Early experience with laparoscopic liver resection for spontaneously ruptured hepatocellular carcinoma

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Abstract

Introduction: There are limited data to date regarding laparoscopic liver resection (LLR) for spontaneously ruptured hepatocellular carcinoma (srHCC). We performed this study to determine the safety and feasibility of LLR for srHCC.

Materials and Methods: We conducted a retrospective review of all patients who underwent liver resection for srHCC from 2000 to 2018. A total of five patients underwent LLR for srHCC, and they were matched to 10 patients who underwent open liver resection (OLR) for srHCC to perform a 1:2 comparison. A separate cohort of patients who underwent LLR for non-ruptured HCC (nrHCC) was also compared against the laparoscopic group.

Results: The comparison between LLR versus OLR for srHCC demonstrated no significant differences in baseline characteristics between both groups. There was also no significant difference in perioperative outcomes such as median operating time, estimated blood loss (EBL), rate of blood transfusion, post-operative median length of stay (LOS), overall complication rates, major morbidity rates and 90-day mortality rates. Comparison between LLR for srHCC and LLR for nrHCC demonstrated no significant differences in baseline characteristics between both groups. There was also no significant difference in key perioperative outcomes such as median operating time, EBL, rate and volume of blood transfusion, median post-operative LOS, morbidity rates or mortality rates.

Conclusion: LLR may be performed safely in selected cases of srHCC. These patients have comparable perioperative outcomes as those who undergo OLR for srHCC and LLR for nrHCC.

Keywords: Hepatectomy, hepatocellular carcinoma, laparoscopic, liver resection, ruptured

INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth-most common tumour globally and the second most common cause of cancer-related death.[¹] As many as 3%–26% of patients may present with spontaneous rupture,[²] in which mortality rates may be as high as 25%–75% secondary to circulatory shock and liver failure.[³] Management priorities in such cases include urgent resuscitation and stabilisation, followed by haemostasis of on-going bleed. This may be performed by various modalities such as transarterial chemoembolisation (TACE), radiofrequency...
ablation (RFA) or surgical intervention, which includes perihepatic packing, suture plication, hepatic artery ligation or partial liver resection. In a meta-analysis of 67 studies comprising of 4941 patients with ruptured HCC, partial heptectomy was proven to result in superior short-term and long-term outcomes compared to other modalities.\textsuperscript{[6]} This can be performed either as an emergency 1-stage procedure or as a delayed 2-stage procedure after initial temporising measures to arrest haemorrhage.

Nearly 3 decades have passed since the first laparoscopic liver resection (LLR) was reported by Gagner et al.\textsuperscript{[9]} Initial concerns about technical complexity, bleeding control and oncologic margins have been overcome by improvements in surgical technique and advances in technology.\textsuperscript{[10]} Today, indications for LLR have been extended to include major heptectomies, heptectomies for tumours located in difficult posterosuperior segments,\textsuperscript{[7]} repeat liver resection for recurrent HCC,\textsuperscript{[10]} living donor liver resection, associating liver partition with portal vein ligation for staged heptectomy (ALPPS).\textsuperscript{[9]}

The role of laparoscopic resection for ruptured liver tumours is still very limited and has only been discussed in a few case reports.\textsuperscript{[10,11]} Owing to the paucity of data regarding LLR for spontaneously ruptured HCC (srHCC), we performed this study to determine the safety and feasibility of LLR for srHCC by analysing our experience with the procedure.

**MATERIALS AND METHODS**

We conducted a retrospective review of all patients who underwent partial liver resection for srHCC in the Singapore General Hospital from 2012 to 2018. This study was approved by our Institution Review Board. A total of five patients who underwent LLR for srHCC were identified from a cohort of 460 consecutive patients who underwent LLR. All 5 LLR were performed by a single surgeon who performed 190 LLR during the study. Two of these cases were reported previously.\textsuperscript{[11,12]} These patients were matched 1:2 against 10 patients, selected from a cohort of 78 patients who underwent open liver resection (OLR) for srHCC,\textsuperscript{[14]} based on tumour location, type of surgery, presence of cirrhosis and tumour size. The five patients were also compared against a matched cohort of 18 patients who underwent LLR for non-ruptured HCC (nrHCC) by the same surgeon.

