Original Article

Long-Term Oncological Safety of Minimally Invasive Hepatectomy in Patients with Hepatocellular Carcinoma: A Case-Control Study

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Abstract

Introduction: Minimally invasive hepatectomy (MIH) for patients with hepatocellular carcinoma (HCC) is technically challenging, especially with large posteriorly located tumours or background of liver cirrhosis. This is a case-control study comparing the long-term oncological safety of HCC patients who underwent MIH and open hepatectomy (OH). Most of these patients have liver cirrhosis compared to other studies. Materials and Methods: Sixty patients were divided into 2 groups, 30 underwent MIH and 30 underwent OH for HCC resection. The patients in both groups were matched for extent of tumour resection, age and cirrhosis status. Patient characteristics, risk factors of HCC and all oncological data were studied. Results: Negative resection margins were achieved in 97% of patients in both groups. The mean blood loss during surgery was significantly lower in the MIH group compared to the OH group (361 mL vs 740 mL; 95% CI, 222.2, 734.9; *P* = 0.04). Hospitalisation is significantly shorter in MIH group (7 days vs 11 days; 95% CI, 6.9, 12.2,; *P* = 0.04). Eight patients (27%) in the MIH group and 13 patients (43%) in the OH group developed HCC recurrence (*P* = 0.17). One, 3 and 5 years disease-free survival between MIH and OH groups are 76% vs 55%, 58% vs 47%, and 58% vs 39% respectively (*P* = 0.18). One, 3 and 5 years overall survival between MIH and OH groups are 93% vs 78%, 89% vs 70%, and 59% vs 65% respectively (*P* = 0.41). Conclusion: MIH is a safe and feasible curative treatment option for HCC with similar oncological outcomes compared to OH. MIH can be safely performed to remove tumours larger than 5 cm, in cirrhotic liver, as well as centrally and posterior located tumours. In addition, MIH patients have significant shorter hospitalisation and intraoperative blood loss.

Ann Acad Med Singapore 2016;45:91-7

Key words: Laparoscopy, Liver cirrhosis, Primary liver cancer

Introduction

Minimally invasive hepatectomy (MIH) is well established and routinely done for benign and malignant hepatic lesions in suitable cases.[1] The advancements in video systems, energy devices and stapling equipment[2] in recent years have also made it feasible and safe for malignant hepatic lesions.[3,4]

However, the development and adoption of MIH compared to other forms of minimally invasive surgery has been slow due to the concerns regarding the adequacy of oncologic clearance, achievement of haemostasis, length of operating time, risk of gas embolism[5] and the lack of randomised controlled trials.

In addition, the management of hepatocellular carcinoma (HCC) remains a major challenge to all hepatobiliary surgeons, especially in patients with a background of liver cirrhosis.[6,7] These patients have poorer preoperative status, lower hepatic reserves and higher rates of HCC recurrence, and curative resection is not always possible.

Therefore, few centres worldwide currently offer MIH for HCC, and the majority of hepatectomy studied in published papers are wedge resections and left lateral sectionectomies.[1] The role of MIH in more challenging hepatectomies such as hemihepatectomy and posterior sectionectomy, even in patients with a background of liver cirrhosis, has not been very well documented.

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This paper aims to study the oncological outcomes of MIH performed for HCC compared to open hepatectomy (OH) in a tertiary centre with a full spectrum of capabilities for MIH in Singapore. Most of the patients studied have cirrhosis, and some underwent minimally invasive surgery for challenging hepatectomy.

Materials and Methods

Patient Selection

More than 100 cases of MIH for benign and malignant liver diseases at a university hospital with advanced laparoscopic facilities and liver transplant services were retrospectively studied. Thirty consecutive patients who underwent MIH for HCC over a period of 54 months (August 2006 to February 2011) were included in this study. They were matched for extent of tumour resection, age and cirrhosis status with 30 patients who underwent OH for HCC mostly during a similar period. Presence of liver cirrhosis and portal hypertension was determined by preoperative imaging (mainly computed tomography [CT] or magnetic resonance imaging [MRI]), and all cases were discussed in our multidisciplinary tumour board meeting.

