

Review

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# Current status of laparoscopic repeat liver resection for recurrent hepatocellular carcinoma

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## Abstract

Repeat liver resection (RLR) is an effective treatment approach for recurrent hepatocellular carcinoma (HCC) and can provide acceptable long-term outcomes in select patients. Recent randomized controlled trials comparing RLR with radiofrequency ablation revealed that the latter approach was associated with a higher rate of early recurrence compared with RLR. With recent advances in laparoscopic liver resection (LLR), RLR has been increasingly performed using laparoscopy. Several propensity score-matched studies reported that laparoscopic RLR achieved lower blood loss and shorter hospital stays compared to open RLR. However, laparoscopic RLR requires more advanced techniques because of adhesions formed after the previous liver resection, changes in anatomical landmarks, and deformity of the remnant liver. The recently described difficulty classification of laparoscopic RLR is based on five factors including type of previous liver resection (open or laparoscopic), number of previous liver resections, surgical procedure used in previous liver resections, tumor location in previous liver resections, and difficulty score of LLR for recurrent HCC. We reviewed the available literature to summarize available evidence suggesting that laparoscopic RLR might be considered a more minimally invasive surgical treatment approach for recurrent HCC as long as the indication for laparoscopic RLR is carefully determined.

**Keywords:** Hepatocellular carcinoma, repeat liver resection, laparoscopic repeat liver resection

## INTRODUCTION

Repeat liver resection (RLR) is an effective treatment approach for recurrent hepatocellular carcinoma (HCC) and can provide acceptable long-term outcomes for select patients<sup>[1-3]</sup>. However, RLR is considered



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a difficult procedure due to adhesions associated with previous liver resection and changes in anatomical recognition. In fact, several studies have reported high morbidity rates after RLR<sup>[4-6]</sup>. With advances in laparoscopic liver resection (LLR), RLR has been increasingly performed laparoscopically<sup>[7]</sup>. LLR is a less invasive procedure that is associated with better short-term outcomes compared with open liver resection (OLR)<sup>[8,9]</sup>. Similarly, the superiority of laparoscopic RLR over open RLR in short-term outcomes has been reported<sup>[10-12]</sup>. However, none of the studies were randomized controlled trials and laparoscopic RLR might be performed in select patients. Laparoscopic RLR was discussed at the first European Guidelines Meeting on Laparoscopic Liver Surgery (Southampton 2017) and considered an appropriate option<sup>[13]</sup>. However, most laparoscopic liver surgeons suggest that repeat liver resection significantly increases the difficulty of LLR<sup>[14]</sup>. Currently, the indications for laparoscopic RLR vary between centers. Considered a difficult procedure, RLR poses a range of challenges depending on the location of recurrent tumor and previous liver resections. A recent report has introduced a difficulty classification for laparoscopic RLR<sup>[15]</sup>. Specifically, the level of difficulty was determined on the basis of the type of previous liver resection (open or laparoscopic), number of previous liver resections, surgical procedure and tumor location in previous liver resections, and difficulty score of LLR for recurrent HCC<sup>[16]</sup>. RLR after LLR has been increasing in parallel with the increasing number of LLR for HCC. In colorectal surgery, the laparoscopic approach has been reported to reduce adhesion formation<sup>[17]</sup>. Similarly, RLR after LLR is associated with less adhesion formation compared with RLR performed after OLR. Therefore, RLR in the era of LLR has distanced characteristics. Conversely, percutaneous radiofrequency ablation (RFA), a technique developed in the last two decades<sup>[18,19]</sup>, has been demonstrated to be useful in small HCCs<sup>[20]</sup>. In general, patients who previously undergo hepatectomy for HCC are examined regularly by imaging studies, which facilitate the frequent detection of small-diameter recurrent HCCs. Within this framework, the role of liver resection for recurrent HCC might be changing. In this review, we describe the current status of laparoscopic RLR for HCC in the era of LLR and RFA.

