Surgical and Oncological Outcomes of Hepatic Resection for Hepatocellular Carcinoma: Report from a Low Volume Centre in a Developing Country

Muhammad Rizwan Khan[1], Saleema Begum[2] and Muhammad Tayyab ul Hasan Siddiqui[1]

[1]*Department of Surgery, The Aga Khan University Hospital, Karachi, Pakistan*
[2]*Department of Surgery, Shaukat Khanum Memorial Cancer Hospital, Lahore, Pakistan*

ABSTRACT

Objective: To review the surgical and oncological outcomes of patients who underwent hepatic resection for hepatocellular carcinoma (HCC).

Study Design: Cohort study.

Place and Duration of Study: Department of Surgery of the Aga Khan University Hospital Karachi, from 2008 to 2019.

Methodology: Consecutive patients who underwent hepatic resection for HCC at the Hospital were included. The data were collected and analysed on aspects including demographics, liver function status, tumour characteristics, perioperative management, and surgical and oncological outcomes. Survival analyses were performed using the Kaplan-Meier method, and log-rank test was applied to determine the influence of variables on overall and disease-free survival.

Results: A total of 59 patients underwent hepatic resection for HCC during the study period including 38(64%) males. The majority of the patients had a single lesion (88%), unilobar disease (95%), underlying cirrhosis (75%) and BCLC stage B (73%). Major hepatic resection was performed in 27(46%) patients. The mean duration of surgery was 288±101 minutes and the mean estimated blood loss was 986±637 mls. Postoperative complications developed in 22(37%) patients including surgical complications in 11(19%), liver decompensation in 4(7%) and systemic complications in 9(15%) patients. The overall 30-day mortality was 7%. With a mean follow-up of 2.8 years, disease recurrence was documented in 25(42%) patients and the median overall survival was 45 months.

Conclusion: Hepatic resection for HCC is an effective treatment option in this setup. Despite low volumes, surgical and oncological outcomes of hepatic resection for HCC were comparable to the international standards.

Key Words: *Hepatocellular carcinoma, Liver resection, Cirrhosis.*

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common cancer and the fourth leading cause of cancer-related death worldwide.[1] The incidence of HCC is on rise due to the increasing prevalence of chronic hepatitis C virus (HCV) infection.[2] Pakistan is ranked second in HCV burdened countries in the world.[3] Published data suggest that HCV is the underlying risk factor for the development of HCC in 87% patients in Pakistan.[4]

Correspondence to: Dr. Muhammad Rizwan Khan, Department of Surgery, The Aga Khan University Hospital, Karachi, Pakistan
E-mail: doctormrkhan@yahoo.com
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A number of treatment options are available for treatment of hepatocellular carcinoma ranging from transarterial embolisation with chemo-radiotherapy, percutaneous thermoablation, surgical resection, and liver transplantation to various means of palliation. Unfortunately, the majority of patients from this part of the world have advanced disease at the time of diagnosis and are candidates for palliative therapies only.[5]

In view of the absence of effective chemotherapy and the insensitivity of HCC to radiotherapy, complete tumour resection in the form of resection or transplant represents the only opportunity for a long-term cure.[6] But these options have limited application due to various factors related to the stage of the disease at presentation, physiological status of the liver, technical resources and infrastructure for perioperative care.

Despite being a norm in the developed world, the underlying cirrhosis and limited infrastructure make hepatic resection a major challenge in the developing world. Moreover, the centres offering hepatobiliary services are only a handful, resulting in limited published data on the surgical and oncological outcomes

of HCC from this part of the world. This study was conducted with the primary objective to review the surgical and oncological outcomes of patients who underwent hepatic resection for hepatocellular carcinoma by a single hepatobiliary surgeon.

METHODOLOGY

Consecutive patients who underwent hepatic resection for HCC at the Aga Khan University Hospital from 2008 to 2019 were included in the study. Data were retrieved through the International Classification of Disease (ICD)-9 coding system and collected on a structured questionnaire including information on demographics, liver function status, tumour characteristics, perioperative management, and surgical and oncological outcomes. Ethical approval was obtained from the Institutional Ethical Review Committee for the study (ERC # 2020-5442-14042).

