Review Article

Laparoscopic liver resection for the patients with hepatocellular carcinoma and chronic liver disease

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Abstract: Liver resection (LR), liver transplantation (LT), transarterial chemoembolization, and local ablation therapy are the treatment options for hepatocellular carcinoma (HCC). Although LR, LT and local ablation therapy (only for small tumor) provide the best hope for cure, most patients with HCC have also chronic liver disease (CLD) backgrounds, including HCV-liver cirrhosis. Therefore, they are at high risk for development of postoperative complications—sometimes fatal—and metachronous multicentric recurrent tumors occurring from the preneoplastic CLD background. Appropriate treatment is selected for HCC patients, on the combined evaluations of tumor condition and liver function. However, not small number of patients cannot undergo any treatment option due to poor liver function and/or complicated tumor condition. After repeated treatments, it can happen more often. It is thought that the features of laparoscopic LR could lead to the expansion of the LR indication to those patients, in the settings of severe CLD, repeat LR and bridging to LT. In our experience, Child-Pugh (CP) score is one of the promising candidates as a selection indicator which correlates well to our indication criteria of surface small laparoscopic LR to severe CLD patients, patient's performance status, and prognosis. Portal hypertension should be also counted in the selection criteria.

Keywords: Hepatocellular carcinoma (HCC); hepatectomy; laparoscopic surgery; liver cirrhosis

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General therapeutic situation of the patients with hepatocellular carcinoma (HCC) patients and chronic liver disease (CLD), including HCV liver cirrhosis

HCC is one of most common primary cancer and most common cause of cancer-related deaths in the world (1,2). Liver resection (LR) (3), liver transplantation (LT) (4), transarterial chemoembolization, and local ablation therapy (5) are the treatment options for the disease. Although LR, LT and local ablation therapy (only for small tumor) provide the best hope for cure (5-8), most patients with HCC have also CLD backgrounds, including HCV-liver cirrhosis. Therefore, they are at high risk for development of postoperative complications—sometimes fatal—and metachronous multicentric recurrent tumors occurring from the preneoplastic CLD background.

In addition to the oncological therapeutic effects, the degree of invasive stress, especially that affecting the diseased liver, and residual liver function should be considered at the consideration of the treatment options for HCC patients with CLD. Patients with CLD have various symptoms (9) and in a high risk following anesthesia and surgery according to their Child-Pugh (CP) class (10,11). For severe CLD patients, refractory ascites can be often occurred even after limited LR and lead to fatal complications (12,13).

Currently, the choice of LR, LT, local ablation therapy or transarterial chemoembolization is made based on each patient's tumor condition and liver function (14). However, not a small number of patients with HCC and CLD cannot undergo any such option because of poor liver function and/

or complicated tumor condition. After repeated treatments, it can happen more often.

Among the treatment options mentioned above, LT should be ideal for HCC patients with CLD in the aspect of removing both existing tumors and injured/preneoplastic underlying liver. However, it cannot be applied on a large scale due to the high prevalence of HCC and the donor shortage (15). LT application with immunosuppression afterward is also limited to the patients who have minimal risk of tumor recurrence (16). Expansion of the LT indication for HCC patients is now in its trial stage and controversial (17,18). Therefore, LR has traditionally been accepted as the preferred treatment for the patients with resectable HCC and adequate liver reserve (8,19,20).

Considerable progress in screening, early diagnosis, treatment of CLD, and surgical techniques has expanded the indications of LR during a couple of decades (21). Improvements of the assessment for liver function and understanding of liver anatomy by the sophisticated imaging studies, as well as surgical techniques, are most important impacts on the decreasing mortality rate of HCC; today, the 5-year survival is expected in the range of 38–61% (22). However, less than 30% of the patients undergo LR even nowadays (23,24).

Emerging laparoscopic LR (LLR) (25,26) may lead to expand the indication of LR in the therapeutic system for HCC patients with CLD. In this article, the current reports on LLR for HCC patients with CLD are reviewed and our experiences are described.

LLR for the patients with HCC/CLD and repeat resection

The beginnings of LLR were at the start of the 1990s, with its initial reports (27-29) being published in 1991 and 1992. Thereafter, the indication of LLR has been expanded as a less invasive procedure than open LR (OLR). LLR has the same benefits as other laparoscopic procedures, such as earlier intake, recovery and discharge, and reduced postoperative pain (30). An early meta-analysis of 26 studies found that, although LLR had longer operation time, there were no differences in oncologic outcomes compared to OLR (31). Furthermore, studies showed the specific advantages of LLR, smaller amount of blood loss, shorter portal clamp time, and less overall and liver-specific complications, for selected patients and within the technical capabilities of each experienced center.

