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Short-term outcome of hepatocellular carcinoma resection in elderly cirrhotic patients

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Abstract: Background: Advanced age and liver cirrhosis predispose to suboptimal regenerative response after partial liver resection. Clinical outcome of hepatocellular carcinoma (HCC) resection in elderly cirrhotics was not adequately addressed in Upper Egypt onco-surgery programs. **Methods:** Medical records of adult patients who underwent elective liver resection for HCC at Sohag University Hospital (February 2014 – August 2017) were retrospectively analyzed. Elderly patients (≥ 65 years) were compared regarding postoperative hepatic failure, morbidity and mortality with non-elderly matched control group (< 65 years). **Results:** Twenty-two patients were enrolled, 11 per group. All patients had HCC on top of compensated, hepatitis C-related liver cirrhosis. The elderly group showed significantly worse grades of postoperative complications ($p< 0.05$), prolonged hospital stays ($p< 0.05$) and significantly deranged markers of posthepatectomy liver failure, including increased levels of bilirubin and reduced prothrombin concentration ($p< 0.05$). Postoperative mortality occurred only in the elderly group (2 postoperative deaths following major hepatectomy). Mortality was associated with postoperative day-1 thrombocytopenia $<100 \times 10^9$/L. **Conclusion:** Elderly cirrhotic patients are more vulnerable to worse outcome after major liver resections. To ensure satisfactory results of HCC resection in this category of patients, strict selection criteria should be considered.

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1. Introduction

Hepatocellular carcinoma (HCC) is among the most frequently diagnosed cancers worldwide, ranking fifth in men.[1] Older population is at increased risk of cancer, with more than 60% of newly diagnosed cancers and about 70% of cancer-related deaths occurring among patients aged 65 years or more.[2]

Restitution of liver volume after partial hepatectomy involves hyperplasia and hypertrophy of hepatic parenchymal cells.[3] However, optimal functional recovery of the liver depends not only on the volume but also the quality of the future liver remnant.[4] Among several causes of impaired quality of hepatic parenchyma, advanced age and liver cirrhosis are particularly associated with attenuation of liver regeneration. Thus, there is increased likelihood of complications after HCC resection in elderly cirrhotic patients.[5,6] Eighty to ninety percent of HCC patients show evidence of liver cirrhosis due to chronic infections with hepatitis C virus (HCV) and B viruses.[7,8]

Cirrhotic patients with HCC who are eligible for liver transplantation have the best opportunity for long overall and recurrence-free survival. [9,10] In highly selected liver graft recipients with advanced age, few studies have shown comparable short and long-term outcomes compared with younger patients.[11,12] Nonetheless, this policy has not gained wide popularity owing to the shortage of donor pool and increased co-morbid conditions with advanced age.[2] Therefore, liver resection remains essentially the best treatment strategy with potential cure for HCC in elderly cirrhotic patients in whom other curative treatment options are not feasible.

In spite of the high rates of cirrhosis-related HCC in Egypt[13], the influence of advanced age and coexisting cirrhosis in HCC patients on posthepatectomy liver failure (PHLF), morbidity and mortality has not been adequately investigated. Therefore, this study aims at addressing the short-term outcome of liver resection in elderly cirrhotic patients with HCC, for the first time, in Egypt's Southern region (Upper Egypt).

2. Patients and Methods

Medical records of adult patients (age > 18-year-old) with compensated liver cirrhosis who underwent upfront elective liver resection for HCC (> 3cm) at Sohag University Hospital (February 2014 - August 2017) were analyzed. A group of elderly patients (≥ 65 years, the elderly group) was compared with

younger control group (< 65 years, the non-elderly group) with matching gender, Child class, technique of liver transection, cycles of intermittent inflow occlusion of the portal triad (intermittent Pringle's maneuver), and extent of liver resection (number of resected liver segments). Exclusion criteria were age <18 years, preoperative platelet count <100 $\times 10^9$/L, emergency resection, combined visceral resections and any form of preoperative therapy, including ablative interventions and/or chemo-embolization.

