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Laparoscopic resection of hepatocellular carcinoma in patients with and without cirrhosis: the Brisbane experience

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ABSTRACT

Aim: Laparoscopic liver resection for hepatocellular carcinoma (HCC) is increasingly common around the world. There may be significant advantages over open resections. However, due to technical difficulties, they are performed in few centers with expertise in liver and advanced laparoscopic surgery. In this study the authors summarize the experience to date. **Methods:** A retrospective analysis of consecutive patients undergoing laparoscopic liver resection for HCC in 2 tertiary academic hepatobiliary units in Brisbane, Australia, between 1999 and 2015 was performed. Operative characteristics, perioperative morbidity, and pathological data were described. Patients with and without cirrhosis were analyzed and compared. **Results:** Fifty-two patients underwent resection of 79 HCCs. Sixty-five percent of patients had cirrhosis. Fourteen percent of patients underwent a major hepatectomy. There was a trend towards more parenchyma-sparing resections for cirrhotic patients. Blood loss was higher in cirrhotics. Conversion to an open procedure occurred in 9%. There was one 90-day mortality due to liver failure (1.9%), and 7 patients (13%) experienced a complication. R0 resection was achieved in 92%. Overall survival at 1, 3, and 5 years was 88%, 81%, and 61%, respectively. **Conclusion:** Laparoscopic liver resection for HCC, particularly in cirrhotic patients, is technically challenging. It can be performed with acceptable morbidity and adequate surgical margins.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cause of cancer and the third most common cause of cancer-related death worldwide. Furthermore, it is the leading cause of death for patients with cirrhosis.[1,2] In North America and Europe, the incidence of HCC has been rising, likely due to changing risk factors for cirrhosis, including hepatitis C infection in baby-boomers, alcohol use, obesity, and non-alcoholic fatty liver disease.[3,4] At presentation, only 10-15% of patients are candidates for surgical resection. Other treatment options include liver transplantation, ablation, transcatheter artrial chemoembolisation, and systemic chemotherapy. Liver resection, more commonly reported as an open procedure, is a well-established, potentially curative treatment for patients with HCC, and is the procedure of choice in many patients with preserved liver function.[5,6]

Minimally invasive management of HCC is increasing in frequency, including patients with underlying cirrhosis.[2,7-11] There may be a number of benefits of laparoscopy over laparotomy for HCC, which have been widely reported. Potential benefits include decreased blood loss and need for blood transfusion, decreased complications (i.e. less postoperative ascites, wound infection), decreased length of stay, and reduced technical difficulty with subsequent surgery, including transplantation.[2,9,10,12,13] Oncological principles can be maintained with laparoscopy and outcomes are comparable, if not better, with laparoscopy compared to open HCC resection.[13-17] The benefits may derive from the pathophysiological changes that occur with laparoscopy compared to laparotomy, which may be accentuated in the presence of cirrhosis. These include less disruption of the abdominal wall, reduced immune response, and the tamponade effect of pneumoperitoneum.

Laparoscopic resection of HCC is technically challenging. It requires both laparoscopic skills and advanced liver surgical skills. The limited viewing angles, fulcrum effect of laparoscopic ports, instrument clash, reduced tactile feedback, and reduced operating dexterity pose significant challenges in complex surgery. Liver exploration and mobilization, hemorrhage control during parenchymal transection, the use of laparoscopic ultrasound, ensuring adequate oncological margins, and suturing can be more difficult with laparoscopy, especially in the presence of cirrhosis.[18] The operative time is generally longer than open surgery. Skilled assistance is essential, and for long cases surgeon and assistant fatigue is common. The cirrhotic poses additional complexity with potentially altered vasculature in the abdominal wall, hilum and retroperitoneum, and a stiffened liver that resists laparoscopic handling. However, laparoscopic resection of HCC in both non-cirrhotic and cirrhotic patients can provide good clinical outcomes, act as bridge-to-transplant and deliver acceptable survival rates.[19]

The worldwide experience in laparoscopic liver resection for HCC is increasing, although major resections are still limited to few centers. The current study describes our experience in Brisbane, Australia, with focus on perioperative outcomes.