## **SIGNIFICANCE OF REPEAT LIVER RESECTION FOR RECURRENT HEPATOCELLULAR CARCINOMA**

Relatively good survival outcomes of RLR for HCC have been reported since the 1990s<sup>[21-24]</sup>. These earlier studies reported that 5-year survival rate after RLR was around 50%, which was comparable to the prognosis of primary liver resection and was better than the prognosis of transarterial chemoembolization<sup>[25,26]</sup>. However, RLR was performed in select patients with relatively better liver function and tumor factors compared to those undergoing transarterial chemoembolization. Moreover, disease-free survival rates were significantly lower with RLR compared to initial liver resection<sup>[2,3]</sup>. Studies investigating prognostic factors after RLR for HCC reported that portal vein invasion at the time of first liver resection, portal vein invasion in RLR, multiple HCCs at the time of first liver resection, and disease-free interval of less than one year were independent prognostic factors after RLR<sup>[1,3,27]</sup>. The 5-year survival rate was 86.0% in patients without prognostic factors<sup>[1]</sup>. These results provide clear evidence that RLR for recurrent HCC is a useful treatment option for select patients.

In the last decade, several studies investigating long-term outcomes in patients undergoing three or more RLRs reported that the 5-year survival and disease-free survival rates after the third RLR were 40.0%-68.2% and 12.8%-33.8%, respectively<sup>[6,28,29]</sup>. These results were comparable to those observed after the second RLR. Regarding short-term outcomes, Mise *et al.*<sup>[6]</sup> reported significantly longer surgical duration and higher postoperative morbidity with three or more RLRs, whereas Yamashita *et al.*<sup>[28]</sup> reported no significant differences. These results indicated that three or more RLRs might be considered an acceptable treatment approach in patients whose liver function and tumor factors were within surgical indications.

## ADVANCES IN LAPAROSCOPIC REPEAT LIVER RESECTION

Progress in surgical procedures and devices has enabled the expansion of surgical indications for LLR<sup>[30-32]</sup>. However, laparoscopic RLR demands a more advanced technique due to adhesion formation following prior liver resection, changes in anatomical landmarks, and deformity of the remnant liver. In 2009, Belli *et al.*<sup>[33]</sup> reported 12 patients who underwent laparoscopic RLR for recurrent HCC. The authors concluded that laparoscopic RLR was feasible and that the degree of adhesion was mild in patients undergoing LLR as initial liver resection. In 2011, Hu *et al.*<sup>[34]</sup> reported six patients who underwent laparoscopic RLR for recurrent HCC. No intra- or postoperative complications were observed; however, the authors noted that the patients were carefully selected. Another report in 2011 was a tri-institutional analysis of 76 patients undergoing laparoscopic RLR<sup>[35]</sup>. The study cohort comprised 63, 3, and 10 patients with metastatic liver tumors, HCC and benign tumors, respectively. Seven patients (9.2%) were converted to open surgery, and there were no perioperative deaths. The patients who underwent OLR as initial liver resection experienced higher intraoperative blood loss compared to those who underwent LLR. In 2016, a review by Goh *et al.*<sup>[36]</sup>, which included 103 patients who underwent laparoscopic RLR for recurrent HCC, reported that only 2 patients (1.9%) were converted to open surgery. These retrospective analyses have provided evidence for the feasibility and safety of LLR in select patients.

In 2018, Noda *et al.*<sup>[37]</sup>, and Ome *et al.*<sup>[38]</sup>, reported their findings on the comparison between laparoscopic RLR and open RLR in their institutions indicating that blood loss was less and hospital stay shorter with laparoscopic RLR; there were no differences in operative duration and postoperative complications. Thereafter, similar results have been reported from several single centers<sup>[7,12,39]</sup>. In 2019, a multicenter propensity score-matched study compared laparoscopic and open RLR for colorectal liver metastasis<sup>[40]</sup>. After matching, 105 pairs were extracted from the initial cohort of 271 patients who underwent laparoscopic RLR and 154 patients who underwent open RLR. Laparoscopic RLR was associated with a significantly shorter operative duration (200 min *vs.* 256 min), less intraoperative blood loss (200 mL *vs.* 300 mL), and shorter postoperative hospital stay (5 days *vs.* 6 days), whereas postoperative morbidity and mortality rates were similar between the groups. Similar results of laparoscopic RLR for HCC were reported in another multicenter propensity score based study<sup>[11]</sup>. Table 1 summarizes the comparison between laparoscopic RLR and open RLR of these reports.