The safety and feasibility of LLR and its short-term benefits for the patients with HCC and CLD have also been demonstrated (32-34). LLR may be especially advantageous for the patients of severe CLD, who often develop refractory ascites after OLR, a potentially fatal complication (12,13). LLR has the advantage of minimal ascites, due to the preservation of venous and lymphatic collateral flows (35), which reduces the risk of water/electrolyte imbalance and hypoproteinemia that could lead to fatal liver failure. This feature should be the most noteworthy advantage of LLR.

Patients who undergo LR are exposed to three different types of stresses: (I) general, whole-body surgical stress; (II) reduced liver function due to reduced liver volume after resection; (III) surgery-induced injury to the environment surrounding the liver and liver parenchyma (caused by disruption of the collateral blood and lymphatic flows with laparotomy and mobilization and mesenchymal injury with compression) (36). Reduction of the third surgery-induced injuries by LLR, especially in the patients with HCC and CLD, decreases the risk of refractory ascites. That facilitates a smoother recovery without liver failure.

The impact of LLR on this issue depends on the severity of the CLD, the operative technique (extent of dissection of the peritoneal attachments and adhesions), and extent of resection. Our previous study compared the short-term outcomes of liver surface small LLR for the patients with severe CLD [CP-B or -C and indocyanine green retention rate at 15 min (ICGR15) ≥40%] to those for the patients with mild-moderate CLD (35). Although the study was a small, retrospective unmatched study, it revealed comparable perioperative outcomes, including postoperative ascites, between patients with severe and mild-to-moderate CLD in LLR. This is an important difference from OLR.

LLR also allows for better visibility and manipulation in a small operative field under some conditions, such as repeat hepatectomy with adhesions (34). Laparoscopic surgery makes subsequent surgeries easier by the reduction of adhesions (37). It was reported that the salvage transplantation after previous LLR is associated with reductions of operation time, blood loss, and transfusion requirements, compared to that after OLR (38). Treatment of recurrence is another major issue for the patients with HCC and CLD, as they harbor potential for multicentric metachronous lesions occurring from the CLD background. Modifications of the anatomy and the formation of adhesions increases the difficulty of repeat LR. Several studies compared LLR and OLR in the setting of repeat LR (39,40). The operation time of repeat LLR in patients undergone LLR as the initial surgery was significantly

Table 1 Treatment options with hope for cure for HCC patients with CLD (Modification from *World J Gastroenterol*. 2014;20:14381-92)

Local ablation therapy
Only for small tumors (in size and number)
Liver resection
Most available and efficient treatment
5-year survival of 38–61%, depending on the tumor stage
1. Applicable to <30% of all HCC patients
Not applicable due to:
a. Tumor condition
b. Liver functional condition
2. 80% of patients recur within 5 years after resection
Need for repeat treatments
Liver transplantation
Ideal treatment for removal of existing tumor and underlying injured/preneoplastic liver tissue
Limited by:
1 Shortage of donors
2 Tumor progression while on waiting list
3 Patients with advanced/extensive HCC having very poor outcomes

Note: laparoscopic liver resection, with its unique approach (i.e., good visualization and manipulation capacities) could help to overcome the problems listed. Specifically, for liver resection 1-b by low incidence of ascites and liver failure, for liver resection 2 in its production of less adhesions and reduced need for adhesiolysis at repeat resection (easy access to repeat resection), and for liver transplantation 2 as a bridging therapy. CLD, chronic liver disease; HCC, hepatocellular carcinoma.

shorter than that in patients undergone initial OLR. On the other hand, regardless of the initial approach, repeat LLR was associated with reduced blood loss, reduced transfusion rates, reduced postoperative complications, and a shorter hospital stay, compared to repeat OLR (39,40). It can be translated that LLR is advantageous not only in producing fewer adhesions but also in reducing the needs for adhesiolysis in repeat LR. As mentioned above, the laparoscopic view and manipulation (41-43) facilitate the better access in a small operative field and lead to the decreased need for adhesiolysis. This could be explained as similar to the advantages of LLR for CLD patients noted above.

The characteristics described above indicate that LLR could be superior than OLR under certain conditions. Also, LLR could be an option as the bridging therapy to LT. The instrumental development and accumulation of surgeon's experience have expanded the indication of LLR (44). Although the number of studies reported has been small and comprising various settings, we believe that the specific features of LLR will expand the indications for LR to HCC patients with background CLD, particularly in the settings of severe CLD, repeat LR and bridging to LT (*Table 1*).