METHODS

Data acquired from a prospectively collected laparoscopic liver surgery database from multiple centers in Brisbane, Australia, were examined and retrospectively reviewed. Ethics approval was obtained prior to the commencement of the study. Consecutive patients who underwent laparoscopic resection of HCC between January, 1999 and September, 2015 were selected. All patients underwent high quality preoperative imaging with contrast-enhanced computer tomography and magnetic resonance imaging. Selection for laparoscopic resection took into consideration tumor size and location, the degree of underlying liver disease and portal hypertension, and the patient's fitness and ability to tolerate a prolonged pneumoperitoneum. Patients with Child-Pugh B and C cirrhosis were generally excluded. All patients were discussed and management was agreed upon at a multi-disciplinary team meeting.

Collected intraoperative data included details of the surgical procedure (minor *vs.* major; anatomic *vs.* non-anatomic), operation duration, blood loss and conversion to laparotomy. A wide range of clinicopathological factors were collected regarding underlying liver disease (METAVIR score), etiology, number and size of tumors, lymphatic or vascular invasion, tumor differentiation, presence of satellite nodules, and pathological margins. A microscopic margin of ≥ 1 mm was defined as R0.

Surgical technique had been described previously.[20,21] In brief, pneumoperitoneum was established via an open access technique and maintained at 12-15 mmHg. Four to 6 working ports were used. The Pringle maneuver was used selectively. In selected patients with dome lesions, additional intercostal and transthoracic trocars were used. For major hepatectomies, inflow vascular structures were controlled with clips or vascular staplers and the hepatic veins were controlled extrahepatically. Parenchymal transection was performed using LigaSure (Covidien, Mansfield, MA, USA), harmonic

Table 1: Baseline characteristics

Baseline characteristics	Median (range) or *n* (%)
Age, years	58 (44-81)
Female	26
α-fetoprotein, ng/mL	8.5 (1.7-59,000)*
No cirrhosis	18 (35)
Cirrhosis	34 (65)
Child-Pugh class	
A	33
B	1
C	0
Known underlying liver disease	37 (71)
HBV	2 (4)
HCV	23 (46)
Alcohol	3 (6)
NASH	5 (10)
Unknown (with cirrhosis)	4 (8)

*14.6% of patients had an α-fetoprotein level ≥ 200 ng/mL. HBV: hepatitis B virus; HCV: hepatitis C virus; NASH: non-alcoholic steatohepatitis

Table 2: Operative characteristics

Operative characteristics	Total	Non-cirrhotic	Cirrhotic
Laparoscopic liver resection	52	18	34
Major hepatectomy, *n* (%)			
Right hepatectomy	4 (8)	4 (22)	0 (0)
Left hepatectomy	1 (2)	1 (6)	0 (0)
Extended right hepatectomy	2 (4)	0 (0)	2 (6)
Left lateral sectionectomy, *n* (%)	11 (21)	4 (22)	6 (18)
Segmentectomy, *n* (%)	24 (46)	7 (39)	17 (50)
Subsegmental resection, *n* (%)	10 (19)	2 (11)	9 (26)
Posterosuperior (segments 1, 4a, 7, 8) resections, *n* (%)	8 (15)	3 (17)	5 (15)
Conversion to laparotomy, *n* (%)	5 (9)	2 (11)	3 (9)
Operating time, min, median (range)	120 (75-300)	117 (75-240)	120 (90-300)
Blood loss, mL, median (range)	300 (20-1,600)	150 (20-600)	350 (30-1,600)

shears, or the 10 mm laparoscopic Cavitron Ultrasonic Surgical Aspirator (Integra Life sciences Corporation, NJ, USA), combined with use of locking clips (Hem-o-lok, Teleflex Medical, Durham, NC, USA) and staplers. Drains were reserved for patients deemed to be high risk for bile leak. Postoperatively, patients who underwent major resections (> 3 segments) were admitted to the intensive care unit (ICU). Patients with minor resections (< 3 segments) were admitted to the general surgical ward. Chemical and mechanical thromboprophylaxis were used routinely. Early mobilization and return to a normal diet was encouraged.

Postoperative parameters examined included duration of ICU and total hospital stay, postoperative morbidity (stratified according to the Clavien-Dindo system of classification), and 30-day and 90-day mortality. One-, 3- and 5-year survival and disease-free survival status was recorded and actuarial survivals were estimated using the Kaplan-Meier method. Mid and long-term follow up included clinical, biological and radiological assessment 1-month post surgery and every subsequent 6-month. Survival follow-up was achieved through updated medical records and phone calls.