The extent of resection was classified as minor resection (wedge resection and single segment resection), partial resection (2 to 3 liver segments resection) and major resection (4 or more liver segments resection) for matching purposes. This classification is chosen for matching because it is widely recognised that morbidity and mortality rate is inversely proportionate to remnant liver volume.[8]

Data Collection

Patient data recorded include age and gender, risk factors for HCC, presence of comorbidities, presence of liver cirrhosis and portal hypertension changes on preop imaging, cirrhosis status, Ishak's fibrosis score on histology of the resected specimen and the Child-Pugh classification.

Operative data recorded include surgical approach (fully laparoscopic or hand-assisted), extent of resection, operative time, blood loss, blood transfusion required, need for conversion, presence of complications, days to ambulation, length of hospitalisation and treatment for recurrence.

Oncologic data recorded includes tumour size and location, resection margins, histological features (tumour differentiation, and capsular, perineural/lymphatic/vascular involvement), multifocality and time to HCC recurrence, follow-up period and survival status.

The oncological and surgical outcomes were compared between the patients who underwent MIH and OH. The patients who developed HCC recurrence in both groups were also studied to look for differences in risk factors for recurrence, such as tumour size, resection margins, histological features, age and gender and cirrhosis status.

Data Analysis

All data was analysed with SPSS software, through which continuous variables were compared using the Mann-Whitney U test and categorical variables using the Chi-square test. Disease-free and overall survival periods were analysed with the Kaplan-Meier test; 95% confidence interval (CI) was calculated for continuous variables. Statistical significance was defined as $P < 0.05$.

Results

Patient Data

There was a majority of male patients, patients with a background of liver cirrhosis, patients with Child's A status and Hepatitis B carriers in both groups. There is no statistically significant difference in cirrhosis and portal hypertension changes on preop imaging, Ishak's fibrosis score on the resected specimens and preop Child's score. Table 1 shows the patients' characteristics.

Operative Data

Within the group of patients who underwent MIH, 10 patients (33%) had a minor resection, 14 patients (47%) had a partial resection and 6 patients (20%) had a major resection. Thirteen patients (43%) had fully laparoscopic hepatectomy and 17 patients (57%) had hand-assisted laparoscopic hepatectomy.

The extent of resection and cirrhosis status are identical and the age distribution is similar in the group of patients who underwent OH compared to the group who underwent MIH, as a result of patient matching.

The mean intraoperative blood loss was significantly lower in the MIH group compared to the OH group (361.5 ± 376.9 mL vs 740.0 ± 1106.6 mL; 95% CI, 222.2, 734.9; $P = 0.04$). The patients in the MIH group also had a shorter length of hospitalisation compared to those in the OH group (7.0 ± 3.0 days vs 11.0 ± 9.3 days; 95% CI, 6.9, 12.2; $P = 0.01$). There was no statistically significant difference in the mean operative time between the patients in the MIH and OH groups (288 vs 301 minutes; 95% CI, 244.7, 299.5; $P = 0.15$). Table 2 shows operative variables in both groups.

Oncological Data

All resected specimens in both MIH and OH groups were proven to be HCC after histological examination. The median tumour size was also similar between both groups, 33 mm (14-120) vs 43 mm (11-140); 95% CI, 34.8, 50.7; $P = 0.18$.

Table 1. Patient Characteristics

	MIH, n = 30	OH, n = 30	*P* Value	95% CI
Mean age, years (SD)	60 (± 9.7)	58 (± 11.6)	0.28	57.5 – 63.1
Male, n (%)	22 (73%)	25 (83%)	0.35	NA
Features of cirrhosis on preop imaging, n (%)	20 (67%)	20 (67%)	1.00	NA
Features of portal hypertension on preop imaging, n (%)	15 (50%)	8 (27%)	0.15	NA
Ishak's fibrosis score			0.22	NA
F0 – F3, n (%)	12 (40%)	17 (57%)		
F4, n (%)	7 (23%)	6 (20%)		
F5, n (%)	5 (17%)	3 (10%)		
F6, n (%)	6 (20%)	4 (13%)		
Child's status			0.45	NA
A, n (%)	27 (90%)	26 (87%)		
B, n (%)	2 (7%)	4 (13%)		
C, n (%)	1 (3%)	0 (0%)		
Risk factors			0.68	NA
Hepatitis B, n (%)	20 (67%)	25 (83%)		
Hepatitis C, n (%)	3 (10%)	1 (3.5%)		
Others, n (%)	4 (13%)	3 (10%)		
None, n (%)	3 (10%)	1 (3.5%)		