Although no randomized controlled trials to date have compared laparoscopic RLR and open RLR, evidence from previous studies indicate that laparoscopic RLR is feasible and safe as long as the indications are within the capabilities of institutions and surgeons.

## DIFFICULTY CLASSIFICATION OF LAPAROSCOPIC REPEAT LIVER RESECTION

Several factors affect the level of difficulty in laparoscopic LLR. Previous OLR was reported to increase difficulty in laparoscopic RLR<sup>[33,35]</sup>. In 2014, Ban *et al.*<sup>[16]</sup> described the first difficulty scoring system for LLR. The difficulty score was based on tumor location, extent of liver resection, tumor size, tumor proximity to major vessels and liver function. The difficulty of LLR was classified into low, intermediate and high levels. This score can be effortlessly utilized for risk assessment in patients undergoing laparoscopic RLR. Recently, Kinoshita *et al.*<sup>[15]</sup> reported on difficulty classification of laparoscopic RLR. They reviewed 60 cases of laparoscopic RLR in their institution and analyzed the factors accounting for prolonged operative duration or severe adhesion. As a result, an intermediate or high LLR difficulty score, two or more previous liver resections, a history of previous major liver resection, and tumor location near the resected surface of previous liver resection were identified. These five factors were reported to be correlated with operative duration in laparoscopic RLR. The authors then classified the patients undergoing RLR into low-risk (score, 0-1), intermediate-risk (score, 2-3), and high-risk (score, 4-5) categories and found that the risk was significantly correlated with operative duration<sup>[15]</sup>.

**Table 1. Outcome of treatment after recurrent hepatocellular carcinoma**

	Laparoscopic repeat liver resection (laparoscopic RLR)	Open repeat liver resection (open RLR)	P value
Morise <i>et al.</i> <sup>[11]</sup> (2020)			
Blood loss (mL)	268	497	0.001
Duration of operation (min)	272	232	0.007
90-day morbidity, beyond Clavien-dindo II (%)	15.1	13.0	0.611
90-day Mortality (%)	0.42	0.84	0.623
Postoperative hospital stay (days)	10.4	9.6	0.327
van der Poel <i>et al.</i> <sup>[40]</sup> (2019)			
Blood loss (mL)	200 (50-450)	300 (100-600)	0.077
Duration of operation (min)	200 (123-273)	256 (199-320)	< 0.001
90-day morbidity, beyond Clavien-dindo II (%)	5.7	5.7	0.319
90-day Mortality (%)	1.9	0	0.5
Postoperative hospital stay (days)	5 (3-8)	6 (5-8)	0.028
Onoe <i>et al.</i> <sup>[39]</sup> (2020)			
Blood loss(mL)	100 (0-1050)	435 (30-1920)	0.001
Duration of operation (min)	276 (125-589)	292 (96-972)	0.861
90-day morbidity, beyond Clavien-dindo III (%)	6.75	14.3	0.297
90-day Mortality (%)	0	0	1
Postoperative hospital stay (days)	10 (4-50)	14.5 (10-76)	0.002
Goh <i>et al.</i> <sup>[12]</sup> (2019)			
Blood loss (mL)	200 (100-425)	250 (125-475)	0.345
Duration of operation (min)	315 (181-395)	125 (99-184)	< 0.001
30-day morbidity, beyond Clavien-dindo III (%)	0	5	0.48
30-day Mortality (%)	0	10	0.56
Postoperative hospital stay (days)	4 (3-5)	7.5 (6-10)	0.001
Ome <i>et al.</i> <sup>[38]</sup> (2018)			
Blood loss (mL)	30 (0-1012)	652 (20-12046)	< 0.001
Duration of operation (min)	217 (43-356)	222 (84-923)	0.56
30-day morbidity, beyond Clavien-dindo III (%)	6.1	10.8	0.393
30-day Mortality (%)	3	0	0.471
Postoperative hospital stay (days)	6.5 (3-47)	9.0 (5-78)	< 0.001
Noda <i>et al.</i> <sup>[37]</sup> (2018)			
Blood loss (mL)	159	502	0.004
Duration of operation (min)	225	237	0.601
30-day morbidity, beyond Clavien-dindo III (%)	0	14.5	0.009
30-day Mortality (%)	0	0	1
Postoperative hospital stay (days)	14.2	19.2	0.028