A total of 59 patients underwent liver resection for hepatocellular carcinoma during the study period. All patients who underwent liver resection for other indications during this period were excluded. Triphasic computerised tomography scan or multiparametric magnetic resonance imaging was performed to assess the resectability of tumour. Surgical intervention was offered to the patients with preserved liver functions preferably Child-Pugh A, platelet count of more than 100,000/mm^3, and after discussion in a multidisciplinary tumour board meeting. Additional assessment of liver function and portal hypertension was made by using Fibroscan, liver biopsy, endoscopy, and measurement of hepatic venous pressure gradient, where indicated. Although, volumetric assessment of remnant liver was not used routinely, a gross future liver remnant volume of at least 40% and 30% were aimed for patients with and without cirrhosis, respectively.[7]

Patients undergoing hepatic resection received general anaesthesia with invasive monitoring. After liver mobilisation, intraoperative ultrasound was performed to assess the extent of tumour, and its relation to vascular structures and to look for any additional lesions in the liver. An inflow and outflow control was achieved for the liver segment and lobes to be resected. An intermittent Pringle manoeuver was employed. Parenchymal transection was carried out using Harmonic scalpel, diathermy and Cavitron Ultrasonic Surgical Aspirator (CUSA). A low CVP was maintained intraoperatively and epidural analgesia or patient-controlled analgesia was used for pain control.

Statistical analysis was performed using the Statistical Package for the Social Science (SPSS) version 22.0 for windows. Mean and standard deviation were used to assess the quantitative data and frequencies with percentages for qualitative data. Non-parametric variables were expressed as median with range. Survival analyses were performed using the Kaplan-Meier method, and log-rank test was applied to determine the influence of variables on overall and disease-free survival. A p-value of <0.05 was considered significant at 95% confidence interval.

Table I: Demographics and perioperative details of patients.

Demographics	Number (percentages)
Gender	
Male	38 (64%)
Female	21 (36%)
Age in years (mean ± standard deviation)	57±13
Comorbid conditions	
Yes	35 (59%)
No	24 (41%)
ASA* class	
I and II	28 (48%)
III and above	31 (52%)
Cirrhosis	
Yes	44 (75%)
No	15 (25%)
BCLC* stage	
0	03 (05%)
A	13 (22%)
B	43 (73%)
Number of lesions	
Single	52 (88%)
More than one	07 (12%)
Types of hepatic resection	
Right hepatectomy	21 (35.6%)
Left hepatectomy	05 (8.5%)
Central hepatectomy	01 (1.7%)
Left lateral segmentectomy	07 (11.8%)
Bisegmentectomy	06 (10.1%)
Segmentectomy / non-anatomical resection	19 (32.2%)
Median duration of surgery in minutes (range)	300 (85-570)
Median estimated blood loss in ml (range)	900 (100-3500)
Pack cell transfusion	
Yes	22 (37%)
No	37 (63%)
Tumour size (mean ± SD)	6.6 ± 4.13
Maximum bilirubin level postresection (mg/dl, mean ± SD)	2.78 ± 6.3
Median days for normalisation of bilirubin (range)	1 (0-150)
Median length of hospital stay in days (range)	9 (4-40)

**SD: Standard deviation; *ASA Score: American society of anesthesiology score; *BCLC: Barcelona clinic liver cancer stage.*

RESULTS

More than 150 total hepatic resections were performed at the hospital during the study period for various indications, including 59 liver resections performed for hepatocellular carcinoma. Table I summarises the demographic and perioperative details of patients included in the current study. Table II depicts the surgical and oncological outcomes of patients. Wound infections were managed with the opening of the wound and daily dressings, while intraabdominal collections secondary to bile leak were managed with image-guided drain placement and antibiotics. No endoscopic intervention was required for the management of bile leak in this group. Ascites wereresponsive to diuretics and salt-free albumin in all patients, while pneumonia was managed with antibiotics and drainage of effusion in selected patients. The cause of 30-day mortality included hepatic decompensation in three patients and acute myocardial infarction in one patient.

Table II: Surgical and Oncological outcomes of study population.

Surgical outcomes	Numbers (percentage)
Overall Morbidity	22 (37%)
Wound infection	6 (10%)
Intraabdominal collection	5 (8%)
Ascites	4 (7%)
Encephalopathy	3 (5%)
Pulmonary infections	8 (14%)
Myocardial infarction	1 (1.7%)
Total 30-day mortality	4 (7%)
Liver decompensation	3
Myocardial infarction	1
Total 90-day mortality	7 (12%)
Oncological outcomes	
Resection margin	
Negative (R0)	58 (98.3%)
Positive (R1)	01 (1.7%)
Microscopic resection margin (mean ± SD, cm)	1.02 ± 0.13
Microvascular invasion	
Present	10 (17%)
Absent	49 (83%)
Alpha fetoprotein	
Normal	19 (32%)
Elevated	23 (39%)
Not known (missing data)	17 (29%)
Type of HCC on histopathology	
Well differentiated	15 (25.4%)
Moderately differentiated	32 (54.2%)
Poorly differentiated	12 (20.4%)
Overall recurrence	25 (42%)
Early recurrence (within two years)	15 (60%)
Late recurrence (after two years)	10 (40%)
Mean overall survival	45 months
Mean disease-free survival	9 months

Table III: Log-rank test showing the influence of variables on overall and disease-free survival.