**Data collection**

Data on patient baseline demographics, clinical, biochemical and radiological variables were collected retrospectively from a prospective computerised clinical database (Sunrise Clinical Manager version 5.8, Eclipsys Corporation, Atlanta, Georgia). Complete blood count, serum albumin, liver function, renal function, hepatitis B and C status, American Society of Anaesthesiologist (ASA) scores, serum alpha-fetoprotein (AFP) levels and tumour locations were recorded. In certain instances, transarterial embolisation was necessary before surgical intervention, and this was documented. We also calculated the number of hours from initial presentation till definitive surgery. All patients had pre-operative computed tomography (CT) or magnetic resonance imaging scans, and HCC was diagnosed based on characteristic cross-sectional imaging features, presence of risk factors and/or AFP levels. The diagnosis of srHCC was confirmed either via imaging showing features of active contrast extravasation from the liver tumour or intraoperative findings of tumour rupture and haemopertitoneum. Surgical data were collected from another prospective computerised database (OTM 10, IBM, Armonk, New York, USA). This included the length of surgery, extent of resection, estimated blood loss, need for and volume of blood transfusion. Information about tumour specific characteristics such as size, multinodularity, margins, grade, microvascular invasion as well as the presence of underlying liver cirrhosis was determined from histopathologic reports.

**Definitions**

Nomenclature of resection was defined according to the Brisbane 2000 classification.\textsuperscript{[13]} Major heptectomy was defined as the resection of three or more segments and minor heptectomy defined as the resection of fewer than three segments.\textsuperscript{[16]} Post-operative complications were categorised according to the Clavien et al. classification.\textsuperscript{[17]} Length of stay (LOS) was calculated from the date of surgery to date of discharge, inclusive of both dates. Readmissions within 30 days of surgery were recorded. On discharge, patients were followed with physical examination, liver function test, AFP and multiphasic CT scan according to local protocol. Operative mortality up to 90 days after surgery was reported.

**Patient selection**

Only patients with srHCC who were haemodynamically stable after resuscitation and who had good liver function were considered for LLR. In addition, in this early experience, we only considered patients with tumours located in the accessible anterolateral segments.

**Statistical analysis**

Propensity score (PS) analyses were undertaken to reduce confounding and multidimensionality by accounting for baseline characteristics which could influence a patient’s likelihood of undergoing LLR or OLR for ruptured HCC. Covariates considered for inclusion into the PS model
were hypotension (blood pressure <90/60), haemoglobin, platelets, bilirubin, albumin, prothrombin time, ASA status, Hepatitis B status, cirrhosis, time to surgery, largest tumour size and tumour location (segments 5/6/7 or 2/3). Multivariable models were then developed using combinations of the top five most significant covariates in univariable analyses, and PS models were assessed for their model fit. The final PS model took into account hypotension, haemoglobin concentration and time to surgery, and exhibited a pseudo $R^2 = 0.5597$, likelihood ratio Chi-square statistic of 8.55 ($P = 0.0359$), and good calibration and discrimination [Supplementary Figures 1 and 2].

Inverse probability of treatment-weighted analyses was undertaken as it has been shown to reduce confounding bias even in sparse datasets. For comparison of the perioperative and post-operative outcomes between LLR versus OLR for ruptured HCC, marginal IPT-weighted quantile and logistic regression and the weighted log-rank test were used for continuous, dichotomous and survival outcomes, respectively. All other (non-weighted) comparisons were performed using Mood’s median test and Pearson’s Chi-square test for continuous and dichotomous variables, respectively.

