Laparoscopic repeat hepatectomy for treating recurrent liver cancer

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INTRODUCTION
Liver cancer is one of the most common malignancies in the world. Liver tumours include hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma and metastasis tumour of the liver. The treatment of liver cancer mainly adopts comprehensive treatment based on hepatectomy, especially for liver without cirrhosis. However, due to the characteristics of HCC, easy invasion of blood vessels and formation of tumour thrombosis and the background of cirrhosis, the recurrence rate of liver cancer after radical resection for 5 years is still as high as 50%–70%. Moreover, the recurrent rate for patients with colorectal liver metastases (CRLM) is estimated at 60%. Therefore, an effective treatment strategy of intrahepatic recurrence is the key to prolong survival after the previous hepatectomy. Over the past 20 years, repeated hepatectomy has been considered to be safe and can significantly prolong the survival of patients. Due to the complexity of post-operative adhesions, as well as changes in anatomical landmarks, repeat hepatectomy has traditionally been performed through the open approach. At present, laparoscopic technology has been widely used in various fields, and the surgical...
operation has gradually matured and standardized. Laparoscopic hepatectomy is associated with lower blood loss, fewer post-operative complications and shorter hospital stay and equivalent long-term oncologic compared to the traditional open approach.\(^6\) However, there are still limited reports on the laparoscopic repeat hepatectomy (LRH) of the recurrent HCC (rHCC) and metastases tumour of liver, especially of CRLM. The objective of the present systematic review was to identify and evaluate available data of LRH for rHCC and CRLM, focusing on the safety and feasibility.

**METHODS**

**Literature search and selection**

A comprehensive search of the PubMed database was performed for all studies published in English evaluating LRH for rHCC and recurrent metastases tumour of liver from 1st January, 2005 to 1st June, 2019. Pubmed and Embase were searched using the following combination of terms: rHCC, CRLM, laparoscopic repeat liver resection, LRH, laparoscopic surgery and open surgery, using the Boolean Operators AND and OR. The reference lists of articles identified were subsequently examined to find relevant studies that had not been identified by the database search. In this study, only original clinical studies with full-text descriptions were included. The search was updated to 10th June, 2019. All the search results were evaluated according to the preferred reporting items for systematic reviews and meta-analyses statement. The inclusion criteria were as follows: (1) English language studies, (2) full-text articles, (3) studies reporting on LRH for rHCC or CRLM and (4) case series (≥5 patients). The exclusion criteria were as follows: (1) animal or experimental studies, editorials, expert opinions, letters, abstracts, case reports (<5 patients) and reviews; (2) studies of non-English language and (3) studies with insufficient data. As can be seen in Figure 1, our study was conducted according to PRISMA guidelines.\(^7\)

**Data extraction and outcomes**

Data extracted from the full-text articles using standardized forms were conducted independently by two investigators (JWC and JHZ). Data recorded all available information included baseline details, details of the first hepatectomy and pathology, information on patient cirrhosis status and perioperative, intraoperative and post-operative outcomes of LRH. Grades were assigned as follows: grade 0, no adhesion; Grade 1, a thin layer of adhesion that can be separated by blunt dissection; Grade 2, a thin layer of adhesion that can be separated easily by sharp dissection; Grade 3, a wide range of vascular adhesion requiring careful sharp dissection and Grade 4, dense adhesion that may result in visceral injury.\(^8\)