MIH: Minimally invasive hepatectomy; NA: Not applicable; OH: Open hepatectomy

Table 2. Operative Variables

	MIH	OH	*P* Value	95% CI
Surgical technique			NA	NA
Fully laparoscopic, n (%)	13 (43%)	NA		
Hand-assisted laparoscopic, n (%)	17 (57%)	NA		
Type of resection			NA	NA
Minor, n (%)	10 (33%)	10 (33%)		
Partial, n (%)	14 (47%)	14 (47%)		
Major, n (%)	6 (20%)	6 (20%)		
Extent of resection			NA	NA
Central hepatectomy	0 (0%)	1 (3.3%)		
Right hepatectomy	2 (6.7%)	3 (10%)		
Left hepatectomy	2 (6.7%)	2 (6.7%)		
Left lateral sectionectomy	6 (20%)	5 (16.7%)		
Right anterior sectionectomy	0 (0%)	1 (3.3%)		
Right posterior sectionectomy	6 (20%)	5 (16.7%)		
Posterior-superior segmentectomy/wedge resection (seg. 7-8)	3 (10%)	4 (13.3%)		
Anterior-lateral segmentectomy/wedge resection (seg. 2-6)	11 (36.7%)	9 (30%)		
Anatomical resection, n (%)	27 (90%)	26 (87%)	0.86	NA
Mean operative time, minutes (SD)	288 (± 178)	301 (± 108)	0.15	244.7 – 299.5
Mean blood loss, mL (SD)	361.5 (± 376.9)	740 (±1106.8)	0.04	222.2 – 734.9
Mean length of hospitalisation, days (SD)	7 (± 3)	11 (± 9.3)	0.01	6.9 – 12.2

MIH: Minimally invasive hepatectomy; NA: Not applicable; OH: Open hepatectomy

Table 3. Specimen Characteristics, Recurrence during Follow-up

	MIH	OH	*P* Value	95% CI
Median tumour size, mm (range)	33 (14 - 120)	43 (11 - 140)	0.18	34.8 – 50.7
Resection margin			0.24	
Median, mm (range)	8.9 (0-30)	4.2 (0 - 52)		6.5 – 11.6
>10 mm, n (%)	11 (37%)	10 (33%)		
1 mm – 10 mm, n (%)	18 (60%)	19 (64%)		
Positive, n (%)	1 (3%)	1 (3%)		
Differentiation			0.52	NA
Well, n (%)	11 (37%)	8 (27%)		
Moderate, n (%)	18 (60%)	21 (70%)		
Poor, n (%)	1 (3%)	1 (3%)		
Vascular invasion, n (%)	3 (10%)	4 (13.3%)	0.58	NA
Perineural/lymphatic involvement, n (%)	5 (17%)	6 (20%)	0.67	NA
Capsular involvement, n (%)	4 (13%)	6 (20%)	0.49	NA
Multifocality, n (%)	1 (3.3%)	2 (6.7%)	0.78	NA
Overall recurrence, n (%)	8 (27%)	13 (43%)	0.17	NA
Recurrence in non-anatomical resection	0 (0%)	1 (7.7%)	0.33	NA
Median time to recurrence, months (range)	9.1 (6.2 - 33.4)	8.5 (1.2 - 47.8)	0.29	2.3 – 17.2
Median follow-up period, months (range)	42.5 (3 - 71)	36.5 (0 - 113)	0.73	21.1 – 43.4

MIH: Minimally invasive hepatectomy; NA: Not applicable; OH: Open hepatectomy

Negative resection margins were achieved in 97% of patients in both groups, with median resection margins of 8.9 mm (0-30) and 4.2 mm (0-52) for the MIH and OH groups respectively (95% CI, 6.5, 11.6; $P = 0.24$).

