

## WJG 20<sup>th</sup> Anniversary Special Issues (1): Hepatocellular carcinoma

# Safety of hepatectomy for elderly patients with hepatocellular carcinoma

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Received: March 12, 2014 Revised: May 11, 2014

Accepted: July 22, 2014

Published online: November 7, 2014

## Abstract

The number of elderly patients with hepatocellular carcinoma (HCC) has been increasing. Characteristics of elderly HCC patients are a higher proportion of females, a lower rate of positive hepatitis B surface antigen, and a higher rate of positive hepatitis C antibodies. Careful patient selection is vital for performing hepatectomy safely in elderly HCC patients. Treatment strategy should be decided by not only considering tumor stage and hepatic functional reserve, but also physiological status, including comorbid disease. Various assessment tools have been applied to predict the risk of hepatectomy. The reported mortality and morbidity rates after hepatectomy in elderly HCC patients ranged from 0% to 42.9% and from 9% to 51%, respectively. Overall survival rate after hepatectomy in elderly HCC patients at 5 years ranged from 26% to 75.9%. Both short-term and long-term results after hepatectomy for strictly selected elderly HCC patients

are almost the same as those for younger patients. However, considering physiological characteristics and the high prevalence of comorbid disease in elderly patients, it is important to assess patients more meticulously and to select them strictly if scheduled to undergo major hepatectomy.

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**Key words:** Hepatocellular carcinoma; Hepatectomy; Elderly

**Core tip:** The number of elderly patients with hepatocellular carcinoma (HCC) has been increasing. Careful patient selection is vital for performing hepatectomy safely in elderly HCC patients. Treatment strategy should be decided by not only considering tumor stage and hepatic functional reserve, but also physiological status, including comorbid disease. Both short-term and long-term results after hepatectomy for strictly selected elderly HCC patients are almost the same as those for younger patients. However, considering physiological characteristics and the high prevalence of comorbid disease in elderly patients, it is important to assess patients more meticulously if scheduled to undergo major hepatectomy.

Oishi K, Itamoto T, Kohashi T, Matsugu Y, Nakahara H, Kitamoto M. Safety of hepatectomy for elderly patients with hepatocellular carcinoma. *World J Gastroenterol* 2014; 20(41): 15028-15036 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i41/15028.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i41.15028>

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the third-leading cause of death worldwide. Age-standardized incidence

rates in Eastern Asia are 35.5 per 100000 in males and 12.7 per 100000 in females. An estimated 748300 new liver cancer cases and 695900 cancer deaths occurred worldwide in 2008<sup>[1]</sup>. Hepatitis B virus (HBV) infection or hepatitis C virus (HCV) infection is recognized as the major risk factor for development of HCC. In fact, it has been estimated that HBV infection is associated with 50%-80% of HCC cases worldwide, whereas HCV infection is implicated in the pathogenesis of 10%-25% of HCC cases. The incidence of HCC in cirrhotic liver associated with HBV or HCV infection is between 1% and 7% per year. Another cause of cirrhosis in which HCC can develop is alcohol abuse. Non-alcoholic steatohepatitis-related cirrhosis is also a risk factor for the development of HCC. A recent study has suggested that aging itself might be a factor affecting hepatocarcinogenesis<sup>[2]</sup>.

Average life expectancy at birth has been increasing worldwide. In Japan, 75-year-old men and women have average expected life spans of around 5 and 10 years, respectively. An 80-year-old male has an average life expectancy of 8.26 years, while a female aged 80 years can expect to live another 11.04 years<sup>[3]</sup>.

The number of elderly HCC patients has been increasing<sup>[4,5]</sup>. The average age of HCC patients and the proportion of elderly HCC patients in Japan are increasing. A recent report showed that the mean ages at diagnosis of HCC were 66.4 years in males and 69.9 years in females<sup>[6]</sup>. Another recent report showed that patients over 70 years of age constitute more than 50% of those undergoing hepatectomy for HCC<sup>[7]</sup>. HCC is considered to be a life-limiting factor even in very old patients. Therefore, in patients with good liver function and performance status (PS), hepatectomy for HCC might improve the survival rate, even in very old patients<sup>[8]</sup>. Aging causes several problems due to a decline in the functional reserve of multiple organ systems and the high prevalence of comorbidity in the treatment of HCC.

