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CLINICAL TRIALS STUDY

Liver resection in hepatitis B related-hepatocellular carcinoma: Clinical outcomes and safety in elderly patients

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Abstract

AIM: To compare the morbidity and mortality in young and elderly hepatocellular carcinoma (HCC) patients undergoing liver resection.

METHODS: We retrospectively enrolled 1543 consecutive hepatitis B (HBV)-related HCC patients undergoing elective hepatic resection in our cohort, including 207 elderly patients (≥ 65 years) and 1336 younger patients (< 65 years). Patient characteristics and clinical outcomes after liver resection were compared between the two groups.

RESULTS: Elderly patients had more preoperative comorbidities and lower alanine aminotransferase and aspartate aminotransferase levels. Positive rates for hepatitis B surface antigen ($P < 0.001$), hepatitis B e antigen ($P < 0.001$) and HBV DNA ($P = 0.017$) were more common in younger patients. Overall complications and their severity classified using the Clavien system were similar in the two groups (33.3% *vs* 29.6%, $P = 0.271$). Elderly patients had a higher rate of postoperative cardiovascular complications (3.9% *vs* 0.6%, $P = 0.001$), neurological complications (2.9% *vs* 0.4%, $P < 0.001$) and mortality (3.4% *vs* 1.2%, $P = 0.035$), and had more hospital stay requirement (13 d *vs* 12 d , $P < 0.001$) and more intensive care unit stay (36.7% *vs* 27.8%, $P = 0.008$) compared with younger patients. However, postoperative hepatic insufficiency was more common in the younger group (7.7% *vs* 3.4%, $P = 0.024$).

CONCLUSION: Hepatectomy can be safely performed in elderly patients. Age should not be regarded as a contraindication to liver resection with expected higher complication and mortality rates.

Key words: Elderly; Hepatocellular carcinoma; Hepatectomy; Complication; Hepatitis B

Core tip: Elderly patients are regarded as unsuitable for liver resection due to the presence of comorbidities. Our study found that elderly patients did have more comorbidities than younger patients, but also had better liver function and reduced hepatitis B infection. Elderly patients had similar overall morbidity and higher mortality compared with younger patients. Older patients also had more cardiovascular complications, neurological complications and a longer hospital stay, but less hepatic insufficiency. Our study suggested that liver resection can be safely performed in carefully selected elderly patients with accepted higher complication and mortality rates.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer and the third most common global cause of cancer-related deaths[1]. Fifty to fifty-five percent of HCC cases are attributed to chronic hepatitis B virus infection worldwide, and up to 80% in China[2]. There will be more elderly patients as people live longer, especially in China, which has the world's largest population. Moreover, aging itself is a risk factor for HCC carcinogenesis and development[3]. Therefore, the number of elderly HCC patients will increase[3], which may also result in social problems. The elderly tend to be considered clinically "fragile" due to comorbidity and a poorer performance status, which make them less amenable and tolerant to resection[4]. Liver resection is the treatment of choice in HCC patients, however, elderly HCC patients with comorbidity may have an increased surgical risk and may have higher morbidity and mortality[5]. These age-related contraindications have prevented elderly HCC patients from receiving optimal surgical treatment. With the refinement of surgical techniques and perioperative management in liver surgery during the last few decades, liver resection in elderly HCC patients has become safer[3].

Many studies have reported the safety of liver resection in elderly HCC patients, but have drawn inconsistent conclusions. The aim of our study was to evaluate the safety of liver resection in a large sample of elderly HCC patients, by comparing the outcome of liver resection performed in patients younger and older than 65 years.

MATERIALS AND METHODS

Population and study design

We carried out a retrospective study. Between January 2009 and March 2013, 1543 consecutive hepatitis B virus (HBV)-related HCC patients undergoing elective hepatic resection were included in this study. All included patients were diagnosed with HCC by histology and with current or a history of HBV infection. All patients underwent surgery only when the Child-Turcotte-Pugh (CTP) class was A. Patient data on pre-, intra-, and postoperative parameters were collected prospectively from the West China Hospital of Sichuan University HCC database (HCCWCHSU System). The protocol was approved by the West China Hospital Ethics Committee and written informed consent was obtained from all patients before inclusion. Based on the age distribution, the patients were divided into the elderly group ($\geqslant$ 65 years) and the younger group ($<$ 65 years). The primary outcomes were preoperative mortality and postoperative complications in the elderly group compared with the younger group.