**RESULTS**

**Patient baseline characteristics and operative outcomes**

A total of 15 studies which comprised 444 patients and reported outcomes for the efficacy and safety of LRH in the treatment of rHCC or CRLM were included in the present review as shown in Table 1. Four studies were prospective study and one study was a case series involving 13 patients.\(^9\) One study was a multicentre retrospective propensity score-matched study which combined the experience of LRH in nine highly experienced hepatopancreatobiliary centres from seven European countries.\(^12\) All the studies included patients assessed and operated on from the years 2000 to 2017. Clinicopathologic outcomes data are summarized in Table 2. The median age of the patient ranged from 49 to 73 years, and there are 283 men reported in 14 studies.\(^9\) There are 84 patients in eight studies which were reported with cirrhosis background of the liver.\(^12,16,17,19,21,24\) LRH was performed in 213 patients whose previous surgery approach was open hepatectomy.\(^9,14,16,17,19,22,24\) Recurrent tumour median size ranged from 17 to 40 mm. Moreover, a total of 193 patients in seven studies received R0 resection.\(^10,11,14,17,19,23,24\) It was reported in ten studies that 35 cases of recurrent tumours located in posterosuperior segments.\(^12,13,15,19,21,22,24\) Most of the studies (nine studies) had reported the treatment of LRH in HCC patients.\(^11,13,15,17,19,21,24\) while a small number of studies reported the LRH treatment for metastatic tumours such as CRLM.\(^9,10,14,20,22,23\) Perioperative outcomes are summarized on Table 3. Thirty-two patients

**Table 1: Characteristics of the included studies**

| Study              | Years | Country       | n   | Study period | Study type     |
|--------------------|-------|---------------|-----|--------------|----------------|
| Belli et al.       | 2009  | Italy         | 12  | 2004-2008    | Retrospective  |
| Hu et al.          | 2011  | China         | 6   | 2003-2008    | Retrospective  |
| Shafaei et al.     | 2011  | The US        | 76  | 1997-2009    | Prospective    |
| Kanazawa et al.    | 2013  | Japan         | 20  | 2006-2011    | Retrospective  |
| Chan et al.        | 2014  | China         | 11  | 2004-2013    | Retrospective  |
| Shetal et al.      | 2014  | The Netherlands | 20 | 2003-2013    | Prospective    |
| Isetani et al.     | 2015  | Japan         | 12  | NR           | Retrospective  |
| Zhang et al.       | 2016  | China         | 31  | 2014-2014    | Prospective    |
| Goh et al.         | 2017  | Singapore     | 8   | 2013-2015    | Retrospective  |
| Hallet et al.      | 2017  | France        | 27  | 2006-2013    | Retrospective  |
| Liu et al.         | 2017  | China         | 30  | 2008-2015    | Retrospective  |
| Goh et al.         | 2018  | Singapore     | 20  | 2015-2017    | Retrospective  |
| Noda et al.        | 2018  | Japan         | 20  | 2005-2016    | Retrospective  |
| Ome et al.         | 2018  | Japan         | 33  | 2014-2017    | Retrospective  |
| Yu et al.          | 2018  | China         | 13  | 2013-2017    | Retrospective  |
| Van der Poel et al.| 2019  | The UK        | 105 | 2000-2016    | Retrospective  |

NR: Not reported.
### Table 2: Summary of clinicopathologic outcomes of the patients who underwent laparoscopic repeat hepatectomy