Next, we also compared LLR for rHCC versus nrHCC. To reduce selection bias, controls were selected from a consecutive cohort of 140 nrHCC patients undergoing laparoscopic wedge resection using unsupervised algorithms. The baseline similarity between patients was represented using the Mahalanobis distance from a centroid reference, which was calculated taking into account tumour size, age, ASA status, cirrhosis, number of resected segments, tumour location, tumour grade, microvascular invasion, and multifocality. rHCC patients were matched to nrHCC by greedy matching to minimise the Mahalanobis distance between patients. After matching, each of the 5 rHCC patients was matched to 9, 5, 1, 1 and 2 patients, for a total of 18 controls. To preserve the structure of the matched data, mixed-effects quantile regression and conditional logistic regression were respectively used to compare continuous and dichotomous outcomes.

Analyses were conducted in STATA version 13.0 (StataCorp) and R version 3.4.1 (R Foundation, Vienna, Austria), and $P < 0.05$ was regarded to indicate nominal statistical significance.

RESULTS

A total of five consecutive patients underwent LLR for srHCC, as shown in Table 1. Hand-assisted laparoscopic surgery (HALS) was performed for 1 patient, and 1 patient required conversion to open surgery. All the tumours were located in the right lobe of the liver.

Comparison between laparoscopic liver resection for spontaneously ruptured hepatocellular carcinoma and open liver resection for spontaneously ruptured hepatocellular carcinoma

There were no significant differences in baseline demographic characteristics between patients who underwent laparoscopic versus OLR for srHCC, as shown in Table 2. Most patients were male, in the 7th–8th decades of life. Four (80%) patients were ASA 2 and 1 (20%) ASA 3 in the LLR group, while 5 (50%) were ASA 1 and 5 (50%) were ASA 2 in the OLR group. Majority of the patients had solitary HCCs which were mostly located in segments 5/6/7 of the liver, although 2 (20%) patients in the OLR group had tumours in segments 2/3. About 80%
of patients in LLR group had ≥2 segments resected, as compared to 60% of those in the OLR group. There was a longer median time to surgery in the OLR group although this was not statistically significant (124.5 h, range 2–1440 versus 87 h, range 280.5, \( P = 0.5403 \)). Four patients in the OLR group had TAE preoperatively as compared to none in the LLR group (\( P = 0.0986 \)).

Table 3 compares the peri and post-operative outcomes of patients who underwent LLR versus OLR for rHCC.

### Table 1: Summary of the five patients who underwent laparoscopic liver resection for ruptured hepatocellular carcinoma

| Age/sex | Type of resection | Operation time, min | Morbidity | Blood loss, cc | Postoperative LOS, days |
|---------|-------------------|---------------------|-----------|---------------|------------------------|
| 69/male | Laparoscopic hand assisted resection of ruptured segment 6 HCC | 165 | No | 500 | 5 |
| 51/female | Laparoscopic resection of ruptured segment 5/6 HCC | 170 | No | 300 | 7 |
| 81/female | Laparoscopic resection of ruptured segment 6/7 HCC | 215 | No | 400 | 5 |
| 81/male | Laparoscopic resection of ruptured S5/6 HCC, adhesiolysis and cholecystectomy | 215 | No | 300 | 4 |
| 88/male | Laparoscopic converted to open adhesiolysis, resection of ruptured segment 5/6 HCC and subtotal cholecystectomy | 230 | Yes, Grade 2 | 1100 | 9 |

HCC: Hepatocellular carcinoma, LOS: Length of stay

### Table 2: Comparison between the baseline demographic data of patients who underwent laparoscopic versus open resection for ruptured hepatocellular carcinoma and laparoscopic resection for ruptured hepatocellular carcinoma versus non-ruptured hepatocellular carcinoma