This review summarizes the physiology, characteristics, preoperative risk assessment, and clinical outcomes in elderly HCC patients undergoing hepatectomy.

## DEFINITION OF ELDERLY

The "elderly" are not clearly defined as a homogeneous population because different age subsets, divided with ages ranging from 65 to 80 years, are mixed. Elderly individuals have been defined in reports as individuals of 65, 70, 75, or 80 years of age and older. Elderly HCC patients were defined as patients of 70 years of age and older in most reports before 2010<sup>[9-15]</sup>. However, due to the change to a more aged society, reports in which elderly HCC patients are defined as patients of 75 years of age and older have been increasing in recent years<sup>[16-21]</sup>. Caratozzolo *et al.*<sup>[22]</sup> reported that the cut-off age related to complications after hepatectomy was 75 years. However, there have been a few reports in which elderly HCC patients were defined as patients of 80 years of age and

older<sup>[23-25]</sup>. At present, a definition of elderly as 75 years of age and older is appropriate. However, due to the advance to a more aged society in the near future, a definition of elderly as 80 years of age and older will become appropriate.

## PHYSIOLOGICAL ALTERATION OF THE LIVER CAUSED BY AGING

Aging changes biological functions in many organs. Several vital proteins such as albumin, prothrombin, and fibrinogen are produced in the liver; albumin maintains the isotonic environment of the blood (with serum albumin level being a good indicator of the nutritional index in elderly people), prothrombin is related to coagulation ability, and fibrinogen is related to hemostasis by helping blood clots to form. With advancing age, the ability to synthesize proteins (especially albumin) and the metabolic function of the liver generally declines. Furthermore, the volume and blood flow of the liver in elderly people is decreased<sup>[26]</sup>.

The liver is a characteristic organ that is able to regenerate itself after hepatic resection<sup>[27]</sup>. It is known that after hepatic resection, the remaining liver expands in volume to compensate for lost tissues. The volume of the liver after remnant liver regeneration is not different between elderly and young people. However, findings after surgical resection have revealed that the effect of aging on the liver is delayed and there is reduced proliferation immediately after loss of liver mass<sup>[28]</sup>. The liver in living-related older donors does not regenerate as quickly as those in younger donors<sup>[29]</sup>. In an animal experiment, it was found that synthesis of DNA isolated from regenerating livers of aged rats was reduced and delayed compared with that of DNA from young rats<sup>[30]</sup>.

An early study demonstrated that major hepatectomy for elderly patients with primary liver cancer resulted in a high mortality rate (23%), with the main cause of death being hepatic insufficiency. It was reported that cirrhosis led to an unacceptable mortality rate of 44% after hepatic resection of 5 or more segments of the liver<sup>[31]</sup>. The loss of regenerative capacity in older livers may cause serious problems in recovery after major hepatectomy in elderly patients. However, a recent study showed that mortality rate in elderly patients (70 years of age or more) who underwent major hepatectomy was 7.9%, which was not so different from that in younger patients (5.4%), although most patients enrolled in that study had metastatic cancer<sup>[32]</sup>.

## COMORBID DISEASE

In general, the proportion of comorbid disease such as cardiovascular, cerebrovascular, pulmonary disease, renal disease, hypertension, and diabetes mellitus is higher in elderly patients than in younger patients<sup>[10,11,18,19,21,23,33-35]</sup>. The proportion of comorbid disease in elderly patients

**Table 1** General surgical risk model in hepatectomy

POSSUM/pPOSSUM	E-PASS	APACHE II score
Physiological parameters		
Age	Age	Age
Cardiac history	Severe heart disease	Chronic health point
Respiratory history	Severe pulmonary disease	Temperature
Blood pressure	Diabetes mellitus	Blood pressure
Pulse rate	Performance status	Heart rate
Glasgow Coma scale	ASA score	Respiratory rate
Hemoglobin level		Oxygenation
White cell count		Arterial pH
Urea concentration		Serum sodium
Serum sodium level		Serum potassium
Serum potassium level		Serum creatinine
Electrocardiography		Hematocrit
		White blood cell count
		Glasgow Coma Score
Operative parameters		
Operative severity	Blood loss/body weight	
Multiple procedures	Operation time	
Total blood loss	Extent of skin incision	
Peritoneal soiling		
Presence of malignancy		
Mode of surgery		

is double that of younger patients. More than 80% of cancer patients over 65 years of age have at least one comorbid disease requiring treatment<sup>[36]</sup>.