Preoperative evaluation:

Standard clinical assessment including abdominal ultrasonography and routine laboratory tests were carried out. Every patient was assigned Child-Pugh score. Alfa-fetoprotein (α-FP) levels were measured in all patients while carbohydrate antigen 19:9 and/or carcinoembryonic antigen were selectively tested. Diagnosis of portal hypertension was established with endoscopic detection of esophageal varices and/or remarkable splenomegaly with platelet count <100 $\times 10^9$/μL. Preoperative imaging comprised triphasic computed tomography (CT) scanning of the liver and contrast enhanced CT of the chest. Liver resection was carried out for technically resectable tumor (s) on condition that an adequate future liver remnant is anticipated. Patients within Milan criteria for liver transplantation were offered the option of surgical resection only if they reject or cannot afford liver transplantation. Resected specimens were histologically evaluated for the number, size and grade of tumor differentiation, vascular invasion, and resection margins.

Anesthesia and surgical procedures:

Surgical procedures were consistently conducted by the same team of surgeons. Extensive mobilization of the liver and unnecessary dissection of ligaments were avoided whenever possible to reduce bleeding and to prevent exacerbation of portal hypertension. Parenchyma transection was executed under intermittent inflow occlusion using a vessel loop as tourniquet to encircle the hepatoduodenal ligament. While transection is being performed, low central venous pressure (0–5 mm H_2O) was planned with preservation of sufficient urine output.

Postoperative assessment:

Patients were monitored daily for platelet count since postoperative day-1 (POD-1) thrombocytopenia of <100 $\times 10^9$/L correlates with incidence of PHLF and mortality after partial hepatectomy.[14] Furthermore, bilirubin levels and prothrombin activity were regularly checked, particularly during the initial 5 days postoperatively. Persistent derangement of both parameters until POD-5 was shown as strong predictor of PHLF and mortality after liver resection.[15] Postoperative complications entailed hemorrhage, bile leak, abdominal abscess, PHLF and wound infection. The magnitude of postoperative complications was scored according to Clavien-Dindo system.[16] As previously reported, each patient was assigned an overall score of postoperative complications (ranging from one to seven) via allotting one point to each of grades I, II, IIIa, IIIb, IVa, IVb and V in ascending order.[17] Postoperative death during the initial 30 days following liver resection, even after discharge from the hospital, was considered as hepatectomy-induced mortality. Statistical analysis was carried out by unpaired t-test using GraphPad Prism 6.0 software.

3. Results

According to the study protocol, twenty-two patients were eligible (eleven per group). Patients in the elderly group were significantly older than the non-elderly controls. Sixteen patients were males, distributed equally between both groups. All patients had Child-Pugh class A liver cirrhosis which was related to chronic HCV infection. Hypertensive and diabetic patients were adequately controlled preoperatively. A summary of preoperative data is shown in Table 1.

Operative data:

Liver transection was performed using clamp crushing technique in all patients and was assisted by vessel sealing device in 18 (9 per group) cases.

To reduce blood loss, parenchyma transection was carried out during intermittent cycles of non-selective inflow occlusion of the portal triad (Pringle's maneuver) in all patients.

Twelve patients, 6 per group, underwent major liver resection (≥ 3 segments). There was no significant difference between both groups in the duration of surgery, liver ischemic time (during the intermittent cycles of Pringle's maneuver), ventral venous pressure and urine output. However, the amount of blood loss and transfusions were significantly higher in the elderly compared with the non-elderly cirrhotic group. Operative data are summarized in Table 2.

Incidence of POD-1 thrombocytopenia:

All patients in the non-elderly control group have shown normal platelet count (>140 $\times 10^9$/L) on POD-1 and later on with no evidence of PHLF until discharge from hospital. In contrast, 4 patients (36.4%) in the elderly group exhibited POD-1 thrombocytopenia < 100 $\times 10^9$/L, among them 2 patients developed clinical and laboratory criteria of severe PHLF including persistent jaundice, ascites and abnormal levels of bilirubin and prothrombin concentration. Notably, POD-1 thrombocytopenia <100 $\times 10^9$/L developed exclusively after major resections.