Perioperative management

All the included patients were managed by the same surgical team. All patients underwent a thorough history enquiry, physical examination and routine preoperative laboratory measurements. Echocardiography, chest radiography or computed tomography, pulmonary function test and coronary angiography were carried out if necessary. Routine preoperative imaging examinations to evaluate the tumor included contrast computed tomography or magnetic resonance imaging of the abdomen. American Society of Anesthesiologists (ASA) category was used for anesthetic assessment. Patients were explored through an extended right subcostal incision and intraoperative ultrasonography was performed routinely. Hemihepatic vascular inflow occlusion[6] or the Pringle maneuver[7] were used according to the surgeon's preference in most patients. Liver parenchymal transection was performed using the Hooking ligation technique or an ultrasonic dissector with coagulator[6]. Based on preoperative and intraoperative conditions, patients were transferred to the intensive care unit for treatment if necessary.

Definition of the parameters used

Mortality was defined as death within 30 d after surgery or death before discharge involving a hospital stay of more than 30 d. The Clavien-Dindo complications classification system[8] was used to grade postoperative complications. Liver resection of more than 3 segments was defined as major resection, and liver resection of less than 3 segments was defined as minor resection[5]. Portal hypertension was defined as esophageal varices detected by endoscopy or splenomegaly (major diameter $>$ 12 cm) with a platelet count $<$ 100000/mm^3 according to the Barcelona Clinic Liver Cancer Group criteria[9]. For individual pre-existing disease, we used the Charlson index[10,11] to quantify comorbidities. The 50-50 criteria[12] defined as prothrombin time $<$ 50% and serum bilirubin level $>$ 50 μmol/L on day 5 after liver resection, was defined as liver failure. Hepatic insufficiency was defined as serum bilirubin $>$ 60 μmol/L on postoperative day 5. Extrahepatic procedures included all other operations, except liver resection, such as bowel resection, adrenalectomy, diaphragm resection, biliary tract exploration and adhesion separation due to reoperation.

Statistical analysis

Statistical analysis was performed using SPSS Version 17 statistical analysis software and significance was set at $P < 0.05$. The Student t and Mann-Whitney U tests were used to compare continuous variables when appropriate. The χ^2 test and Fisher exact test were used to compare categorical variables.

RESULTS

Patient clinical characteristics

Clinical characteristics of the elderly and younger groups are shown in Table 1. All 1543 patients were diagnosed with HBV-related HCC. Of these patients, 13.4% were elderly, with a median age of 68 years (interquartile range: 66-73 years), and the median age of the younger group was 47 years (interquartile range: 40-56 years). A similar distribution in gender and portal hypertension was seen in both groups. No significant differences were found for platelets, white blood cells and body mass index.

Table 1 Clinical characteristics in elderly and younger hepatitis B virus-related hepatocellular carcinoma patients *n* (%)

Clinical characteristics	Elderly (≥ 65 yr) (*n* = 207)	Younger (< 65 yr) (*n* = 1336)	*P* value
Age (yr), median (IQR)	68 (66-73)	47 (40-56)	< 0.001
Male	166 (80.2)	1128 (84.4)	0.123
Body mass index (kg/m^2), mean (SD)	22.8 (2.9)	22.9 (2.9)	0.899
HBsAg(+)	123 (59.4)	1127 (84.4)	< 0.001
HBeAg(+)	10 (4.8)	236 (17.7)	< 0.001
HBV DNA (+)	50 (24.2)	433 (32.4)	0.017
AST (U/L), median (IQR)	35 (25-55)	40 (29-64)	0.001
ALT (U/L), median (IQR)	34 (24-49)	40 (29-60)	< 0.001
White Blood Cells (10^9/L), median (IQR)	5.34 (4.18-6.67)	5.37 (4.25-6.63)	0.656
Hemoglobin (g/L), median (IQR)	134 (122-144)	143 (130-153)	< 0.001
Platelets (10^9/L), median (IQR)	136 (92-185)	130 (92-183)	0.999
Portal hypertension	52 (25.1)	376 (28.1)	0.366

HCC: Hepatocellular carcinoma; HBV: Hepatitis B virus; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen; HBV-DNA: Positive indicated by hepatitis B virus DNA > 2000U/mL; IQR: Interquartile range; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

Table 2 Comorbidity in elderly and younger patients *n* (%)