| Author (years) | Median age (range):SD years | Sex, male, n (%) | Cirrhosis (%) | Previous open approach (%) | Recurrent tumour median size | R0 resection (%) | Difficult posterosuperior segments, n (%) | Histological type |
|----------------|-----------------------------|-----------------|---------------|---------------------------|-----------------------------|-----------------|---------------------------------|-----------------|
| Belli et al.[24] | 69 (64-75) | NR | 12 (100) | 4 (33.3) | 40 (30-48) | 12 (100) | 3 (25) | HCC |
| Hu et al.[19] | 49 (46-55) | 5 (83) | NR | NR | 25 (20-30) | NR | 1 (16.7) | HCC |
| Shafaei et al.[9] | 61 (29-82) | 48 (63) | NR | 31 (41) | 25 (5-125) | NR | NR | HCC, Met, NETLM |
| Kanazawa et al.[14] | 70 (46-83) | 15 (75) | 7 (35) | 15 (75) | 17 (7-35) | NR | 5 (25) | HCC |
| Chan et al.[19] | 63 (43-80) | 8 (72.7) | 8 (73) | 6 (55) | 20 (12-50) | 11 (100) | 1 (9.1) | HCC |
| Shelat et al.[17] | 61 (29-82) | NR | NR | 0 | 28 (10-80) | 18 (90) | NR | CRLM, NETLM, HCC |
| Isetani et al.[18] | 70 (57-81) | 8 (66.7) | 7 (58.3) | 8 (66.7) | 21 (8-60) | NR | 4 (33.3) | HCC, Met, IPT, GBC |
| Zhang et al.[15] | 57 (37-66) | 26 (83.9) | NR | 31 (100) | 25±10 | NR | NR | HCC |
| Goh et al.[19] | 68 (66-78) | 7 (87.5) | 3 (38) | 6 (75) | 24 (8-50) | 8 (100) | 4 (50) | HCC |
| Hallett et al.[25] | 64 (59-71) | 20 (74.1) | NR | NR | Cases >3 cm: 12 (44.4) | NR | NR | CRLM |
| Liu et al.[15] | 57 (27-79) | 23 (76.7) | 26 (86.7) | NR | 21 (10-50) | NR | 4 (13.3) | HCC |
| Goh et al.[17] | 68.5 (67-72) | 18 (90) | 7 (35) | NR | 20 (11.5-27.8) | 19 (95) | 7 (35) | HCC |
| Noda et al.[22] | 68.8±9.7 | 15 (75) | 8 (40) | 12 (60) | 24.1±12.6 | NR | 4 (20) | HCC, Met |
| Ome et al.[23] | 73 (45-84) | 26 (78.8) | 13 (39.4) | 21 (63.6) | 18 (4-45) | 30 (90.9) | NR | HCC, Met |
| Yu et al.[15] | 56 (43-64) | 8 (61.5) | NR | 13 (100) | 20 (15-25) | NR | 2 (15.4) | HCC |
| Van der Poel et al.[14] | 61.10±7 | 62 (59) | NR | 66 (62.9) | 28 (19-44) | 95 (90.5) | NR | CRLM |

**Notes:** Met: Metastases tumour, NETLM: Neuroendocrine liver metastases, IPT: Inflammatory pseudo-tumour, GBC: Gallbladder cancer, NR: Not reported, SD: Standard deviation, HCC: Hepatocellular carcinoma, CRLM: Colorectal liver metastases

### Table 3: Summary of perioperative outcomes of LRH patients

| Study | Major resection | Adhesion grade 3-4 (%) | Pringle maneuver (%) | Conversion (%) | Duration of operation (min) | Blood loss (ml) | LOS (days) | Morbidity |
|-------|-----------------|------------------------|---------------------|---------------|-----------------------------|----------------|------------|----------|
| Belli et al.[24] | 0 | 5 (41.7) | NR | 1 (8.3) | 73 (40-130) | 297±134[^4^] | 7.4±2.5[^4^] | 4 (27) |
| Hu et al.[19] | 0 | 3 (50) | NR | 0 | 150 (115-190) | 200 (150-800) | 6.5 (4-8) | 1 (16.7) |
| Shafaei et al.[9] | 19 (25) | NR | NR | 7 (9.2) | 180 (80-570) | 300 (0-5000) | 6 (2-42) | 20 (26.3) |
| Kanazawa et al.[14] | NR | NR | NR | 1 (5) | 199 (69-241) | 63 (1-100) | 9 (5-10) | 0 |
| Chan et al.[19] | 0 | 1 (9.1) | NR | NR | 200 (131-352) | 100 (50-500) | 6 (3-17) | NR |
| Shelat et al.[17] | NR | NR | NR | 3 (15) | 285 (195-360) | 400 (150-200) | 4 (1-57) | NR |
| Isetani et al.[18] | 0 | 11 (91.7) | NR | 0 | 301 (104-570) | 50 (0-840) | 12 (9-30) | 0 |
| Zhang et al.[17] | 0 | 5 (16.1) | NR | NR | 116.7±37.5 | 115.7±35.5 | 4.5±1.3 | NR |
| Goh et al.[19] | 0 | NR | NR | 1 (12.5) | 343 (120-530) | 200 (30-500) | 3.5 (3-8) | 1 (12.5) |
| Hallett et al.[25] | 25 | NR | 5 (18.5) | NR | 252.5 (180-322.5) | NR | NR | NR |
| Liu et al.[15] | 1 (3.3) | 6 (20) | 0 | 4 (13.3) | 200.5 (68-525) | 100 (10-600) | 9.5 (5-29) | 2 (6.7) |
| Goh et al.[17] | 2 (10) | NR | 4 (20) | NR | 315 (181.25-395.0) | 200 (100-425) | 4 (3-5) | 2 (10) |
| Noda et al.[22] | NR | NR | 1 (5) | NR | 225±85 | 159±256 | 14.2±5.4 | 0 |
| Ome et al.[23] | NR | NR | NR | 0 | 217 (4-356) | 30 (0-1012) | 6.5 (3-47) | 2 (6.1) |
| Yu et al.[15] | 3 (23.1) | 1 (7.7) | 7 (53.8) | 1 (7.7) | 142±34 | 251±92 | 9±3 | 0 |
| Van der Poel et al.[14] | 27 (25.7) | NR | 22 (21) | 11 (10.5) | 200 (123-273) | 200 (50-450) | 5 (3-8) | 6 (5.7) |

