Original Research Article

Feasibility and safety of liver resection for huge hepatocellular carcinoma in cirrhotics

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ABSTRACT

Background: With the current high incidence of hepatocellular carcinoma (HCC), more patients even with large and huge HCC are considered for liver resection.

Methods: Medical records of consecutive adult cirrhotic patients who underwent partial hepatectomy for huge HCC (≥10 cm, huge HCC group) versus small HCC (<5 cm, small HCC group) at Sohag university hospital (January 2016 to December 2020) were analyzed. Both groups were compared regarding postoperative morbidity and risk of mortality following post hepatectomy liver failure (PHLF) as defined by the 50-50 criteria (50% mortality occurs among patients who developed increased plasma bilirubin >50 μml/l and reduced prothrombin activity <50% on postoperative day 5 (POD-5).

Results: Thirty two patients were enrolled (16 per group), with median age of 56 (range 38-81) years, 22 were males. In correlation with resection of more liver segments in the huge HCC group, post hepatectomy alteration of liver functions (bilirubin rise and reduction of albumin and prothrombin concentration) was significantly pronounced among patients who had resection for huge compared with small HCC (p<0.05). Huge HCC group exhibited significantly worse postoperative complication score (p< 0.05) and needed significantly prologed periods of hospital stay (p<0.05). Concurrent persistence of PHLF and thrombocytopenia until POD-5 occurred in 3 patients (2 with huge HCC and 1 with small HCC). Among those patients, only one from huge HCC group died (mortality 6%) postoperatively.

Conclusions: Liver resection provides safe and effective treatment strategy for carefully selected cirrhotic patients with huge HCC.

Keywords: Huge HCC, Liver resection, Cirrhosis

INTRODUCTION

HCC is a very common cancer, ranking sixth among the most frequent malignant tumors worldwide and the third cause of cancer-related mortality.[1] In Egypt, given the high incidence of chronic viral hepatitis, particularly infection with hepatitis C virus (HCV) and subsequent rise of the rates of liver cirrhosis, HCC is increasingly diagnosed to the extent that it represents the second most commonly diagnosed cancer among Egyptian men.[2,3]

The liver responds to partial resection by regenerating its parenchyma.[4] Restitution of liver volume requires hyperplasia of various types of its parenchymal cells and cellular hypertrophy afterward.[5] This unique capacity of restoration of the liver volume after partial hepatectomy resulted in notable progress in hepatic resectional surgery in the non-cirrhotic liver.[6,7]

However, the recovery of liver functions after partial hepatectomy depends not only on the volume but also on the quality of the remaining liver parenchyma.[8] It is well

established that liver cirrhosis is implicated in the increased susceptibility of the liver to resectional hepatic surgery and the deleterious consequences after liver resection in cirrhotic poorly selected patients.[9]

In the setting of HCC in cirrhotic patients, liver transplantation (LTx) is the definitive treatment for small (<5 cm) HCC, while liver resection is reserved for patients with adequate functional reserve who cannot afford LTx.[10,11] In contrast, for patients who suffer from larger HCC, particularly those who have HCC with huge size (≥10 cm), liver resection remains the only treatment that provides hope for cure since LTx cannot be recommended.[12,13] However, liver resection must be considered with much caution in these patients due to the increased risks of postoperative fatal complications, particularly PHLF.[14]

In this study, we studied the safety and outcome of liver resection for large HCC in careful selected cirrhotic patients.

METHODS

Consecutive adult patients with cirrhosis-related HCC who underwent elective liver resection at Sohag university hospital (January 2016 to December 2020) were identified, their prospectively collected medical data were extracted and analyzed. Patients with huge (≥10 cm) HCC (huge HCC group) were compared with a control group of small HCC <5 cm (small HCC group) for which LTx was not affordable. Exclusion criteria were age <18 years, uncorrected coagulopathy, emergency (such as ruptured HCC) resections, trauma, combined resection of the liver and other viscera, preoperative chemotherapy or radiotherapy, transarterial chemoembolization and any form of pre and/or postoperative ablative procedure or percutaneous ethanol injection. Ethical approval of the study was obtained from the Sohag faculty of medicine committee on medical research ethics.

