra degree of difficulty (4).

Cherian *et al.* (95) indicated several reasons for LLR to be complicated by cirrhosis: (I) stiff liver is difficult to manipulate; (II) presence of portal hypertension; (III) underlying clinical or sub-clinical coagulopathy which is often not easy to control precisely; (IV) deep tumors or lesions might be hard to palpate when compared to normal soft livers; (V) pneumoperitoneum with its impact on portal flow, might have a unpredictable influence on post-operative liver function; (VI) a fibrotic liver is likely to increase overall bleeding as the stiff and deranged architecture does not allow vessel to collapse/constrict when injured as they might in normal tissue; and (VII) patients with chronic liver disease are less likely to tolerate complications when compared to patients with no liver disease and need a greater future liver remnant. However, the current review of the literature shows that LLR in HCC patients with LC has some benefits, and is indeed safe and feasible.

In OLR, an extremely long incision is necessary for mobilization and resection of the liver because the liver is anatomically surrounded by the rib cage. In cirrhotic patients, these surgical procedures can result in significant blood loss or the development of intractable postoperative ascites, because of the destruction of collateral circulation in the abdominal wall and the ligaments surrounding the liver. These complications may result in longer postoperative hospital stays and fall into liver failure in some patients (35). By avoiding large abdominal incisions, the laparoscopic approach allows preservation of the collateral vessels often present within the abdominal wall in patients affected by LC. In addition, it is often possible to avoid transection of the round ligament and liver resection is generally carried out without extensive liver mobilization or excessive liver compression and manipulation. In this way, it is possible to preserve collateral blood and lymphatic flow, which play an important role in reducing the incidence of postoperative morbidity and ascites formation (10).

Shehta *et al.* (70) reported no significant differences between 141 cirrhotic and 91 non-cirrhotic HCC patients regarding operation time, blood loss, transfusion requirements, intraoperative complications, hospital stay, and postoperative complications. In addition, long-term oncologic outcomes were comparable between the two groups regarding the recurrence rates, overall survival rates in their recent comparative study. Two of the included meta-analyses (57,59) addressed HCC patients with LC; LLR provided better intraoperative and short-term outcomes than OLR. However, no significant survival benefit was shown between them. The laparoscopic approach for the treatment of HCC in cases of cirrhosis seems to be advisable as the first procedure whenever feasible (96).

Current indications and extension of LLR

Indications for LLR in patients with HCC are not different from those for OLR, which are based on tumor characteristics, liver function, and patient's general performance status (72). The First International Consensus Conference on Laparoscopic Liver Surgery held in Louisville in 2008 categorized LLR into three types: biopsies and small wedge resections, resections of the left lateral section or anterior hepatic segments (4b, 5, 6), and hemihepatectomies, trisectionectomies and resections featuring difficult posterior segments (4a, 7, 8) (14).

Form the viewpoint of a caudal vision of the liver in laparoscopy, Couinaud segments can be categorized into laparoscopic segments and non-laparoscopic segments. Laparoscopic segments are easily accessible left lateral section (segments 2 and 3) and the anterior segments (segments 4b, 5, 6). Non-laparoscopic segments indicate the posterior and superior segments (segments 1, 7, 8, 4a). There is a great amount of parenchyma interposed between the surgeon's view and these non-laparoscopic segments, because laparoscopy offers a caudal vision (72). A difficulty scoring system for LLR proposed at the second consensus conference also suggested that easy resections involve solitary lesions of 3 cm or less located in peripheral segments (segment 2–6). Complex resections include major resections (right and left hepatectomies) and anatomical parenchyma-sparing segmentectomies and sectionectomies in the difficult posterosuperior (PS) segments 7/8 and upper part of segment 4 (9,97). For these reasons, the first consensus conference indicated that the most favorable indication for the laparoscopic resection is a solitary lesion 5 cm or less in size located in peripheral liver segments 2 to 6. Tumors that are either large (>5 cm), central, multiple, bilateral, or with connections with the liver hilum, major hepatic veins or the IVC are not current candidates for the laparoscopic approach (14).

These are most frequently adopted indications. But they are not restrictive, once indications can be shifted and extent of resection can be expanded according to the expertise of an experienced center. Until now, surgical indications have continued to evolve. In expert hands, a tumor size larger than 5 cm is not a formal contraindication to the laparoscopic approach anymore. Ai *et al.* (36) reported the feasibility of completely laparoscopic hepatectomy for HCC larger than 5 cm (96).

In particular, for tumors in the PS segments, LLR has disadvantages of poor visualization of posterior lesions and difficulty in bleeding control compared with OLR. Since first large comparative study between anterolateral (AL) segments and PS segments by Cho *et al.* (98) was reported in 2008, few studies were reported that several modifications have been proposed to facilitate the operative approach to overcome limitations of LLR of PS lesions in experienced centers.