Comorbidity	Elderly (≥ 65 yr) (*n* = 207)	Younger (< 65 yr) (*n* = 1336)	*P* value
ASA grade (Ⅲ + Ⅳ)	133 (64.3)	95 (7.1)	< 0.001
Charlson index, median (IQR)	2 (1-3)	1 (1-3)	< 0.001
Charlson index > 3	37 (17.9)	114 (8.5)	< 0.001
Comorbidity	122 (58.9)	326 (24.4)	< 0.001
Hypertension	89 (43)	188 (14.1)	< 0.001
Cardiovascular disease	14 (6.8)	28 (2.1)	< 0.001
Pulmonary disease	22 (10.6)	25 (1.9)	< 0.001
Diabetes mellitus	39 (18.8)	78 (5.8)	< 0.001
Renal-related disease	6 (2.9)	21 (1.6)	0.285

Cardiovascular diseases included coronary heart disease, previous coronary revascularization, cerebral arterial occlusive disease, and/or peripheral vascular occlusive disease. Pulmonary diseases indicated chronic obstructive pulmonary disease, asthma, chronic bronchitis and tuberculosis. Renal disease indicated chronic glomerulonephritis, renal insufficiency, hydronephrosis, lithangiuria, and diabetic nephropathy. ASA: American Society of Anesthesiologists category; IQR: Interquartile range.

Compared with younger patients, elderly patients had a significantly lower positive rate of hepatitis B surface antigen (HBsAg) (59.4% *vs* 84.4%, $P < 0.001$), hepatitis B e antigen (HBeAg) (4.8% *vs* 17.7%, $P < 0.001$), HBV DNA (24.2% *vs* 32.4%, $P = 0.017$) and lower hemoglobin concentration ($P < 0.001$). Although liver resections were performed for CTP grade A, elderly patients had better liver function, with lower aspartate aminotransferase (AST) ($P = 0.001$) and alanine aminotransferase (ALT) levels ($P < 0.05$).

Table 3 Intraoperative parameters in elderly and younger patients *n* (%)

Intraoperative parameters	Elderly (≥ 65 yr) (*n* = 207)	Younger (< 65 yr) (*n* = 1336)	*P* value
Major resection	77 (37.2)	497 (37.2)	1.000
Extrahepatic procedures,	38 (18.4)	266 (19.9)	0.601
Inflow occlusion	82 (39.6)	560 (41.9)	0.532
Liver resection with Hooking			
with ligation	78 (37.7)	460 (34.4)	0.361
Liver resection with ultrasonic dissector	129 (62.3)	876 (65.6)	0.361
Laparoscopic hepatectomy	4 (1.9)	15 (1.1)	0.519
Blood loss (mL), mean ± SD	432 ± 327	496 ± 528	0.092
Blood transfusion	38 (18.4)	250 (18.7)	0.903
Anatomic resection	76 (36.7)	481 (36)	0.843

With regard to comorbidities (Table 2), 122 of 207 (58.9%) elderly patients had more than one comorbidity, compared with 326 of 1336 (24.4%) in the younger group ($P < 0.001$). In addition, elderly patients had a significantly higher Charlson index, a higher proportion of Charlson index > 3 (17.9% *vs* 8.5%, $P < 0.001$) and ASA grade Ⅲ-Ⅵ (64.3% *vs* 7.1%, $P < 0.001$). In the elderly group, the most common comorbid conditions were hypertension, diabetes mellitus, pulmonary disease, cardiovascular disease and renal-related disease, which were all significantly higher, with the exception of renal-related disease, than those in the younger patients.

Intraoperative data

The same proportion (37.2%) of patients undergoing major liver resection was found in both groups (Table 3). For the elderly and younger groups, respectively, 38 (18.4%) and 266 (19.9%) patients underwent a simultaneous non-hepatic procedure, most commonly adhesiolysis, portal vein tumor thrombus resection, biliary tract exploration, diaphragm resection, splenectomy and bowel resection. There were no significant differences between the two groups with regard to the parameters analyzed (Table 3). Information on the Ishak score was available in only 713 patients and there was no significant difference in the rate of cirrhosis (Ishak score ≥ 5) between the elderly and younger groups ($P = 0.404$).

Postoperative outcome

Postoperative complications and their severity are shown in Table 4. The elderly group had similar morbidity and levels of complications (from grade I to Ⅵ) to those in the younger group. However, the elderly patients had a higher mortality than the younger group (3.4% *vs* 1.2%, $P = 0.035$). Cardiovascular complications and neurological complications were more frequent in the elderly patients ($P = 0.001$). In addition, the incidence of hepatic insufficiency was higher in younger patients ($P = 0.024$). The most common complications in elderly patients were pul-

Table 4 Postoperative outcomes in elderly and younger patients *n* (%)