Clinical assessment of eligibility for liver resection

Standard clinical evaluation entailed full clinical assessment including abdominal imaging with ultrasonography. Routine laboratory tests comprised hepatitis B and C viral serology, blood counts, plasma levels of bilirubin, proteins, transaminases, kidney functions and blood glucose level. Coagulation profile was initially assessed by prothrombin time and concentration. Determination of relevant tumor markers included alfa-fetoprotein (α-FP) and carbohydrate antigen 19:9 (CA 19:9). Portal hypertension was evaluated with endoscopic diagnosis of esophageal varices and/or splenomegaly (diameter >12 cm) with thrombocytopenia. Preoperative imaging entailed triphasic abdominal computed tomography (CT) and contrast-enhanced chest CT (CECT). A decision of liver resection was offered to patients with resectable tumor provided that an adequate future liver remnant (FLR) was anticipated.

Operative procedure

Operative interventions were performed consistently in all patients by the same surgical team. The abdominal cavity was entered via bilateral subcostal incision. Initially, the abdominal viscera and peritoneum were explored to rule out presence of metastasis and/or malignant ascites. Liver transection was performed under non-selective intermittent inflow occlusion using a vessel loop or small plastic drain as tourniquet to encircle the hepatoduodenal ligament under a low central venous pressure (≤5 mm H2O) and sufficient urine output. Glisson's capsule was incised by diathermy, liver parenchyma was crushed using small artery clamp. Large intrahepatic vessels and bile ducts (3 mm) were ligated or clipped. Bleeding smaller vessels were controlled by bipolar cautery.

Assessment of postoperative complication score

As we previously described, severity of postoperative complications was assessed by Clavien-Dindo system, with conclusion of postoperative complication score (ranging from one to seven) by assigning one point to each of the seven complication grades I, II, IIIa, IIIb, IVa, IVb and V in ascending order.[15,16]

Validation of fifty-fifty (50-50) criteria as postoperative mortality predictor

According to the 50-50 criteria, fifty per cent of patients who exhibit persistent PHLF until POD-5 will die postoperatively.[17,18] Parameters included in the 50-50 criteria are high plasma bilirubin levels of >50 μml/l and reduced prothrombin activity (prothrombin concentration <50%). On this basis, we investigated the correlation between postoperative mortality and PHLF was investigated. Statistical analysis was carried out by GraphPad Prism 6.0 software. Differences between groups were considered significant with p value <0.05.

RESULTS

According to the study protocol, thirty two patients qualified for enrollment (16 per group). Considering all patients, median age was 56 (range 38-81) years. Twenty two patients were males. All patients had ASA (American soceity of anesthesiologists) score I and Child-Pugh score of 5-6 points (class A) (Table 1). Five patients were diabetics (3 in huge HCC and 2 in large HCC group). Fourteen patients, all belonged to the huge HCC group, underwent major liver resection (≥3 segments) (Figure 1). All patients had HCC in relation to cirrhosis following chronic HCV infection.

Assessment of liver functions after resection of huge versus small HCC

We used postoperative plasma levels of albumin in addition to prothrombin concentration as reliable

indicators of recovery of synthetic functions of the remnant liver. In both groups, we observed that despite both markers were diminished compared with preoperative levels. However, on POD-3, albumin and prothrombin levels were significantly lower (p<0.05) among huge HCC compared with small HCC patients.

Total bilirubin levels were significantly elevated in both groups compared with the preoperative values. In the same line, on POD-3, bilirubin levels were significantly high (p<0.05) in the huge compared with small HCC group (Table 2).

Influence of huge compared with small HCC resection on postoperative morbidity and hospital stay