Indications of LLR to severe CLD patients

For the treatment selection of HCC, the Barcelona clinic liver cancer (BCLC) staging system/treatment algorithm (45) and the Japan Society of Hepatology clinical guidelines for HCC (JSH guideline) (46) are used in Western countries and Japan, respectively. Both systems include not only tumor condition but also background liver condition for the treatment selection. The two differ in that the BCLC algorithm uses CP classification (47) for assessments of liver function, while the JSH guideline uses the liver damage (LD) classification of the Liver Cancer Study Group of Japan (48), which has ICGR15 as one of the essential elements.

ICGR15 is a useful modality for assessing hepatic functional reserve and predicting postoperative mortality (49-51). The volume of the liver resected in each patient is basically planned according to the tumor condition, including its location (surface or non-surface area, distance from major vessels, etc.) and size. However, HCC patients sometimes develop postoperative liver failure due to poor liver functional reserve after the planned resection. ICGR15 has been an excellent tool for predicting how much liver volume could be resected in each patient's liver condition (50). On the other hand, nontumorous functioning liver parenchyma is resected minimally in liver surface tumorectomy or small partial resection. In those cases, the most important evaluation point is, not how much liver volume could be resected, but whether the patient and the liver could tolerate the surgical stress. As mentioned before, LLR minimizes the surgery-induced injury by the disruption of the collateral circulation and the compression on the liver parenchyma, and leads to decreased postoperative ascites and liver failure (36). The decision-making process during liver surface small partial LLR should be different from the other LRs.

Our experiences of LLR

We performed 152 LLR for liver tumors. Among these patients, 19 had more than 30% ICGR15 and HCC. The details of these patients are presented in *Table 2*. The 19 patients were composed of 6, 11 and 2 patients with CP-A, -B and -C, respectively. By LD classification, they included 2, 12 and 5 patients of LD-A, -B and -C, respectively. There was a discrepancy between the liver functional assessments of CP and LD. The patients with high ICGR15 values tended to be classified into higher grade of liver dysfunction by the LD classification. Based on liver functional criteria only of BCLC and JHS, there were already 2 and 5 patients out of LR indication in this group, respectively. We applied liver surface small LLR to the CP-B/C (up to CP score of 10) patients only when the patients could have been doing light or household labor for more than 6 months before their surgery, in a stable condition (good performance status).

Excluding the 1 patient whose follow-up period is less than 24 months and the 1 patient who underwent LT at 15 months after LLR, 7 patients died of HCC or liver disease within 24 months after LLR (D group). When the D patients were compared to the group of 10 patients who survived more than 24 months (A group), there are significant difference in the groups' CP scores, but not in the model for end-stage liver disease (MELD) scores (52-54), the albumin-bilirubin (ALBI) scores (55), the ICGR15 values and blood platelet counts (*Table 3*; platelet counts were compared excluding 1 patient after splenectomy from the D group). The values of ICGR15 are similar in the A and D groups. All of the D patients, but only 3 of the 11 A patients, had esophageal varices before surgery. All of the A patients, excluding the patients with LT at 15 months after LLR, had 50,000 or more blood platelet counts, and 5 out of 7 D patients had below 60,000.

It is thought that ICGR15 above 30–40% is out of their reliable range and not well-correlated with actual liver function. Thus, it may not be suitable for the liver functional selection criteria of surface small LLR in severe CLD patients, even though it is very useful and simple criteria for judging how much liver volume can be resected in the range below 30–40%. Although the difficult judgements for the objective presences of ascites and encephalopathy should be needed, CP score is a promising candidate for selection indicator of surface small LLR in severe CLD patients, correlating well to our indication criteria (patient's performance status) and prognosis after surgery. Portal hypertension (56), indicated by the presence of esophageal varices and low platelet counts, should be also counted in the selection criteria of surface small LLR.

Most reported cases of repeat LLR underwent minor resection for the patients with HCC and CLD, as mentioned before. The impact of anatomical alterations to liver parenchyma and intrahepatic structure from the previous LR could be relatively small in such cases. However, there were 3 patients with anatomical resection or resections exposing major vessels [including S8 segmentectomy after 4-time LLR (57)] after previous anatomical resection who developed postoperative bile leakage and longer postoperative hospital stay, among our 33 repeat and 12 three-or-more-time repeat LLRs. Since alterations of the anatomy and surrounding scars and/or adhesion of major vessel structures should have big impacts on anatomical resection or resections exposing major vessels in repeat LLR after previous anatomical resection, further experiences and evaluations of such repeat LLR are needed.