Postoperative outcomes	Elderly (≥ 65 yr) (*n* = 207)	Younger (< 65 yr) (*n* = 1336)	*P* value
Total complications	69 (33.3)	395 (29.6)	0.271
Grade Ⅰ	18 (8.7)	128 (9.6)	0.686
Grade Ⅱ	30 (14.5)	163 (12.2)	0.354
Grade Ⅲ	7 (3.4)	64 (4.8)	0.368
Grade Ⅳ	7 (3.4)	24 (1.8)	0.213
Mortality (grade Ⅴ)	7 (3.4)	16 (1.2)	0.035
Bile Leakage	1 (0.5)	20 (1.5)	0.396
Liver failure	2 (1.0)	25 (1.9)	0.523
Hepatic insufficiency	7 (3.4)	103 (7.7)	0.024
Cardiovascular complications	8 (3.9)	8 (0.6)	< 0.001
Pulmonary complications	19 (9.2)	80 (6.0)	0.081
Infectious complications	14 (6.8)	67 (5.0)	0.294
Bleeding	3 (1.4)	17 (1.3)	1.000
Neurological complications	6 (2.9)	6 (0.4)	0.001
Ascites	7 (3.4)	61 (4.6)	0.440
Gastrointestinal complications	5 (2.4)	32 (2.4)	1.000
ICU stay	76 (36.7)	371 (27.8)	0.008
ICU stay (d), median (IQR)	0 (0-1)	0 (0-1)	0.006
Hospital stay (d), median (IQR)	13 (11-17)	12 (10-15)	< 0.001

Neurological complications indicated confusion and epilepsy. Cardiovascular complications included myocardial infarction, arrhythmia, heart failure and sudden cardiac arrest. Pulmonary complications indicated pulmonary infection, respiratory failure, hydrothorax and hydrothorax. ICU: Intensive care unit; IQR: Interquartile range.

monary complications, followed by infectious complications, cardiovascular disease, hepatic insufficiency, ascites, and neurological complications.

DISCUSSION

The incidence rate of HCC among the elderly is progressively increasing[3], however, only a minority undergo curative procedures[13]. Historically, there were biases against cancer treatment for the elderly as life expectancy of elderly patients will be determined by medical comorbidities and not malignancy[14]. Moreover, aging leads to a number of structural and functional changes in the liver, including a decline in liver volume, a reduction in the mass of functional hepatocytes, and alterations in hepatic microcirculation, which may make liver resection less tolerable[15]. With the refinement of surgical techniques and perioperative management in liver surgery during the last few decades, some studies have suggested that liver resection is a safe and effective treatment in elderly patients, even for elderly patients over 80 years old[16]. However, there is still controversy as to whether age influences the postoperative outcome of HCC patients.

Several studies[13,16-19], which included elderly patients aged 70 to 80 years, showed that there were no differences in morbidity and mortality, however, other studies[20-22] found that elderly patients had more complications. The present study assessed the safety of liver resection in a large sample of elderly patients enrolled in a retrospective cohort. Our elderly and younger HCC patients differed with regard to several features. Elderly patients had a higher rate of comorbidity, lower AST and ALT levels, and lower positive rates for HBsAg, HBeAg and HBV DNA, but higher cardiovascular and neurological complications. The overall morbidity was similar in the two groups, but elderly patients had high mortality and longer hospital and more intensive care unit (ICU) stay requirement.

The cut-off age for elderly HCC patients varies widely in the literature from 65 to 80 years[16,23-25]. However, most studies[13,17,20-21,24,26-28] used 70 years as the cut-off age and these studies included HCC due to various etiologies, such as HBV, hepatitis C virus (HCV) and nonalcoholic fatty liver disease. The average age at onset of HBV-related HCC was reported to be 10 years younger than that of HCV-related HCC[3]. In our cohort, HCC was related to HBV infection and we defined elderly patients as aged more than 65 years. That was because the mean age at HCC diagnosis was found to be 55-59 years in China[29], and in South Korea[2], however, the mean age at HCC diagnosis was 63-65 years in Europe and North America and 75 or older in low-risk populations[29]. Thus, 65 years is a more suitable cut-off for elderly patients in China.

Based on the cut-off age of 65 years, 13.4% of the patients in our cohort were elderly, which was less than that in other studies[13-14,17,20,23-24]. This may be because elderly patients were highly selected for liver resection based on preoperative general condition and assessment of hepatic reserve in our center.

In agreement with previous reports[17,20], elderly patients showed a higher rate of comorbidities, ASA grade ≥ Ⅲ and higher quantitative comorbidity (Charlson index). The higher prevalence of hypertension and cardiovascular disease may be the reason for the higher rate of postoperative cardiovascular complications in elderly patients. The function of most organs usually deteriorates with age[16] and this could explain why elderly patients had more neurological complications. Cho *et al*[17] reported that confusion after liver resection was far more common in the elderly than in younger patients.