## LONG-TERM OUTCOMES AFTER LAPAROSCOPIC REPEAT LIVER RESECTION FOR RECURRENT HEPATOCELLULAR CARCINOMA

A global systematic review and meta-analysis in 2013 reported that the long-term outcomes were comparable between LLR and OLR for initial HCC<sup>[41]</sup>. Subsequently, propensity score-matched studies comparing LLR and OLR for initial HCC revealed that overall survival (OS) and recurrence-free survival (RFS) were not different between LLR and OLR, while short-term outcomes were significantly better with LLR<sup>[42-44]</sup>. Similar results were obtained in a study limited to patients undergoing major hepatectomy<sup>[45]</sup>. However, no randomized controlled trials have compared LLR and OLR for initial HCC. LLR might be performed in select patients. Moreover, Stiles *et al.*<sup>[46]</sup> reported that unplanned conversion to OLR from LLR for HCC was associated with inferior OS compared to non-converted cases. Therefore, the long-term prognosis of LLR might be comparable to OLR as long as the indication for LLR is carefully evaluated. Regarding RLR, few studies have compared long-term survival outcomes between laparoscopic RLR and open RLR. A recent multicenter, propensity score-based study by Morise *et al.*<sup>[11]</sup>, which included 42 surgery centers around the world, reported comparable median survival times between laparoscopic RLR and open RLR (12.55 years *vs.* 8.94 years;  $P = 0.086$ ), although intraoperative blood loss was significantly

greater with open RLR (268 mL *vs.* 497 mL;  $P = 0.001$ ) and operative duration was significantly longer with laparoscopic LLR (272 min *vs.* 232 min;  $P = 0.007$ ). These findings suggest acceptable long-term outcomes with laparoscopic RLR for recurrent HCC.

## LAPAROSCOPIC REPEAT LIVER RESECTION AND RADIOFREQUENCY ABLATION FOR RECURRENT HEPATOCELLULAR CARCINOMA

Percutaneous RFA, a technique developed in the last two decades has been reported to be an effective and safe treatment for small HCCs<sup>[18-20]</sup>. Nowadays, RFA is widely used as non-surgical treatment for HCCs because the therapeutic effect was reported to be more effective than microwave coagulation therapy or percutaneous ethanol injection therapy<sup>[47,48]</sup>. In general, recurrent HCCs are detected at a small diameter because of routine screening after initial liver resection. Therefore, RFA for recurrent HCCs could be an effective treatment.

However, a very recent randomized controlled trial comparing RLR with RFA for recurrent HCC revealed that RFA was associated with a higher rate of early recurrence compared with RLR (40.3% *vs.* 23.3%,  $P = 0.04$ )<sup>[49]</sup>. On the other hand, the trial results indicated that RLR had a higher complication rate than RFA (22.4% *vs.* 7.3%,  $P = 0.001$ ). These findings highlight that RLR remains an important treatment approach for recurrent HCC even in the era of RFA. As mentioned previously, laparoscopic RLR can be performed safely, with less blood loss and shorter postoperative hospital stay compared to open RLR in select cases. Therefore, laparoscopic RLR for recurrent HCC might be considered a standard treatment with reduced surgical invasiveness as long as the indication for RLR is carefully considered.

## CONCLUSION

RLR for recurrent HCC remains an important treatment strategy even in the era of RFA. Laparoscopic RLR could be considered a more minimally invasive surgical treatment than open RLR for patients with recurrent HCC.

## DECLARATIONS

### Authors' contributions

Wrote this article: Hokuto D

Supervised this article: Nomi T, Sho M

Treated the patients included in this article: Yoshikawa T, Matsuo Y, Kamitani N

### Availability of data and materials

Not applicable.

### Financial support and sponsorship

None.

### Conflicts of interest

All authors declared that there are no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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