There were no statistically significant differences in histological features (tumour differentiation, multifocality and capsular, perineural/lymphatic/vascular involvement) between the MIH and OH groups.

The median follow-up period of the MIH and OH groups were 42.5 and 36.5 months respectively (95% CI , 21.1, 43.4; $P = 0.73$). Table 3 shows the specimen characteristics and recurrence during follow-up in both groups. Figures 1 and 2 illustrate the tumour location in both groups.

During the follow-up, 8 patients (27%) in the MIH group and 13 patients (43%) in the OH group developed HCC recurrence ($P = 0.17$). The mean time to recurrence was 15.5 ± 9.2 and 13 ± 13.5 months for those in the MIH and OH groups respectively (95% CI, 2.3, 17.2; $P = 0.29$). There were no statistically significant differences between these MIH and OH groups in mean tumour size (43.2 ± 24.0 vs 64.4 ± 37.6 mm; 95% CI, 42.7, 87.1; $P = 0.06$) and median resection margins (4.5 mm (0-18) vs

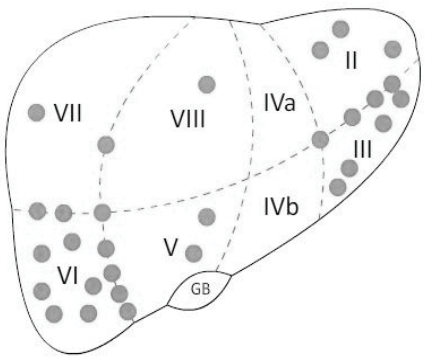


Fig. 1. Tumour locations in patients from the MIH group.

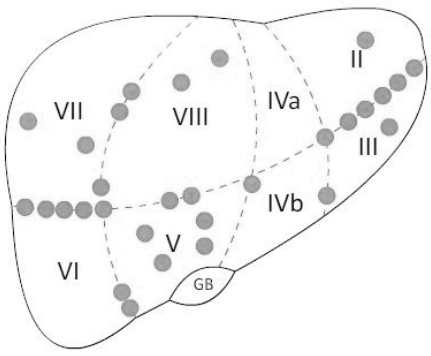


Fig. 2. Tumour locations in patients from the OH group.

Table 4. Comparison of Risk Factors for Recurrence

	MIH	OH	*P* Value	95% CI
n (%)	8 (27%)	13 (43%)	0.17	NA
Mean tumour size, mm (SD)	43.2 (± 24)	64.4 (± 37.6)	0.06	42.7 – 87.1
Resection margin				
Median, mm (range)	4.5 (0 - 18)	3.4 (0 - 35)	0.29	0.1 – 6.7
>10 mm, n (%)	1 (11%)	2 (14%)		
1 mm – 10 mm, n (%)	7 (78%)	11 (79%)		
Positive, n (%)	1 (11%)	1 (7%)		
Perineural/vascular/lymphatic involvement, n (%)	3 (38%)	4 (31%)	0.67	NA
Capsular involvement, n (%)	1 (13%)	2 (15%)	0.58	NA
Cirrhosis, n (%)	5 (63%)	8 (62%)	0.33	NA
Mean age, years (SD)	62 (± 10.7)	54 (± 12.8)	0.07	46.3 – 61.8
Male, n (%)	7 (88%)	13 (100%)	0.36	NA

MIH: Minimally invasive hepatectomy; NA: Not applicable; OH: Open hepatectomy

3.4 mm (0-35); 95% CI, 0.1, 6.7; $P = 0.29$). There was 1 patient with a positive resection margin in each group. There were also no statistically significant differences in the histological features, age, gender and cirrhosis status. One non-anatomical resection in OH group developed recurrence, but it did not reach statistical significance when compared to MIH group. Table 4 shows the comparison of risk factors for recurrence in patients in both groups who developed recurrence.