[^4^]: LRH for previous open hepatectomy patients, ^[^4^]: LRH for previous laparoscopic hepatectomy patients. LOS: Length of stay, NR: Not reported, SD: Standard deviation, HCC: Hepatocellular carcinoma, CRLM: Colorectal liver metastases

### Comparative studies comparing laparoscopic repeat hepatectomy versus open hepatectomy for recurrent hepatocellular carcinoma or colorectal liver metastases

In seven studies were regarded as Grade 3 or 4 peritoneal adhesions intraoperatively.[11,13,15,17,18,21,24] The Pringle maneuver was adopted in five studies as the standard hepatic inflow occlusion technique.[12-14,20,23] Conversion from laparoscopic to open approach was required in 31 of 272 cases.[9,10,13,14,16,19,21,24] The operative time for LRH reported in all the studies ranged from 73 to 343 min. The median blood loss was reported in 15 studies and this ranged from 30 to 400 ml.[9,19,21-24] The median post-operative length of stay in 15 studies was reported ranging from 3.5 to 17 days.[9,19,21-24] The post-operative morbidity was recorded at 58 cases in eight studies.[9,12,14,15,19,21,23,24]

Comparative studies comparing laparoscopic repeat hepatectomy versus open hepatectomy for recurrent hepatocellular carcinoma or colorectal liver metastases

There are nine studies that compared the perioperative outcomes of LRH versus open repeat hepatectomy (ORH) [Table 4]. Six of nine studies had demonstrated that the LRH group had a significance decrease of blood loss compared to ORH group.[11,16,17,21-23] Two studies indicated that the duration of operation in LRH group was significantly shorter than ORH group, including one study that was performed in nine high-volume centres and used the propensity score matching (PSM) method, which provided more reliable
Evidence,[11,12,14] while the other two studies demonstrated the opposite.[12,17] Only two studies demonstrated significantly decreased morbidity in LRH groups.[21,22] Moreover, there are six of nine studies indicating a significantly shorter length of stay in favour of LRH.[11,12,14,16,21,23]