Statistical analyses were performed using R 3.2.0 (R Core Team, 2015). Categorical data were compared using Fisher's exact test; median values from continuous data were compared using the 2-sample rank test; *P*-values of < 0.05 were considered statistically significant.

RESULTS

Fifty patients underwent a total of 52 operations. In total, 79 HCCs were resected. The annual frequency of laparoscopic resection of HCC in our centers gradually increased, from 7 patients during the early period (1999-2004), to 18 in the middle period (2005-2010), to 25 in the later period (2011-2015) [Figure 1]. The percentage of patients having cirrhosis also increased, from 57%, to 67%, to 72% respectively. Overall in this study, 34 patients (65%) had cirrhosis (33 Child-Pugh A, 1 Child-Pugh B). Of the patients with cirrhosis, 56% had evidence of portal hypertension. The most common etiology of cirrhosis was hepatitis C (65%) and non-alcoholic steatohepatitis (non-alcoholic steatohepatitis, 14%). The baseline characteristics of the patients are summarized in Table 1.

Operative characteristics are summarized in Table 2. There were 7 (14%) major hepatectomies, including 2 extended hemihepatectomies. Seventy-six percent of cirrhotic patients underwent a segmentectomy or subsegmentectomy, compared with 50% of non-cirrhotic patients (*P* = 0.068).

There were 52 operations and of these, 51 were pure laparoscopic (including 2 involving the addition of intercostal or transthoracic trocars) and 1 was hand-assisted. There were 5 conversions (9%), 3 of which (pure laparoscopic intent) were due an inability to progress as a result of difficult dissections secondary to intra-abdominal adhesions. One conversion occurred due to uncontrollable hemorrhage in a non-cirrhotic patient. The final conversion occurred in the hand-assisted case of a posterior dome lesion (segment 7/8). This patient had recognised positive margin due to the awkward angle and was opened for wider resection.

Table 3: Postoperative and histopathological data

Postoperative and histopathological data	All patients	Non-cirrhotic	Cirrhotic
Length of hospital stay, days, median (range)	5 (1-72)	5 (3-13)	5 (1-72)
Mortality, 90-day, *n* (%)	1 (1.9)	0 (0)	1 (3)
Overall morbidity, *n* (%)	7 (13)	2 (11)	5 (15)
Infection	3 (6)	1 (6)	2 (6)
Ascites	3 (6)	0 (0)	3 (9)
Bile leak	1 (2)	1 (6)	0 (0)
Tumor margin, mm, median	9	5	15
Margin status, *n* (%)			
R0	48 (92)	17 (94)	31 (91)
R1	4 (8)	1 (6)	3 (9)
Tumor size, mm, median (range)	33 (5-220)	40 (20-150)	28 (5-220)
Number of tumors, median (range)	1 (1-5)	1 (1-2)	1 (1-5)
Multifocality, *n* (%)	17 (33)	2 (11)	15 (44)
Tumor differentiation, *n* (%)			
Well differentiated	13 (25)	6 (33)	9 (26)
Moderately differentiated	36 (70)	11 (61)	23 (67)
Poorly differentiated	3 (5)	1 (6)	2 (6)
Vascular invasion, *n* (%)	17 (33)	8 (44)	9 (26)
Lymphatic invasion, *n* (%)	4 (9)	1 (6)	3 (9)

Subsequent cases involving dome lesions were preferentially performed with a combined transthoracic and transabdominal approach.

Median operative time was 120 min and median blood loss was 300 mL. Patients with cirrhosis experienced more bleeding than those without (median 350 mL in cirrhotics *vs.* 150 mL in non-cirrhotics, *P* = 0.049). The median length of stay was 5 days and was not different between the cirrhotic and non-cirrhotic groups.

Postoperative and pathological data are summarized in Table 3. There was 1 mortality, which occurred early in the series. The patient had Child-Pugh B cirrhosis and underwent a left lateral sectionectomy. Blood loss was 1,600 mL and this patient died due to decompensated liver failure. Overall 7 patients (13%) developed a postoperative complication. Morbidity rates were not different between patients with and without cirrhosis. Apart from the single post-operative mortality, all complications were Clavien-Dindo grade 1 or 2.