| Lapse rHCC (n=5) | OLR (n=10) | P | LLR NRHCC (n=18) | P |
|-----------------|------------|---|-------------------|---|
| Gender, male (n/total, %) | 3 (60) | 8 (80) | 0.4090 | 14/17 (82.4) | 0.5714 |
| Median age (range), years | 81 (51-88) | 75.5 (57-81) | 0.8548 | 66 (44-86) | 0.4921 |
| ASA score, n/total (%) | 1 0 (0) | 5 (50) | 0.0821 | 1 (5.6) | 0.5876 |
| 2 4 (80) | 5 (50) | 0.3266 | 10 (55.6) | 0.4161 |
| 3 1 (20) | 0 (0) | 7 (38.9) | | |
| Median largest tumour size, mm (range) | 62 (45-128) | 65 (28-180) | 0.7144 | 50 (45-85) | 0.1211 |
| Solitary tumour, n/total (%) | 4 (80) | 9 (90) | 0.5912 | 14/18 (77.8) | 0.7644 |
| Tumour location, n (%) | | | | | |
| Sg 5/6/7 | 5 (100) | 8 (80) | 0.2827 | | 0.4481 |
| Sg 2/3 | 0 (0) | 2 (20) | 2 (11.1) | | |
| Number of segments resected, n/total (%) | | | | | |
| 1 | 1 (20) | 4 (40) | 0.4386 | 0.4689 |
| ≥2 | 4 (80) | 6 (60) | 0.3266 | 15 (83.3) | 0.1938 |
| Histology of background liver cirrhosis, n/total (%) | 1 (20) | 5 (50) | 0.2636 | 12 (66.7) | |
| Median number of hours to surgery, (range) | 87 (26-280) | 124.5 (2-1440) | 0.5403 | | |
| TAE preoperative, n/total (%) | 0 (0) | 4 (40) | 0.0986 | NA | NA |

HCC: Hepatocellular carcinoma, LLR: Laparoscopic liver resection, NRHCC: Non-ruptured HCC, rHCC: Ruptured HCC, OLR: Open liver resection, ASA: American Society of Anesthesiologist, TAE: Transarterial embolization

### Table 3: Comparison between the perioperative and postoperative outcomes of patients who underwent laparoscopic versus open resection for ruptured hepatocellular carcinoma and laparoscopic resection for ruptured hepatocellular carcinoma versus non-ruptured hepatocellular carcinoma

| Lapse rHCC (n=5) | OLR rHCC (n=10) | P | LLR NRHCC (n=18) | P |
|-----------------|-----------------|---|-------------------|---|
| Median operating time, min (range) | 215 (165-230) | 127.5 (90-225) | 0.1140 | 162.5 (85-460) | 0.7060 |
| Median estimated blood loss, mL (range) | 400 (300-1100) | 1000 (100-4000) | 0.1199 | 500 (50-1500) | 0.6105 |
| Perioperative blood transfusion, n/total (%) | 2 (40) | 4 (40) | 0.5270 | 7 (38.9) | 0.7644 |
| Median blood transfusion, mL | 500, 1300 (IV) | 700 (range: 500-2000) | NE | 900 (range: 500-1300) | NE |
| Median postoperative LOS, days (IQR) | 5 (5-7) | 7 (5-14) | 0.5867 | 6 (4-16) | 0.3783 |
| Post-operative morbidity, n/total (%) | 1 (20) | 2 (20) | 0.6695 | 5 (27.8) | 0.5065 |
| Post-operative major (> Grade 2) morbidity, n/total (%) | 0 (0) | 1 (10) | 0.2971 | 0 (0) | NE |
| High tumour grade (3/4), n/total (%) | 1 (20) | 5 (50) | 0.2176 | 11 (61.1) | 0.1733 |
| Resection margin <1 mm, n/total (%) | 1 (20) | 2 (20) | 0.4161 | 1 (5.6) | 0.3106 |
| Median closest resection margin, mm (range) | 9 (0-22) | 4 (0-10) | 0.0029 | 4 (0-30) | 0.2127 |
| 30-day readmission rate (n/total, %) | 0 (0) | 1 (10) | 0.3421 | 2 (11.1) | 0.4354 |
| 90-day mortality rate (n/total, %) | 0* | 4.6* | 0.3266 | 0* | 1.0000 |