Markers of posthepatectomy liver failure (PHLF):

Manifestations of PHLF included jaundice, bleeding tendency, ascites and encephalopathy. Plasma levels of bilirubin and albumin in addition to prothrombin concentration on POD-5 were considered as markers of functional recovery of the remnant liver. The values of the bilirubin and albumin were significantly reduced with significantly higher levels of total bilirubin on POD-5 in elderly compared with the non-elderly control group. Persistent rise of bilirubin level > 3 mg/dl with concomitant reduction of prothrombin concentration < 50% was observed in 3 patients who underwent major resection the elderly cirrhotic group.

Postoperative complications and length of hospital stay:

Postoperative complication scores were significantly higher among elderly cirrhotic patients compared with the non-elderly control group. Likewise, the length of hospital stay was significantly prolonged among elderly cirrohtics.

Postoperative mortality:

No mortality was recorded among non-elderly patients. However, two patients from the elderly group who underwent major resection died during the first postoperative month. Of note, both patients had POD-1 thrombocytopenia <100 $\times 10^9$/L which was associated with derangement of bilirubin levels (> 3 mg/dl) and prothrombin concentration (< 50%) on POD-5 and thereafter. A summary of postoperative data is shown in Table 3.

Table 1: Preoperative data

	Elderly (≥ 65 years)	Non-elderly (<65 years)	P-value
Clinical data			
Age, median (range)	72 (65-76)	46 (42-63)	<0.05*
Portal vein diameter (mm, US)	13 (10-15)	11 (9-14)	ns
Spleen (longest dimension in cm, US)	13 (12-16)	13 (12-17)	ns
Tumor size (cm)	6 (4-12)	4 (4-10)	ns
Body-mass index (kg/m^2)	24 (22-28)	23 (21-26)	ns
Laboratory data			
Bilirubin (mg/dl)	0.7 (0.4-1.1)	0.75 (0.4-1)	ns
Albumin (g/dl)	3.9 (3.5-5.0)	4.1 (3.8-5.1)	ns
Prothrombin concentration (%)	75 (88-106)	82 (80-110)	ns
Platelet count × 10^9/L	198 (166-340)	214 (172-405)	ns
Hemoglobin (g/dl)	12 (12-15)	13 (11-15)	ns
Creatinine (mg/dl)	0.8 (0.8-1.0)	0.9 (0.7-1.1)	ns
AFP (ng/ml)	95 (10-310)	105 (15-290)	ns

*Significant difference; ns, non-significant difference; AFP, alfa feto-protein; cm, centimeter; L, liter, mm, millimeter; ng/ml, nanograms per milliliter; US, ultrasonography

Table 2: Operative data

	Elderly (≥ 65 years)	Non-elderly (<65 years)	P-value
Duration of surgery (minute)*	185 (120-290)	165 (95-270)	ns
Number of resected segments*	3 (1-4)	3 (1-4)	ns
Central venous pressure cm/H_2O*	4 (1-5)	3 (2-5)	ns
Blood loss (ml)*	850 (300-1700)	450 (250-1200)	<0.05**
Red blood cell transfusion (unit)*	4 (1-6)	2 (0-3)	<0.05**
Plasma transfusion (units)*	5 (1-8)	2 (0-5)	<0.05**

* Median (range), ** significant difference

Table 3: Postoperative data

	Elderly (≥ 65 years)	Non-elderly (<65 years)	P-value
Markers of liver dysfunction at POD-5:			
- Bilirubin (mg/dl) §	1.8 (0.9-7)	1 (0.8-2.5)	<0.05*
- PC (%) §	71 (42-88)	86 (65-95)	<0.05*
- Albumin (g/dl) §	2.9 (2.5-3.9)	3.7 (2.9-4.2)	<0.05*
Highest complication score§	7 (2-7)	3 (1-3)	<0.05*
Length of hospital stay§	14 (8-32)	10 (3-18)	<0.05*
Length of ICU stay§	4 (1-12)	1 (0-4)	<0.05*