Multifocal HCC was far more prevalent in cirrhotics compared with non-cirrhotics (44% *vs.* 11%, *P* = 0.008). Multifocality was generally diagnosed incidentally on pathology of the resected specimen as patients with multifocal disease were excluded from resection. Microvascular invasion was present in 17 patients (33%). Equivalent R0 resection rates were achieved for cirrhotics and non-cirrhotics (94% *vs.* 91%). Despite the higher rate of subsegmental resections, the median margin in cirrhotics was 15 mm compared with 5 mm in the non-cirrhotics (*P* = 0.067).

Median follow-up was 41 months. Median overall survival was 89 months. Overall survival for the entire cohort at 1, 3, and 5 years was 88%, 81%, and 61%, respectively [Figure 2]. The corresponding survival for non-cirrhosis patients was 93%, 77%, and 67%, and for patients with cirrhosis was 86%, 83%, and 50%. Disease-free survival at 5 years was 57% for all patients, 43% for non-cirrhosis, and 71% for patients with cirrhosis.

DISCUSSION

Laparoscopic liver resection is a technically demanding operation. The presence of cirrhosis increases the operative difficulty, and is considered a relative contraindication to laparoscopic resection in some centers. To our knowledge, there are no data suggesting poorer outcomes for patients who undergo
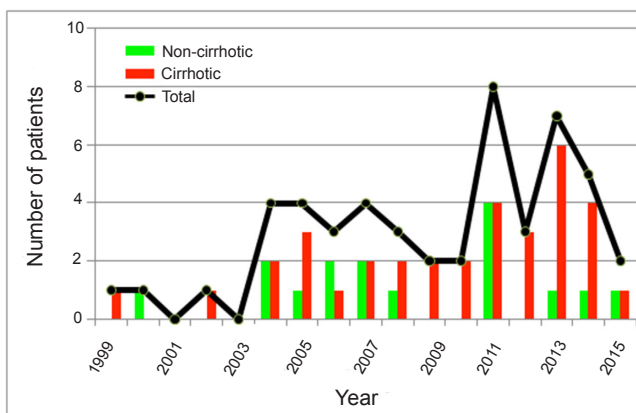

Figure 1: Annual frequency of laparoscopic resection of HCC. HCC: hepatocellular carcinoma

laparoscopic compared to open liver resection in the setting of cirrhosis. In the current study, 65% of patients had cirrhosis (33 Child-Pugh A, 1 Child-Pugh B). There was a trend toward more segmental and subsegmental resections in cirrhotics compared to those without cirrhosis. This reflects the desire to spare parenchyma to reduce post-operative liver insufficiency, but this needs to be balanced against obtaining adequate margins, resecting the "oncological territory" of the tumor, and minimizing blood loss and bile leak. Recent publications have suggested that anatomic resection should be the norm due to the proclivity of HCC to invade the vasculature and metastasize within the liver. However, the heterogeneity with regards to the presence of cirrhosis may be a confounding factor.[22-24]

One patient with Child-Pugh B cirrhosis underwent a laparoscopic left lateral sectionectomy. This patient died within 30 postoperative days due to postoperative liver failure. This case occurred early in the series and as a result, Child-Pugh B status remains a relative contraindication to surgical resection in our center. However, other authors have demonstrated good short and long-term outcomes with reasonable safety in well-selected individuals.[25,26]

Compared to open resection, laparoscopy may have a number of benefits in the setting of cirrhosis. Laparoscopy allows for smaller incisions, which may lead to less disruption of the abdominal wall collateral circulation and cause less fluid shifts from exposure of the peritoneal cavity. In those series, 3 patients (9%) with cirrhosis developed postoperative ascites. Post-operative ascites is common after liver resection, even when a relatively small amount of parenchyma is resected. Some studies have demonstrated less postoperative ascites after laparoscopic liver resection compared to laparotomy.[27-30]
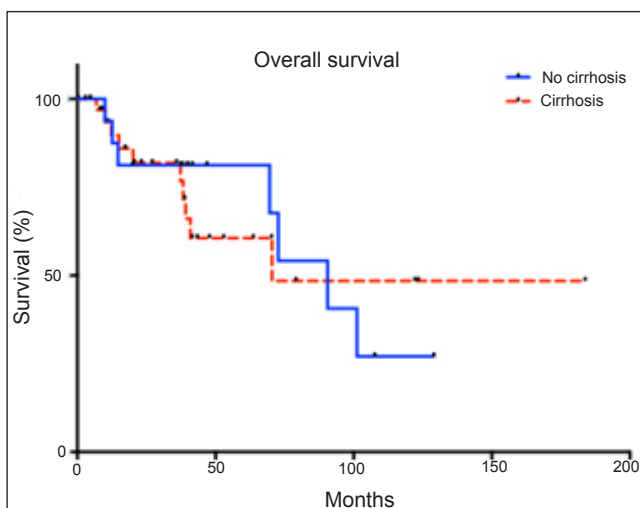