1Weighted using the inverse probability of treatment, after calculation of PSs, 2Obtained from Chi-squared test with probability weights incorporated using Stata’s survey (svy) commands, since \( P \) value corresponding to the OR from weighted logistic regression cannot be estimated, IV: Individual values, NE: Not estimable, for example, due to non-convergence, *Data were collected and analysed as a dichotomous variable. IV: Odds ratio, HCC: Hepatocellular carcinoma, LLR: Laparoscopic liver resection, NRHCC: Non-ruptured HCC, rHCC: Ruptured HCC, OLR: Open liver resection, IQR: Interquartile range, LOS: Length of stay, PS: Propensity score
With regards to perioperative events, there were no significant differences in median operating time, estimated bloodloss (EBL), rate of blood transfusion or median blood transfusion volumes. Post-operative median LOS, overall complication rates as well as major morbidity rates were similar across both groups. Half of the patients in the OLR group had high-grade tumours as compared to 20% of the LLR group ($P = 0.2176$). There was no difference in the proportion of patients with surgical resection margins <1 mm, although the median closest margin was smaller in the OLR group compared to the LLR group (4 mm, range 0–10 vs. 9 mm, range 0–22 mm, $P = 0.0029$). Patients in both groups had similar 30-day readmission rates. There were no mortalities within 90 days in the LLR group, while 14.6% of patients in the OLR group demised.

**Comparison between LLR for srHCC and LLR for nrHCC**

There were no significant differences in baseline characteristics between patients who underwent LLR for srHCC versus nrHCC. In the nrHCC group, 82.4% of patients were male with a median age of 66 years (range 44–86 years). Although the median largest tumour size was smaller, it was not statistically significant (50 mm, range 40–100 vs. 62 mm, range 45–125, $P = 0.1211$). 88.9% of tumours were located in segments 5/6/7 while the remainder were in segments 2/3. More than half of the patients in the nrHCC group had underlying liver cirrhosis. Surgical factors such as median operating time, median EBL, rate and volume of blood transfusion was similar across both groups. More than half of the patients in the LLR for nrHCC group had high-grade tumours compared to 20% of the patients in the LLR for srHCC group, but this difference was not statistically significant ($P = 0.1733$). There were also similar rates of resection margin <1 mm in both groups. On follow-up, there were no significant differences in 30-day readmission rates or 90-day mortality rates between both groups.

**DISCUSSION**

Our early experience confirms that LLR can be safely performed in selected cases of srHCC with comparable short-term outcomes to OLR. To the best of our knowledge, this is the largest reported series on LLR for ruptured HCCs, and only the second one to date in the literature. It is also the first study to compare outcomes of laparoscopic versus OLR for srHCC.

Like most Eastern centres, we adopt an aggressive approach towards srHCC in our institution whereby patients with good surgical risk were offered partial hepatectomy even though there is a potentially higher risk of tumour recurrence. We adopt this policy as we believe that resection reduces the risk of recurrent tumour rupture and other future complications. Several studies including a recent meta-analysis have proven that whenever possible, hepatectomy provides the best outcomes for patients with srHCC compared to other modalities like TAE/TACE, and rupture in itself does not affect survival outcomes following resection. In the only other published study to date on LLR for ruptured liver tumours, Belgaumkar et al.; reported on three patients who underwent LLR for 2 HCCs and 1 hepatic adenoma. In their series, the time intervals to surgery were 4, 12 and 21 days after presentation. In contrast, our patients underwent surgery much earlier, at a median of 87 h after admission. The shorter time interval to surgery in our series can be explained by the fact that 4 of the 5 patients in this study underwent a semi-emergency hepatectomy within the index admission, and none required pre-operative TAE. Although some postulate that emergency hepatectomy may lead to a higher incidence of in-hospital death, of note we had no mortalities within 90 days in the laparoscopic group. All four patients who underwent early surgery in this series were haemodynamically stable following resuscitation and did not require TAE. Following complete staging and evaluation of liver function, we proceeded to perform early laparoscopic hepatectomy to reduce the chance of recurrent rupture and possibly reduce the risk of tumour recurrence.