### DISCUSSION

Reports on the treatment of rHCC with LRH are still very limited due to the technical complexity of the procedure.[22] The risk of haemorrhage and intestinal damage in patients with cirrhosis is significantly higher in patients with non-cirrhosis, and adhesions in previous surgical areas may increase the density of blood vessels in the reoperation area, which may lead to an increased risk of secondary surgery bleeding.[20] Therefore, the history of previous upper abdominal surgery has increased the difficulty of laparoscopic surgery, resulting in longer operation time, increased risk of intestinal injury, intraoperative complications (biliary injury and vascular injury) and intraoperative conversion to laparotomy. Even abdominal adhesions used to be considered as a contraindication to laparoscopic surgery.[24] Therefore, if laparoscopic surgery is used to treat recurrent liver cancer, the adhesion should be fully separated and the remaining liver should be mobilized. The adhesion can destroy the normal anatomy structure of the hilar region and the duodenal ligament, which often seriously hinders the operation of LRH. Recently, some authors reported that LRH can be safely applied for a small number of patients with recurrent liver cancer. Belli et al.[24] analyzed the surgical outcomes of 15 patients undergoing laparoscopic recurrent hepatectomy. It was found that patients received LRH treatment had a low post-operative complication rate of only 27%, and only one patient was converted to laparotomy. It was concluded that LRH is a safe and feasible surgical procedure with good short-term outcomes. In addition, the laparoscopic enlargement of the operating area and the tension of the pneumoperitoneum facilitate the careful dissection of the adhesion. Another possible advantage of LRH is that laparoscopic surgery avoids adhesions in non-surgical areas and does not require the separation of all adhesions in the abdominal cavity.[25] Goh et al.[27] retrospectively analyzed 103 patients from 10 studies demonstrates that LRHR can be safely performed for selected patients with rHCC. LRH can be performed for patients with previous open LR, previous major hepatectomy, two previous LHI, multiple tumours, liver cirrhosis, ipsilateral HCC recurrence, and tumours located in the difficult posterosuperior segments. However, there is still no randomized controlled trial or well-matched case–control studies with large sample size. Hence, we conducted this systematic review using recent data to evaluate the short-term outcomes of the LRH.

The present systematic review of 444 patients from the sixteen studies demonstrates that LRH can be safely
performed for selected patients. In order to minimize case selection bias, we included multi-centre studies which had large quantitative samples and there are three studies performing a propensity-matched and propensity-adjusted comparison between both LRH and ORH groups. Six comparative studies in our analysis performed demonstrated a decreased blood loss during LRH. Regarding the mean time of the LRH procedure, two out of nine comparative studies suggested showed a significantly less comparative studies, while two other comparative studies demonstrated a longer time. Post-operative morbidity during LRH was found to be significantly lower compared to ORH, as two out of nine studies indicated. The length of stay was significantly lower in six out of nine comparative studies. In our analysis, LRH also showed better short-term outcomes with respect to blood loss, intraoperative, morbidity and post-operative hospital stay despite the severe adhesions caused by previous open hepatectomy and liver cirrhosis.

The main limitation of this review was that almost all the studies included were retrospective cohort studies. Its retrospective design always render an inevitable risk of selection and information bias despite one study had high volume and use PSM means, some relevant bias still exists. Possible selection biases for LRH versus ORH in the current review are tumour location of recurrent lesions, liver function, tumour number, previous liver resection approach and anatomical hepatectomy. Four studies included above recruit patients whose recurrent tumours located in segment 2–6, which are considered laparoscopic segments, while segment I and posterosuperior segments (VII, VIII) are considered as difficult to expose. Instead of LRH, radiofrequency ablation (RFA) is recommended to treat these lesions. Regarding the number of tumour, two of studies mentioned that patients were only recruited with solitary exophytic tumour. Only one study described patients with tumours were performed by the same surgeon. In seven studies, the Pringle maneuver was applied to reduce hemorrhage during hepatic transection. The result of operative time of LRH, compared to ORH, in two studies were exactly opposite to the result of the other two studies. It may be due to the fact that in centers with substantial experience in laparoscopic hepatectomy, the duration of operation time can be significantly reduced. And intraoperative time...
can also be affected by surgery experience of operator and surgical technique.

**CONCLUSIONS**

The results of this systematic review demonstrate that LRH can safely performed in rHCC or CRLM patients with cirrhosis, previous open hepatectomy, multiple recurrent lesions and tumours located in difficult posterosuperior segments. Comparative studies have demonstrated that LRH is superior to ORH in terms of perioperative outcomes such as decreased blood loss and length of stay. The long-term efficacy of LRH in the treatment of recurrent liver cancer requires further prospective randomized controlled trials to obtain more comprehensive and accurate results and thus establish relevant guidelines.

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**Conflicts of interest**

There are no conflicts of interest.

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