One, 3 and 5 years disease-free survival between MIH and OH groups are 76% vs 55%, 58% vs 47%, and 58% vs 39% respectively ($P = 0.18$). One, 3 and 5 years overall survival between MIH and OH groups are 93% vs 78%, 89% vs 70%, and 59% vs 65% respectively ($P = 0.41$). Figures 3 and 4 illustrate the Kaplan-Meier curves for disease-free survival and overall survival of both groups.

Discussion

Current Literature on Minimally Invasive Hepatectomy

Minimally invasive surgery has been gradually replacing open surgery in many cases, as it offers better surgical outcomes like reduced intraoperative bleeding,[9,10] shorter hospital stays,[4,10] reduced postoperative pain and faster recovery of surgical wounds and normal physical function.[11,12] With increasing experience, surgeons are also able to achieve comparable operative times[8,12] and complication rates.[13]

MIH has become a more established curative treatment option for HCC over the last decade.[1,4,14] However, it is performed in few centres worldwide as it is technically challenging compared to other forms of minimally invasive surgery. A good amount of surgical experience and advanced laparoscopic equipment are required.

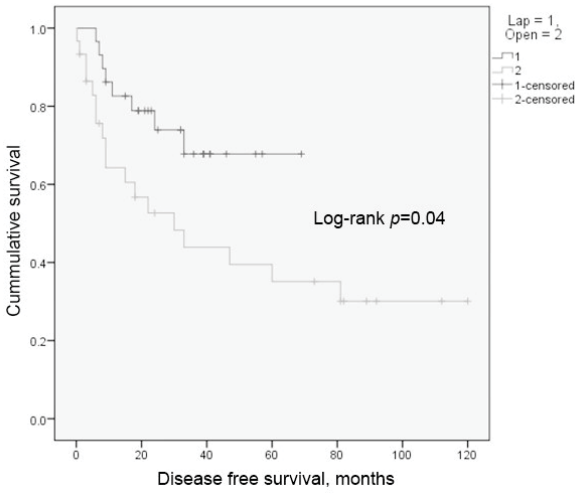
Most of the published literature[15-19] are generic studies on the feasibility of MIH in patient populations with variable demographics and disease characteristics. Our study, done in a tertiary hospital in Singapore, focuses on the oncological outcomes of MIH in patients with HCC and liver cirrhosis.

Experience with Minimally Invasive Hepatectomy

Our centre is a regional referral centre for liver transplantation and a variety of liver diseases, and possesses a full spectrum of capabilities for MIH; 67% of the patients in our study have HCC on a background of liver cirrhosis, which is representative of the patient profile locally.

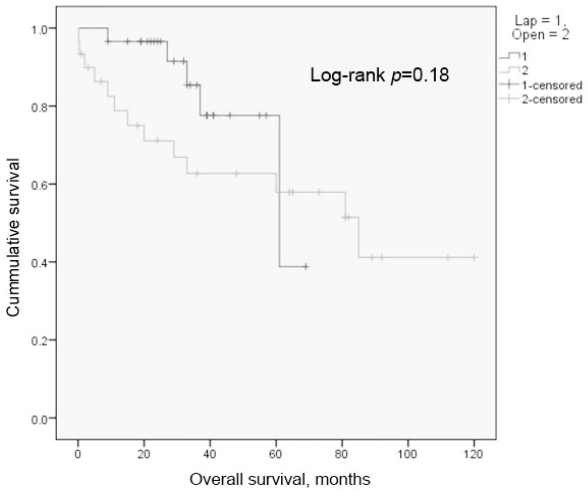
Haemostasis in MIH has always been a concern, especially in patients with liver cirrhosis and poor liver function.[7, 20] However, a series of reports have shown that surgical and oncological outcomes are comparable with that of OH in the hands of experienced surgeons.[3,6,11,21] Furthermore, the use of laparoscopic energy devices and stapling devices help in the dissection of liver parenchyma and ligation of big vascular pedicles respectively.[2]

The liver is routinely assessed in our centre with laparoscopic ultrasound devices during the operation before hepatectomy is performed. This is the gold standard in both MIH and OH in most centres as intraoperative ultrasound (IOUS) has been shown to be more sensitive than MRI and CT scans for detecting lesions smaller than 5 mm in size.[22] In this study, we did not detect any extra lesions in both MIH and OH groups with IOUS, hence no change in surgical strategy intraoperatively.