Conclusions

Although the number of studies reported has been small and comprising various settings, the specific features of LLR could expand the indications of LR to HCC patients with background CLD, including HCV liver cirrhosis, particularly in the settings of severe CLD and repeat LR. LLR could prolong the overall survival of the patients with HCC and CLD as a powerful local therapy which can

Table 2 Our cases of LLR for severe CLD

Age	Sex	Tumor location	Tumor number	Tumor size (mm)	Conversion	Previous surgery	LT after LLR	ICGR15, %	CP [score]	LD	MELD	ALBI	Platelet, $\times 10^4/\mu L$	Varices	Prognosis (month)
73	F	S3	1	18				37.7	A [6]	B	9	−2.11	14.7	No	5 [A]
66	M	S3	1	47		Splenectomy		31.1	B [7]	B	−2	−2.05	26	Yes	5.1 [D]
53	M	S5–6	1	28				41.2	B [7]	B	5	−1.96	8.3	Yes	11.2 [D]
63	M	S5–6	1	40				52	B [9]	C	9	−1.37	4.5	Yes	12 [D]
68	F	S8	1	13				58.2	C [10]	C	12	−1.17	4	Yes	14.1 [D]
75	F	S3	1	20				42.5	B [9]	B	9	−1.83	5.8	EVL	17.4 [D]
67	M	S8	1	20	HALS			55	B [8]	C	11	−1.32	5	Yes	19.3 [D]
69	F	S8	1	24		LLR		33.5	B [7]	B	10	−2.26	5.8	Yes	22.7 [D]
72	M	S5	1	16		LLR		42.3	A [5]	A	6	−2.33	8.6	No	27.8 [A]
64	M	S4, S2–3	2	41				42.8	B [7]	B	4	−1.83	8.9	No	28.5 [D]
81	F	S7	1	100				78.3	A [5]	B	6	−2.65	36.6	No	28.6 [A]
62	M	S3	1	24		LLRX3		43.5	B [8]	B	4	−2.01	7.2	No	30.5 [A]
68	F	S4	1	23				40	B [9]	B	8	−1.51	6.7	Yes	35.4 [D]
80	F	S3	1	18		LLR		40.4	B [7]	B	0	−2.18	8.8	No	35.7 [D]
50	M	S5	1	22			15 M	48.9	C [10]	C	9	−1.26	4.8	No	35.9 [AD]
67	M	S8	1	11		LLR		39	A [6]	B	8	−2.05	5	Yes	47.9 [A]
67	F	S8–4, S5, S6	3	32	Open			34.6	A [6]	B	3	−2.06	7.2	No	58.7 [D]
40	M	S6	1	20			60 M	52.5	B [7]	C	8	−1.41	6	EVL	75.6 [D]
61	M	S5	1	15				70.8	A [5]	A	8	−2.77	11.9	No	127.8 [A]

In "Prognosis" column: A, alive; AD, dead of the other cause; D, dead of hepatocellular carcinoma or liver disease. ALBI, albumin-bilirubin score; CLD, chronic liver disease; CP, Child-Pugh classification and score; EVL, patients who underwent endoscopic varices ligation before LLR; HALS, hand-assisted laparoscopic surgery; LD, liver damage classification; LLR, laparoscopic liver resection; LT, liver transplantation; MELD, Model for end-stage liver disease score; S, segment; LLRX3, LLR were performed three-times previously .

Table 3 Parameters of liver function in the patient groups of those who survived more than 24 months (group A*) and who died of HCC or liver disease within 24 months (group D)

Parameter	Group		Unpaired t two-tailed P value
	A	D	
Platelet counts			0.2093
Patient No.	10	6**	
Mean ± SD, $\times 10^4/\mu L$	10.740±9.426	5.567±1.516	
CP score			0.0216
Patient No.	10	7	
Mean ± SD	6.50±1.35	8.14±1.21	
MELD score			0.244
Patient No.	10	7	
Mean ± SD	5.50±2.72	7.71±4.82	
ALBI score			0.0999
Patient No.	10	7	
Mean ± SD	−2.0800±0.4367	−1.7086±0.4192	
ICGR15			0.5828
Patient No.	10	7	
Mean ± SD, %	48.420±14.600	44.786±10.560	

*, 1 patient who underwent liver transplantation at 15 months after LR was excluded from group A; **, 1 patient after splenectomy was excluded from group D. ALBI, albumin-bilirubin score; CP, Child-Pugh classification and score; HCC, hepatocellular carcinoma; ICGR15, indocyanine green retention rate at 15 min; LD, liver damage classification; LR, liver resection; MELD, model for end-stage liver disease score.

be applied repeatedly with minimal deterioration of liver function.

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Footnote

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