Patients with huge HCC exhibited significantly higher score of overall complications (p<0.05) following HCC resection compared with the small HCC control group. Likewise, huge HCC resection group showed significantly increased overall complications and prolonged length of hospital stay (p<0.05) in comparison with small HCC group (Table 3).
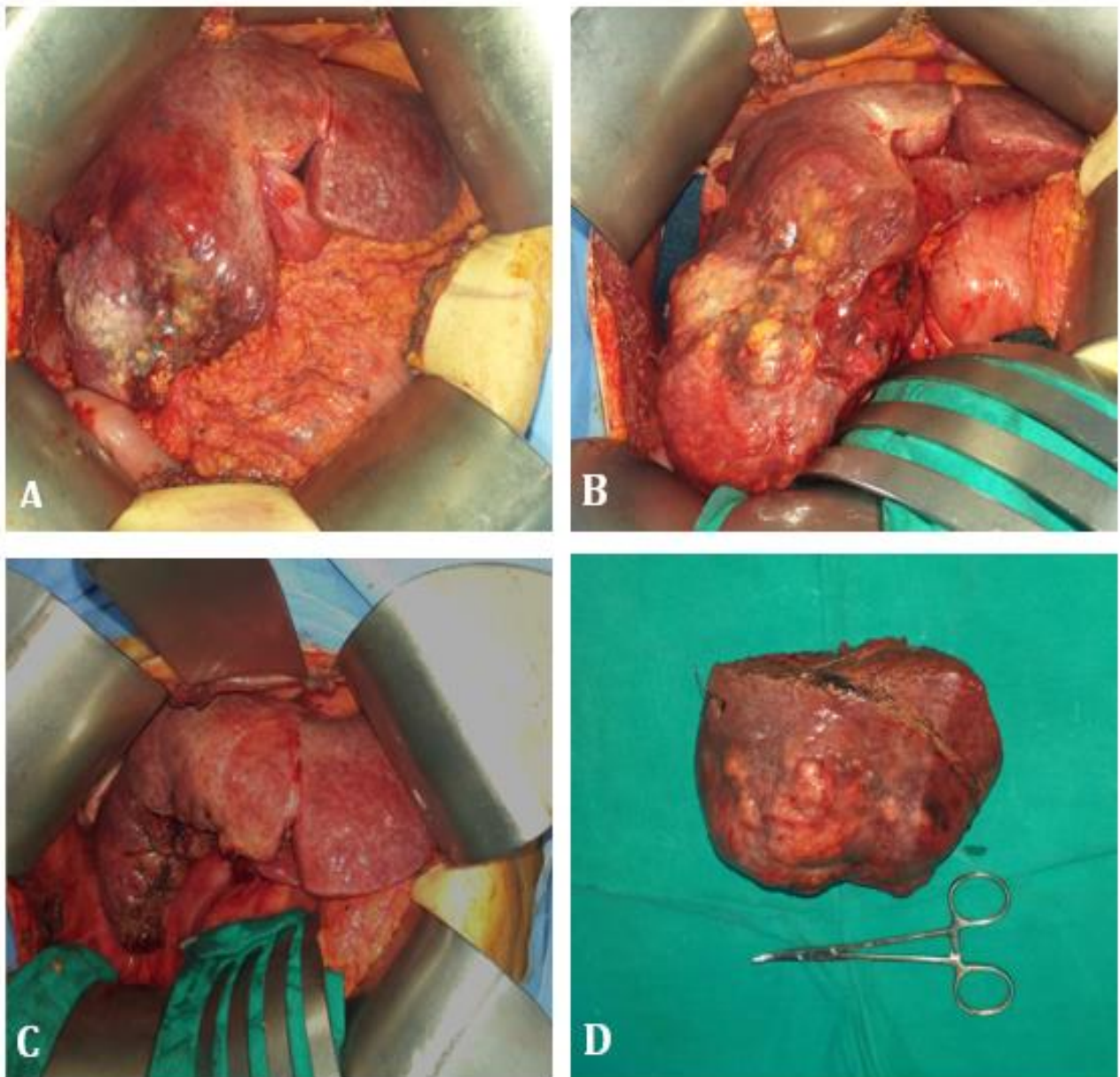
Figure 1: Non-anatomic liver resection for huge HCC occupying segments V, VI and extending to segments VIb, and VII (A) initial exploration; (B) right lobe, including huge HCC was mobilized, cholecystectomy was carried out; (C) remnant liver after HCC resection; (D) resected specimen with macroscopically adequate free resection margin.
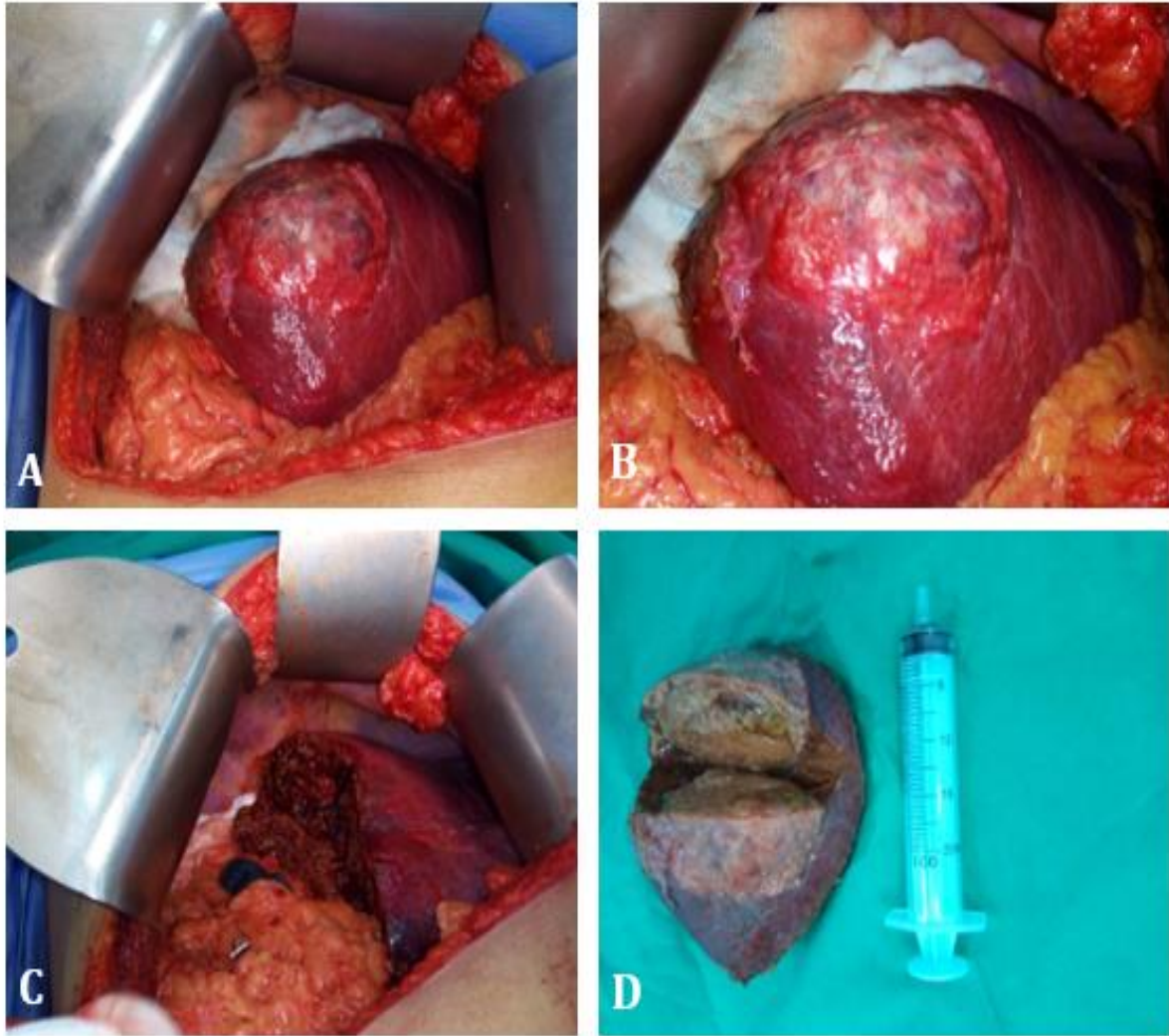
Figure 2: Right hemihepatectomy for huge HCC involving segments V, VI, VII and VIII of the right lobe of cirrhotic liver; (A) huge HCC exposed after mobilization of the right liver lobe; (B) same as A, closer view; (C) remnant left liver lobe after right hemihepatectomy including huge HCC; (D) resected huge HCC with macroscopically adequate free resection margin.