Disease-free Survival	1 Year	3 Year	5 Year	Log-rank *P* Value
MIH	76%	58%	58%	0.18
OH	55%	47%	39%	

Fig. 3. Graph and table showing the disease-free survival (MIH: "Lap", OH: "Open").



Overall Survival	1 Year	3 Year	5 Year	Log-rank *P* Value
MIH	93%	89%	59%	0.41
OH	78%	70%	65%	

Fig. 4. Graph and table showing the overall survival (MIH: "Lap", OH: "Open").

Superior Surgical Outcomes

In our series of patients, some of whom underwent resection of large and posteriorly located tumours via MIH, no conversion to laparotomy was required. In addition, the patients who underwent MIH had a significantly reduced intraoperative blood loss and shorter length of hospitalisation. The mean operative time was also not significantly different.

Some studies do not recommend MIH for tumours exceeding 50 mm,[3,6,8,23] as ideal candidates for MIH are conventionally thought to be patients with small and peripherally located tumours. In our study, 30% of the MIH cases involved posterior part of the liver and 13.4% were major liver resection. In addition to that, we had 6 patients with tumours larger than 50 mm and up to 120 mm who underwent MIH. There is no significant difference in tumour size and location in MIH and OH groups. This initial results show that with proper preoperative planning and use of appropriate surgical devices and technique, MIH can be safely performed in most types of liver resection by experienced hepatobiliary surgeons in patients with HCC and liver cirrhosis.

Comparable Oncological Outcomes

In our series of patients, MIH was shown to be comparable to OH in terms of oncological outcomes. Both groups of patients who underwent either MIH or OH for resection of HCC had similar patient profiles, tumour size, location and histological features. There were no significant differences in the 3-year and 5-year overall survival rates between the 2 groups.

In addition, our centre achieved negative resection margins in 97% of patients in both groups with a mean margin of 9 mm. This result is highly encouraging given that adequate resection margins is a major concern among hepatobiliary surgeons for HCC resection. The proportion of our patients who developed HCC recurrence in both groups was also similar, and there were no cases of port-side recurrence in those who underwent MIH. There was 1 patient in each group who had positive resection margins, and both patients subsequently developed HCC recurrence.

The standard surgical resection margins for HCC remains widely debatable across the world. There are suggestions that bigger margins do not contribute to longer survival and lower HCC recurrence rates in cases that achieved microscopic negative margins.[6,7] Furthermore, there are concerns that unnecessary extension of margins may compromise liver function in patients who have poor liver reserves preoperatively.[20]

The comparable oncological outcomes in our study clearly show that in a highly specialised centre, MIH is not an inferior curative treatment option for HCC and does not compromise oncological resection in all kinds of

hepatectomy compared to OH, even in patients with liver cirrhosis. However, we believe that performing MIH for HCC resection is technically demanding and should be done only by experienced surgeons.

This study is limited by its retrospective nature, small number of patient as well as unmatched tumour location. However, the results demonstrated that MIH can be performed in large tumour, posteriorly or superiorly located tumours and cirrhotic liver. We were able to perform anatomical resection laparoscopically in majority of the cases. We hope to see well designed randomised controlled trials comparing MIH and OH for cirrhotic patients with HCC in the near future to further conclude the oncologic safety of MIH.

Conclusion

MIH is a safe and feasible curative treatment option for HCC with similar oncological outcomes compared to OH. MIH can be safely performed to remove tumours larger than 5 cm, in cirrhotic liver, as well as centrally and posterior located tumours. In addition, MIH patients have significant shorter hospitalisation and intraoperative blood loss.

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