Although both elderly and younger patients had preserved liver function with CTP class A, the AST and ALT levels were significantly higher in younger patients. Approximately 80% of HBV-related HCC cases occur in patients with cirrhosis[1], and cirrhosis severity influences liver function and postoperative complications. The rate of cirrhosis was not different between the two groups in our cohort. We compared the rate of portal hypertension, which caused the underlying liver damage, but no difference was observed between the two groups. The positive rates of HBsAg, HBeAg and HBV DNA were significantly lower in the elderly group, this meant that the younger patients had worse underlying liver damage resulting from HBV infection. This study revealed an

age-related difference in HBV infection status (current or previous infection) and more elderly patients had a history of HBV infection. This difference may also indicate that inflammation of the liver due to HBV infection was less active in elderly patients as younger patients had higher AST and ALT levels. The same phenomenon was observed in the study by Oishi *et al*[30] in which elderly patients > 75 years with HCC had better liver function than younger patients as assessed by prothrombin time, AST and ALT. Several studies have also found[23-24,30] better preoperative liver function in elderly patients. In addition, postoperative hepatic insufficiency was found to be more common in younger patients and Yau *et al*[31] also found that young patients had a significantly higher rate of liver derangement after TACE than elderly patients. Several reasons could explain this result. Firstly, the preoperative AST and ALT levels and HBV infection status may influence postoperative liver function. Secondly, HCC is less frequently associated with cirrhosis in elderly patients[32]. It is possible that patients with cirrhosis and HCC died before reaching elderly status and the surviving patients had well preserved hepatic function[32]. In addition, this result may be due to elderly patients being highly selected for liver resection based on the assessment of hepatic reserve in our center. Thus, considering postoperative liver-related complications, age is not a contraindication to liver resection, although aging may lead to a number of structural and functional changes in the liver.

Compared with younger patients, overall complications and their severity, classified using the Clavien system, were similar in elderly patients, but these patients had higher mortality (3.4%). Despite higher mortality in elderly patients, a mortality rate of 3.4% suggested that liver resection was relatively safe in the elderly, compared with mortality of 3.15% in a meta-analysis which included 35000 hepatic resections[33]. Many studies[13-14,17-19] have also drawn the same conclusion in that there were no significant differences in postoperative complications. These data suggest that hepatic resections can be safely performed in elderly patients. However, elderly patients had a longer hospital stay and more ICU stay requirement. Therefore, although the elderly were not predisposed to postoperative complications, recovery in these patients may be slower due to less physiologic reserve compared with younger patients[14]. Therefore, advanced age is not the major determinant in the incidence and severity of postoperative complications.

The results of our study should be interpreted cautiously, as our analysis was restricted to patients with HBV-related HCC, and may not be appropriate for other etiologies. Moreover, it is important to point out that the elderly patients in our study were highly selected for surgical safety.

In conclusion, liver resection can be safely performed in carefully selected elderly patients. Although elderly patients had more cardiovascular and neurological complications, age should not be regarded as a contraindication to liver resection.

COMMENTS

Background

There will be more elderly patients in the future and this may cause social problems as elderly patients have more comorbidity and a poorer performance status. Hepatocellular carcinoma is a common cancer and usually occurs in older patients. The safety of liver resection in elderly patients is still a concern.

Research frontiers

Aging not only results in more and severe comorbidities, but usually leads to a number of structural and functional changes in the liver, including a decline in liver volume, a reduction in the mass of functional hepatocytes, and alterations in hepatic microcirculation. These may make liver resection less tolerable. The research hotspot is to evaluate the safety of liver resection in elderly patients.

Innovations and breakthroughs

The authors' study found that elderly patients had more preoperative comorbidities compared with younger patients. However, elderly patients did not only have better liver function, but also had less hepatitis B infection. Overall complications were similar in the two groups. However, elderly patients had more postoperative cardiovascular complications, mortality and less hepatic insufficiency.

Applications

In general, hepatectomy can be safely performed in elderly patients with expected higher complications and mortality rates. Aging should not be regarded as a contraindication to liver resection when surgeons make decisions before surgery.

Peer review

The authors present a series of 1543 liver resections in patients diagnosed with hepatitis B virus related hepatocellular carcinoma. There were 1336 young patients and 207 elderly patients. It is a series collected in a period of four years. The article is well redacted and its conclusions are very interesting for the international literature.

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