Nanashima *et al*<sup>[7]</sup> demonstrated that preoperative comorbidity significantly increased with age in HCC patients who underwent hepatectomy. Huang *et al*<sup>[33]</sup> reported that most comorbidities in elderly HCC patients were well-controlled before hepatectomy, although elderly patients did present with a significantly higher frequency of preoperative comorbidities than in younger patients. Especially for elderly patients, it is necessary to assess comorbid disease and to consider the balance with treatment effect of hepatectomy and the risk of morbidity after hepatectomy. The presence of comorbid diseases has been shown to be an important risk factor of mortality or morbidity after surgical procedures in various surgical risk models mentioned below<sup>[36-39]</sup>.

Diabetes mellitus is also a frequent comorbid disease in elderly patients. Diabetes mellitus increases the risk of HCC development<sup>[38]</sup>. Moreover, diabetes mellitus in HCC patients after hepatectomy is related to a higher rate of postoperative morbidity and poorer postoperative survival rates<sup>[39]</sup>. A recent report warns liver surgeons against shocking results of major hepatectomy for patients with metabolic disorders. Postoperative mortality in patients undergoing right hepatectomy with two or more metabolic disorders including diabetes mellitus, hypertension, dyslipidemia, and obesity reached 30%. Moreover, the mortality rate in patients with three or more metabolic disorders reached 54%<sup>[37]</sup>. Although it is essential to control metabolic disorders medically before hepatectomy, the indication of major hepatectomy for patients with serious metabolic disorders should be reconsidered.

## GENERAL SURGICAL RISK MODEL IN HEPATECTOMY

The treatment strategy for HCC patients is decided mainly according to their physiological status, hepatic functional reserve, and tumor stage. Hepatectomy for HCC patients, especially for elderly HCC patients, is still a risky procedure with significant morbidity and mortality. The prevalence of HCC in a series of elderly patients undergoing hepatectomy ranged from 22.7% to 46.7%<sup>[40,41]</sup>. Patient with poor physiological status are not candidates for such invasive procedures as hepatectomy. Careful patient selection is vital to achieving acceptable outcomes after hepatectomy (Table 1).

According to the guidelines of clinical practice for HCC in Japan<sup>[42]</sup>, treatment strategies should be decided by considering both the tumor factor and hepatic functional reserve. There is no restriction for age or PS in said guidelines. Barcelona-Clinic Liver Cancer staging classification and treatment schedule classifies HCC patients by variables related to tumor stage, liver functional status, physical status, and cancer-related symptoms. With regard to physical status, hepatectomy is indicative for a patient with PS 0, 1, or partial 2.

Evidence-based, patient-specific risk prediction is valuable in the decision-making process. Although age by itself is not a strong risk factor of mortality or morbidity, when considering other physiologic factors<sup>[43]</sup>, age may be a proxy for physiological reserve<sup>[44,45]</sup> and a surrogate marker for undeclared comorbidity. Thus, we have to determine candidates for hepatectomy by not only considering tumor stage and hepatic functional reserve, but also *via* the use of physiological assessment tools. The variety of scoring systems for surgical procedures indicates how numerous the variables are that can be analyzed to derive mortality and morbidity rates.

The American Society of Anesthesiologists (ASA) score, which is widely used, is a useful indicator of morbidity after abdominal surgery in elderly patients<sup>[46]</sup>, and is incorporated in a number of other scoring systems. The advantages of the ASA score are that it can be simply applied and is better for risk stratification, while the disadvantages are that it is not designed as an operative risk score, and it is not specific or predictive<sup>[47]</sup>.

Physiological and operative severity score for the enumeration of mortality and morbidity (POSSUM score)<sup>[48]</sup>, Portsmouth POSSUM (P-POSSUM)<sup>[49]</sup>, and estimation of physiologic ability and surgical stress (E-PASS) score<sup>[50,51]</sup> have been reported as measures for surgical audit to objectively evaluate the operative risk by the preoperative condition of the patient and the surgical stress.