	Disease free survival	Overall survival
Microvascular invasion	0.001	0.607
Cirrhosis	0.088	0.999
BCLC stage	0.038	0.390
Size of the tumour	0.175	0.001
Alpha fetoprotein	0.374	0.581
Tumour differentiation	0.671	0.573

A bivariate analysis was performed to identify factors associated with postoperative morbidity, 30 and 90-day mortality. A correlation was sought for variables including gender, co-morbid conditions, underlying cirrhosis of the liver, number of lesions, and BCLC stage at presentation but no significant associations could be identified. Similarly, the magnitude of hepatic resection, duration of surgery, and blood loss also failed to show any statistical correlation with immediate post-operative outcomes. Mean overall survival was 45 months and disease-free survival was 9 months. With a mean follow-up of 2.8 years, 25 (42%) patients developed disease recurrence. For recurrent disease, repeat surgical resection was performed in 2 (3%) patients, trans-arterial chemoembolisation (TACE) in 8 (14%) patients and percutaneous radiofrequency ablation (RFA) in 5 (9%) patients. The other 10 patients were lost to follow-up.

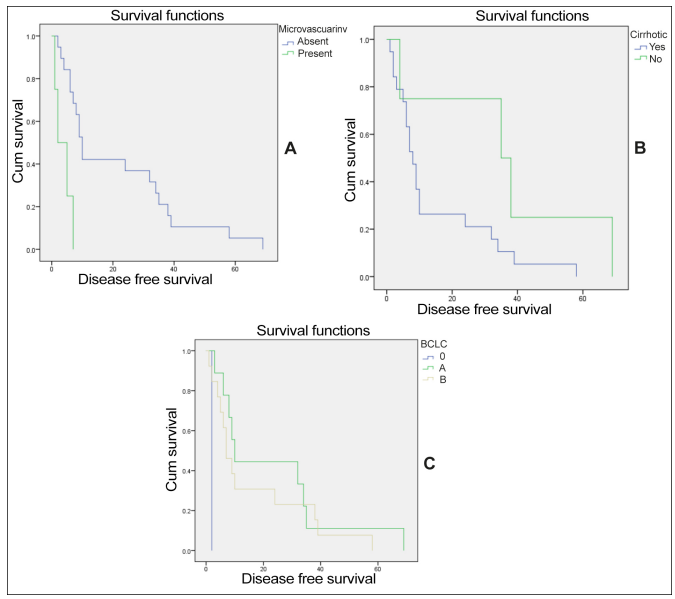

Figure 1: Prognostic significance assessed using Kaplan-Meier survival and log-rank tests. Kaplan-Meier survival curves showing significantly prolonged disease-free survival in patients with (A) absence of microvascular invasion (p= 0.001, log-rank test), (B) absence of cirrhosis (p=0.008, log-rank test) and (C) BCLC stage A (p=0.038, log-rank test).

Table III and Figure 1 (A, B, and C) depict the influence of variables on oncological outcomes including overall and disease-free survival. Disease-free survival was significantly associated with absence of microvascular invasion (p=0.001), absence of cirrhosis (p=0.008), and BCLC stage (p=0.038) on Kaplan-Meier survival curves and log-rank tests. However, tumour size had no significant association with disease-free survival but was significantly associated with overall survival (p=0.009).

DISCUSSION

Liver resection is a curative therapeutic modality for early HCCs (BCLC stage A/B) with preserved liver functions.[8] Asian countries including Pakistan have a high prevalence of HCC secondary to hepatitis virus infections.[9] The study centre is one of the largest tertiary care hospitals of the country and the authors receive a referral from centres across the country; despite that it remains a low-volume centre for liver resection. Out of approximately 150 liver resections performed for various indications over the years, 59 patients underwent resection for HCC. Despite limitations, the surgical outcomes of our patients who underwent hepatic resection for HCC seem comparable to the international literature.