PC, prothrrombin concentration, POD, postoperative day, ICU, intensive care unit,
* significant difference, § Median (Range)

4. Discussion

This study underlines, for the first time in Upper Egypt onco-surgery program, the vulnerability of elderly patients to liver failure, morbidity and mortality after liver resection for HCC that occurs on top of liver cirrhosis. Elderly cirrhotics who develop POD-1 thrombocytopenia <100 $\times 10^9$/L with persistent derangement of bilirubin levels and prothrombin activity until POD-5 showed worse clinical outcome compared with the non-elderly patients.

The quality of liver functions deteriorates with aging.[18] Thus, advanced age should be seriously considered when evaluating the risk for postoperative complications after major hepatectomy.[6] Furthermore, cirrhosis imposes increased risks of PHLF after HCC resection.[19] Therefore, we attempted to address the influence of advanced age with concurrent cirrhosis on the short term outcome after HCC resection, including PHLF, surgical complications and mortality.

Early postoperative thrombocytopenia has been shown as independent predictor of PHLF and mortality after partial hepatectomy.[20] In elderly patients, posthepatectomy reduction of platelet count <100 $\times 10^9$/L was associated with significant escalation of bilirubin levels, reduction of prothrombin concentration and increased mortality.[21]

We monitored our patients for occurrence of early (POD-1) reduction of platelet count down to <100 $\times 10^9$/L. We expected that reduced postoperative platelet count will be associated with increased risk of PHLF. Consistent with published data[21], severe form of PHLF occurred in 2 among 4 patients who had POD-1 <100 $\times 10^9$/L after major resections in the elderly group.

Persistent derangement of prothrombin activity and bilirubin levels until POD-5 strongly predicts impaired hepatic functional recovery and increased mortality after liver resection.[15] Our analysis showed tendency toward slower normalization of bilirubin levels and prothrombin concentration among elderly compared with non-elderly cirrhotic patients. In line with previous reports[15,21], mortality occurred in 2 among 3 elderly cirrhotics patients who showed concurrently high bilirubin level > 3 mg/dl and diminished prothrombin concentration < 50% until POD-5.

We have objectively assessed the severity of postoperative complications.[17] Elderly cirrhotic patients displayed remarkably increased complication scores compared with the non-elderly group. This might be rationally explained by the inferior quality of liver parenchyma due to advanced age.[9] In line with increased incidence of PHLF and postoperative complications, elderly cirrhotic patients needed significantly prolonged duration of hospital stay in comparison with the non-elderly cirrhotic group.

Postoperative mortality occurred in 2 among the elderly cirrhotic patients. Both cases had POD-1 thrombocytopenia <100 $\times 10^9$/L and persistently deranged bilirubin and coagulation profile on POD-5. Our results conform with previous reports which showed that mortality in patients who had HCC resection and immediate postoperative thrombocytopenia <100 $\times 10^9$/L as higher compared with higher platelet counts. [20,22]

The case-matched control design allows study execution in short time with low cost even in small patient cohort, as in our study. Nevertheless, the inherent defects of this methodology, for example the difficult case and matched-control collection, the possible selection bias and confounding elements should be clearly stated. [23,24]

In conclusion, this study is the first, in Upper Egypt, to investigate the influence advanced age on the clinical outcome of HCC resection in cirrhotic patients. In light of increased postoperative

complications and mortality in elderly cirrhotics, rigorous selection criteria should be fulfilled to attain reasonable outcome.

Abbreviations: HCC, hepatocellular carcinoma; PHLF, posthepatectomy liver; POD, postoperative day.

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