Figure 2: Kaplan-Meier survival analysis

Laparoscopy is also associated with less blood loss and subsequent need for blood transfusion compared to open surgery,[28,29,31] possibly due to the tamponade effect of pneumoperitoneum on the exposed veins and intra-abdominal varices. To reduce blood loss, pneumoperitoneum can be transiently increased to pressures of 16-20 mmHg during parenchymal transection. Despite concerns over the risk of CO_2 embolism and respiratory compromise during high-pneumoperitoneum, this was not a feature in our series. Laparoscopic ultrasound guidance assists in identifying major vascular structures during transection, but the sensitivity of intraoperative ultrasound in localizing small tumors is reduced in cirrhosis.

For parenchymal transection, we favor the use of the LigaSure which combines the sealing ability of bipolar coagulation forceps and recapitulates acrush-clamping technique. Laparoscopic staplers were used mainly for pedicle control and avoided for parenchymal transection due to their tendency to tear the cirrhotic liver.

Ensuring adequate margins is fundamental to the overall outcome of the surgery and subsequent patient prognosis. Whilst the benefits of digital palpation in open surgery may be overstated (especially in cirrhosis), laparoscopy eliminates this capability.[7,32] We found the use of laparoscopic ultrasound essential in order to determine a precise transection line in relation to the tumor margin and locate important vascular structures.[32,33]

Straight resection planes are preferred whenever possible. This is relatively easy to achieve for a lateral sectionectomy or a major hepatectomy, dividing the liver along well defined scissura. However, in cases of laparoscopic non-anatomical subsegmentectomies, there is a significant risk of undermining the tumor leading to a positive margin. This is especially true for tumors with a wider circumference deep to the liver surface. Starting the dissection 2 cm wider, particularly on the side of the tumor nearest to the surgeon, helps achieve clearance of the deep margin. Angling the transection away from the tumor may reduce this risk and we frequently employ metal clips as ultrasound visible "markers" which are re-checked through the transection.

Laparoscopic management of liver tumors has been reported more commonly for lesions located within the anterolateral segments of the liver. Some centers consider posterosuperior lesions (segments 1, 4a, 7, 8), particularly dome lesions adjacent to the hepatic veins a contraindication for laparoscopic surgery. This is due to limited visualization, difficult angle of attack, and reduced capability to control the vena cava in the event

of haemorrhage.[34-36] Such difficulties can be partially overcome by performing a formal hepatectomy, but this is often not ideal as it may be important to preserve hepatic volume in the setting of cirrhosis. In our series, we had 8 dome lesions. During our early experience, we approached a segment 8 dome lesion with a hand-assisted technique. Adequate margins could not be obtained and the case required conversion. We have subsequently modified our technique to use intercostal and transthoracic trocars (ITT) for such lesions. We found that the ITT approach offered better visualization, access for resection and ability to control hemorrhage compared with the hand-assisted technique.

This study is limited by its retrospective nature. We showed that laparoscopic resection is feasible and safe, but without an open comparison group, the true perioperative benefits are unclear. The long-term recurrence and survival outcomes in our cohort need to be further investigated in order to further define the oncological equivalence of laparoscopic resection compared with open.

In conclusion, laparoscopic liver resection for hepatocellular carcinoma can be performed with acceptable morbidity and adequate surgical margins. The technical challenges of liver resection are often magnified with laparoscopy, particularly in patients with cirrhosis. However, such difficulties can be overcome with increasing experience. We believe that the benefits of a minimally invasive approach are also more pronounced in cirrhotics, due to the potential to reduce morbidity compared to an open approach. Future studies comparing laparoscopic to open resection with long-term follow-up should be performed to further define its role.

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Conflicts of interest
There are no conflicts of interest.

Patient consent
Necessary consent was obtained.

Ethics approval
Approved by an institutional board at Royal Brisbane Hospital.

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