Outcomes after surgery have association with various factors in liver resection for HCC, including hospital and surgeon volumes of cases per year. High-volume centres are usually considered those performing more than 25 liver resections per year. Chang *et al*. in their study including 13,159 patients from low and high--volume centres demonstrated a better short and long term survival after hepatic resections by high volume surgeons at high volume centres compared to low-volume surgeons in low-volume centres.[10] It emphasised on need for centralisation to a few surgeons and hospitals to improve outcomes. The reported

complication rate varies in the literature due to different criteria but an overall complication rate of 24% to 70% is reported in literature.[11] The overall morbidity in this series was 37% and was comparable to both low and high-volume centres reported in multicentre studies.[12,13] Presence of comorbid conditions and ASA scores have also been identified as a risk factor for overall morbidity after liver resection for HCC.[14] More than half of our patients had at least one comorbid condition like diabetes mellitus, hypertension, ischemic heart disease or chronic obstructive pulmonary disease and had ASA score more than three; but univariate analysis failed to show any association with morbidity or mortality.

It is interesting to note that 43 patients (73%) in this study were classified to have BCLC stage B. The reason for inclusion in BCLC B included the number of the lesion (more than one) in 7 patients and size of the lesion (more than 5 cm) in the remaining 35 patients. The size of the largest lesion in this study ranged from 2.3 cm to 22 cm with a mean size of 6.6 cm. All the patients who underwent surgical resection were in Child-Pugh Class A and within Milan's Criteria. The recommendations made in BCLC guidelines suggest options other than resection for such lesions, but several Asian and European studies have come to the opposite conclusions.[15,16] The major limitation in the region is the availability of liver transplantation as a first-line treatment option for intermediate stage HCC falling in the category of BCLC B. Another interesting area of debate is the huge size tumours falling beyond the traditional transplant criteria but patients have preserved liver function. There is convincing data available to support the fact that hepatic resection may be considered as the first-line treatment option in this specific group of patients because of its associated survival advantage.[17] The present results support the suggestion that comparable outcomes can be achieved in selected patients with intermediate-stage HCC who underwent hepatic resection as the first-line treatment option.

Perioperative blood loss not only adversely affects the morbidity after hepatic resection including the risk of post hepatectomy liver failure, but it also has been shown that massive blood loss and blood transfusions increase the risk of tumour recurrence in HCC patients.[18,19]Intraoperative blood loss in this series was relatively high compared to high-volume centres, but still comparable to low-volume cantres performing hepatic resections. Cawich *et al.* and Meir *et al.* reported blood loss of 1405 ml and 1090 ml respectively in their series of patients at low-volume centres.[12,20] Factors associated with increased blood loss in our setup are the lack of sophisticated devices for bloodless surgery and the presence of cirrhosis in majority of the authors' patients. A study by Lee *et al.* demonstrated that blood loss of more than 800 ml was an independent risk for major surgical complications after hepatectomy for HCC.[11] Daniel *et al.* reported operative time more than 180 minutes as an independent factor for major postoperative complications in an analysis of 156 patient undergoing hepatic resection,[21] but no such association was found in this study. The operative time in this study was comparable with low-volume contemporary series but higher than high-volume centres.[21]One potential reason for the longer duration of surgery is the ongoing training of residents and fellows in major surgical procedures, as the institution is a teaching hospital with general surgery residency and fellowship programs to train future surgeons.

Despite recent advancements in liver surgery techniques, novel devices for bloodless surgery and evolving postoperative care, there is substantial risk associated with the procedure. Recent studies reported perioperative mortality rates of 2.6% to 8.4% for HCC patients.[22] The definition of perioperative mortality in most studies was hospital mortality or death within 30 days after the operation. The 30-day mortality was 7% which is comparable to other studies for patients with HCC.

The median recurrence-free survival was lower than other studies due to the higher number of patients in BCLC stage B in this series.[23] Recurrence was seen in 42% patients and more than half of our patients had early recurrence within two years of resection. Patients with microvascular invasion and BCLC stage B had significantly lower disease-free survival than their counterparts and these findings have already been seen in other studies.[24] Locoregional therapies and resections were performed in patients after recurrence which can prolong the overall survival.

CONCLUSION

Despite low volumes and limited infrastructure, surgical and oncological outcomes of hepatic resection for HCC at the centre are comparable to the international standards. Factors associated with poor oncological outcomes include the presence of cirrhosis, microvascular invasion and BCLC stage B.

ETHICAL APPROVAL:
An exemption was sought from the Institutional Ethics Committee for the study (ERC # 2020-5442-14042).

COMPETING INTEREST:
The authors declared no competing interest.

PATIENTS' CONSENT:
All patient give a consent to participate in the research activities.

AUTHORS' CONTRIBUTION:
MRK: Concept and design, analysis and interpretation of data, and critical revision of the article.
SB: Concept and design, analysis and interpretation of data, and drafting of article.
MTS: Acquisition, analysis and interpretation of data.
All the authors have approved the final version of the manuscript to be published.

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