At our institution, we have been performing LLR since 2006, of which approximately 95% were undertaken from 2012 onwards. The procedures which have been performed at our institution included many complex surgeries such as major liver resections, tumours in posterosegmental segments and repeat liver resections for recurrent HCCs. This relatively large experience has enabled us to confidently attempt LLR for srHCC. In this early experience, we found that laparoscopy offers certain advantages in LR, which can be useful specifically in cases of srHCC. The reverse Trendelenburg position commonly used helps to lower the central venous pressure, and the pneumoperitoneum of 10–12 mmHg also provides counter pressure which is useful in minimising tumour bleeding. Temporary increase in pneumoperitoneum pressure to 15–18 mmHg may be performed to tamponade bleeding in cases of venous injury, although there is may be an increased risk of CO₂ gas embolism with this. In addition, the magnified view offered by the laparoscope aids in meticulous dissection and haemostasis, and also is also useful for careful inspection of the entire abdominal cavity to rule out peritoneal
metastasis. Particularly in srHCC, dense adhesions may also form between the ruptured formerly-bleeding tumour and the abdominal wall or adjacent organs/omentum. Pneumoperitoneum insufflation produces stretching of these adhesion bands, which facilitates adhesiolysis. Most of the patients in our series who underwent LLR for srHCC were elderly (≥65) and underwent mainly limited resection. In our institutional experience, we have found that performing laparoscopic minor hepatectomies in elderly patients also reduced the risk of post-operative pulmonary complications and resulted in a shorter LOS, albeit at the expense of increased surgical time and blood loss, although this was not the case in the present study.

Despite these potential advantages, we recognise that many surgeons may have reservations about performing laparoscopic surgery in patients presenting with srHCC who may be in shock due to haemoperitoneum. Concerns include difficult visualisation, suboptimal exposure and prolonged operating times. Patient safety is of utmost importance; and hence, we were very careful in our selection process and only performed LLR in haemodynamically stable patients with good liver function, with tumours in easily accessible locations and low difficulty scores for LLR. HALS was also employed in one of our cases, whereby the surgeon’s hand was instrumental in rapid evacuation of clots for improved visualisation and optimising exposure, and also allowed manual compression of the liver to decrease blood loss. Performing major resections in patients with srHCC who often have borderline liver function carries an extremely high risk of morbidity and mortality; hence we restricted ourselves in this early experience to minor hepatectomies. Very recently, Yoshiya et al. published the first report of a major LLR for ruptured HCC. The patient presented with a ruptured segment IV HCC which was initially controlled with TAE of the feeding arteries, and a laparoscopic left hepatectomy was subsequently performed. This study provided evidence that indications of LLR for srHCC may well be expanded to include major hepatic resections, in highly selected cases.

Laparoscopy may also be utilized in order to avoid an unnecessary laparotomy in certain cases of srHCC. Lang et al. performed diagnostic laparoscopy in 33 patients with srHCC and were able to avoid an unnecessary laparotomy in 12 patients with irresectable disease. These patients benefitted from quicker recovery, shorter hospital stays and were able to commence TACE earlier than those who were found to have irresectable HCC only at open laparotomy. Patients in the laparoscopy group also enjoyed similar overall survival and disease-free survival rates as those who did not undergo laparoscopy. None of the patients in the laparoscopy group developed post-site metastases or peritoneal metastases, similar to the patients in our series. This adds to the growing body of evidence that pneumoperitoneum insufflation in itself does not cause dissemination of tumour cells into the peritoneal cavity in srHCC. Hai et al. demonstrated that even when peritoneal recurrence does occur following resection of a srHCC, laparoscopic extirpation of the peritoneal metastatic lesions can be effectively performed even if the index surgery was performed open. There are also reports of successful local ablation of srHCC in the emergency setting via laparoscopic-guided RFA and microwave ablation.

The main limitation of this study is the small sample size and its retrospective nature. Hence, the results of this study are likely to be affected by selection bias and its susceptibility to Type 2 error.

CONCLUSION

Our early experience demonstrated that LLR may be safely performed in highly-selected cases of srHCC. These patients may enjoy comparable perioperative outcomes as those who undergo OLR for ruptured tumours and LLR for nrHCC.

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Conflicts of interest
There are no conflicts of interest.

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