For lesions located in the liver dome, a transthoracic approach using additional intercostal trocar has been described to overcome the difficulties of limited visualization and access to the target lesions and to obtain an optimal triangulation of the laparoscopic tools (10,99-101).

For laparoscopic resection of HCC located in segments 6 and 7, the patient can be positioned in the left lateral decubitus or even in the prone position to facilitate liver mobilization and to optimize the exposition of the parenchymal transection line (10,102,103). In addition, a modified hanging maneuver that was recently introduced provides an accurate transection plane easy retraction and effective bleeding control by inserting hanging tape between the adrenal gland and the inferior vena cava (104,105). According to the three representative comparative studies on LLR for HCC located between PS and AL segments, although the differences in perioperative outcomes, including operation time and blood loss, are indicative of greater difficulty of LLR of PS lesions, the similar complication rates suggest that LLR can be performed safely for PS and AL lesions (12,102,106).

For a centrally located tumor close to the hilum, major hepatic veins, or IVC, which are other unfavorable locations, Yoon *et al.* (107) reported that the laparoscopic group showed a similar length of operative time and similar rates of intraoperative transfusion and postoperative complications but had the advantage of shorter postoperative hospital stays compared with the open group. The authors suggested the technical feasibility of laparoscopic anatomic or major liver resection contributes to the successful application of LLR for centrally located tumors.

Nevertheless, such complex and highly demanding procedures should be attempted with caution and by experienced hands, these complex resections are still in an exploration phase (Baillol 2b) (10,97).

Limitations

Two decades after the first reported LLR (6), there has been an exponential growth of reports of LLR. LLR continues to grow in popularity, with over 9,000 cases reported (76). Recently, the largest review of LLR with a much larger number of patients including a higher proportion of major resections than previous reviews confirmed the safety of laparoscopic approach to liver surgery in selected cases (76). Nevertheless, possible limitations of LLR include the loss of tactile feedback and palpation of the liver, potential bleeding that may be harder to control laparoscopically, as well as the learning curve (108).

Intraoperative sonography may compensate for the inability to palpate the tumor. On the other hand, some surgeons prefer hybrid or hand-assisted LLR to allow manual guidance of the operative procedure. However, this technique can decrease the visibility of the operative field compared with pure laparoscopic method. Nevertheless, in laparoscopic procurement for right lobe graft, this technique is recommended due to donor safety (109).

Fear of uncontrollable major bleeding is one of causes of initial gradual development of laparoscopic approach in liver surgery. The largest review including malignant and benign indications reported one mortality case due to intraoperative bleeding among 37 deaths of the 9,527 LLR procedures (76). However, in most cases, bleeding can be controlled during laparoscopy and, if not, the conversion can be performed without any vital compromise. Nevertheless, laparoscopic vascular reconstruction is difficult (77).

Surgeons need different technical skills according to the tumor site or the extent of liver resection. LLR features a steep learning curve because both hepatobiliary surgical skill and advanced laparoscopic skill are needed for LLR. Nomi *et al.* (68) suggests that the learning phase of major LLR should include 45 to 75 patients. In addition, a learning curve effect due to technique improvement and standardization is present, especially for parenchymal transection, which represents the most difficult part of

LLR. During the past few decades, many new devices like ultrasonic scalpels, sealing devices, coagulation systems, and staplers have been developed, and these can warrant in controlling potential bleeding during parenchymal transection. The speed and ease of transection improves with experience, with a significant decrease in the duration of surgery over time. Recently, Lee *et al.* (110) analyzed a learning curve using cumulative sum and moving average technique, the learning curve for major LLR, left lateral sectionectomy and tumorectomy were accomplished after 50, 25, and 35 cases, respectively. The limitations of applying LLR according to tumor location also will be overcome if the advanced techniques of LLR are more widely applied and more experience is achieved.

Conclusions

Most comparative studies and meta-analysis of studies comparing laparoscopic to open liver surgery for HCC shows that laparoscopy is associated with less complications, less blood loss, less transfusion requirements, and shorter hospital stay, and comparable operation time, comparable positive resection margin rates, and comparable overall survival and disease-free survival rates. The data are not from randomized controlled trials. However, several reports used propensity score matching to reduce the different distribution of covariates. To date, LLR for HCC seems to be superior to OLR regarding operative outcomes without compromising the oncological outcomes in selective patients. A prospective randomized controlled study of laparoscopic versus OLR for HCC is currently recruiting participants (NCT00606385). The authors hope that the results will clarify the benefits and disadvantages of LLR for HCC.

Although LLR requires expertise in both open liver surgery and advanced laparoscopic surgery, LLR has been developed and continues to evolve with development of new technologies. Minor LLR such as left lateral sectionectomies or non-anatomical resections of AL segments are already considered a standard practice in most centers, and major LLR or resections of PS segments will be more extended as overcoming the limitations by application of advanced techniques and accumulation of experiences.

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Footnote

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