Table 1: Demographic, clinical and preoperative laboratory data.

Data	Huge HCC	Small	P value
Demographic and clinical data*			
Age (median)	54	52	ns
Child-Pugh points	5	5	ns
HCC diameter	12	3	ns
Laboratory data**			
Bilirubin (mg/dl)	0.7 (0.4-1.1)	0.75 (0.4-1)	ns
Albumin (g/dl)	4 (3.5-4.0)	4.4 (3.9-5.1)	ns
PC (%)	80 (72-98)	90 (82-100)	ns
α-FP (ng/dl)	58 (20-410)	26 (6-160)	<0.05§

*median; **median (range); §significant difference; ns, non significant difference; PC, prothrombin concentration.

Table 2: Operative data.

Operative data	Huge HCC	Small HCC	P value
Duration of surgery (minute)§	290 (180-430)	140 (120-190)	<0.05*
Number of resected segments§	3§	2	ns
Duration of ischemia	25	10	<0.05*
Central venous pressure cm/H_2O	4	4	ns
Blood loss (ml)§	500 (300-1250)	250 (100-600)	<0.05*
Red blood cell transfusion (unit)§	2 (0-6)	1 (0-2)	<0.05*
Plasma transfusion (units)§	3 (0-8)	0 (0-1)	<0.05*

*significant difference; §median (range); ns, non significant difference.

Table 3: Postoperative data.

Postoperative data	Large HCC	Small	P-value
Markers of liver dysfunction at POD-3			
Albumin (g/dl)§	3.0 (2.5-3.9)	3.8 (3.1-4.8)	<0.05*
PC (%)§	72 (46-88)	90 (75-96)	<0.05*
Bilirubin (mg/dl)§	1 (1.2-4)	0.9 (0.6-1.5)	<0.05*
Highest complication score§	7 (2-7)	2 (0-3)	<0.05*
Length of hospital stay§	14 (8-42)	9 (4-17)	<0.05*
Postoperative death**	1/16	0/16	
Survivors at 3 years**,§§ (%)	75	100	

*significant difference, §median (range), **numbers too small for statistical analysis, §§median follow up; **PC, prothrrombin concentration, POD, postoperative day.

Correlation between postoperative mortality after huge versus small HCC resection and the 50-50 criteria of PHLF

Persistent PHLF until POD-5 occurred in 3 patients (2 in the huge HCC and 1 in the small HCC group). Further analysis showed that among all patients who were enrolled in the study, these 3 patients showed simultaneous thrombocytopenia <100,000/µl starting on the first POD. Among those patients, postoperative in-hospital mortality occurred only in one patient from huge HCC group. Notably, this patient was the only one in whom platelet count failed to increase above 100,000/µl until death.

DISCUSSION

This study highlighted the reasonable safety and effectiveness of liver resection in cirrhotic patients with huge HCC. Despite the increased postoperative complications compared with the small HCC control group, all patients who had liver resection for huge HCC recovered their normal liver functions except one patient whose death was related to persistent PHLF and thrombocytopenia.

LTx provide the best overall and recurrence-free survival for patients with early HCC.[19-21] However, in the context of huge HCC in the cirrhotic liver, treatment options include liver resection, TACE, TARE and targeted therapy.[22-25]

The current literature showed that in carefully selected patients with huge HCC would benefit from liver resection as upfront treatment approach.[10,26-28] Likewise, several comparative studies documented the superiority of liver resection for huge HCC compared with TACE regarding overall and recurrence-free survival.[1,29,30]

Liver cirrhosis, the most common risk factor for development of HCC, was known to impair liver regeneration.[31] Thrombocytopenia, which commonly developed in cirrhotic patients, was associated with failure of liver regeneration after partial hepatectomy.[32] Coexistence of cirrhosis and thrombocytopenia carried high risk for development of PHLF.[33,15] In accordance with these data, patients in the huge HCC group exhibited remarkable deterioration of the markers of synthetic and excretory functions (albumin, prothrombin concentration and bilirubin) of the liver compared with those who had liver resection for small HCC.

We had objectively assessed the severity of postoperative complications using Clavien-Dindo system. To simplify the ranking process, complication score in each patient was concluded via assigning one points to each complication level in ascending order.[16] We found that cirrhotic patients who had major resections (all in the huge HCC group) developed more serious complications and required longer periods of hospital stay. These findings were in agreement with previous studies which showed increased postoperative complications following

huge HCC ≥10 cm resection in cirrhotics compared with those with smaller HCCs.[34,35]

Persistence of elevated bilirubin level >50 μml/l with concomitant reduction of prothrombin concentration <50% in POD-5 can strongly predict PHLF and mortality rate of 50% (the 50-50 criteria).[17,18] In this study, conforming with the previous reports, PHLF developed exclusively in 2 patients in huge HCC group. One patient was able to recover normal liver functions after prolonged treatment in the intensive care unit while the other patient died.

Given the essential role of blood platelets in post hepatectomy liver regeneration, we compared both study groups regarding postoperative platelet count on POD-1.[33,36] Platelet counts were significantly lower in the huge HCC compared with small HCC group. This could be implicated in the increased postoperative complication score in the huge HCC group. Furthermore, we observed persistence of thrombocytopenia <100,000/μl until POD-5 only in 2 patients in the huge HCC group. While one patient could regain normal platelet count, the other patient died.

It should be emphasized that limitations of this study included the relatively small number of patients and the potential of selection bias, which was an inherent defect in the retrospective studies.

CONCLUSION

In conclusion, we demonstrated that in the context of huge HCC in the cirrhotic liver, carefully selected patients would benefit from liver resection with reasonable safety.

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