POSSUM and P-POSSUM provide information on predicted risk in terms of morbidity and mortality. Clinical parameters included in POSSUM/P-POSSUM and E-PASS scoring are shown in Table 1. Both scoring systems consist of physiologic and operative parameters. At present, the predicted mortality and morbidity rates from the POSSUM or P-POSSUM scoring systems can be eas-

ily calculated by entering the appropriate numerical values online. However, there are some problems in the scoring systems, including occurrence of an error due to differences among facilities or ethnic groups and difficulty in examining numerous parameters.

The E-PASS scoring system was initially developed by Haga *et al.*<sup>[50]</sup> to predict adverse postoperative effects in a study population of approximately 300 patients requiring elective gastrointestinal surgery. This scoring system is composed of a Preoperative Risk Score (PRS), Surgical Stress Score (SSS), and Comprehensive Risk Score (CRS). E-PASS uses coefficients to combine pre-operative factors with operative ones. E-PASS also incorporates age and the ASA score. Haga *et al.*<sup>[50]</sup> reported that the in-hospital mortality and morbidity rates in patients with liver cancer increased as the CRS increased. The E-PASS scoring system requires no special examination compared with the POSSUM and P-POSSUM scoring systems. Estimated mortality rates are obtained from equations including CRS. Age is an important risk factor for these scoring systems, as well as cardiovascular disease and diabetes mellitus. PRS in the E-PASS scoring system and the POSSUM morbidity and mortality risk in elderly HCC patients are higher than those in younger HCC patients<sup>[20]</sup>. However, Banz *et al.*<sup>[52]</sup> reported that the E-PASS scoring system effectively predicted mortality but not morbidity in hepatectomy for patients with benign or malignant liver tumors. They concluded that the E-PASS scoring system cannot be used in its current form and requires further evaluation and validation to better fit the postoperative predictions specific to liver surgery. Nanashima *et al.*<sup>[7]</sup> demonstrated that PRS in the E-PASS system increased with age and was strongly correlated to the postoperative systemic complications rate, but not to liver-related complications, such as hepatic insufficiency, ascites or plural effusion, and bile leakage, in HCC patients who underwent hepatectomy. Recently, Haga *et al.*<sup>[53]</sup> demonstrated that both E-PASS and P-POSSUM have high discriminatory power for predicting postoperative outcomes even in liver surgery, but overpredicted the overall mortality rate by more than twofold. Therefore, they proposed that E-PASS should be refined to make it more suitable for predicting liver surgery outcomes.

The Acute Physiology and Chronic Health Evaluation (APACHE) method for predicting hospital mortality enables accurate estimation of the probability of in-hospital death in patients admitted to the intensive care unit (ICU)<sup>[54]</sup>. Gagner *et al.*<sup>[55]</sup> reported that the APACHE II score could predict the risk of morbidity and mortality in elective hepatectomy for malignancy. However, the APACHE II method is complex and time-consuming, and raw data are not always easily obtainable, particularly outside the ICU setting.

## RISK ASSESSMENT SPECIFIC FOR ELDERLY PATIENTS UNDERGOING HEPATECTOMY

There are a few scoring systems, in which age of the pa-

tient or physiological status is factored, that are specific to HCC patients for hepatectomy to estimate the risk of in-hospital death after hepatectomy. Recently, Simons *et al.*<sup>[2]</sup> developed a simple risk scoring system to estimate the risk of in-hospital death after resection of HCC. The five patient characteristics used to predict in-hospital mortality after hepatectomy include age group, sex, Charlson comorbidity score group, procedures for HCC, and teaching hospital status. The strongest predictors of in-hospital death were a Charlson score of 3 or more (indicating at least 2 comorbid conditions or those of greater severity) and a more invasive procedure (lobectomy). The total possible score was 22. They graded the patients into 4 groups: low, scores from 0 to 4; low to moderate, scores from 5 to 9; moderate to high, scores from 10 to 14; and high, scores from 15 to 22. The estimated mortality rates in these 4 groups were 1.48%, 3.98%, 10.33%, and 28.30%, respectively. The risk score for patients older than 75 years was 3 (Table 2).

A preoperative nomogram using a population-based database in the USA to predict perioperative mortality risk after liver resections for malignancy has recently been developed<sup>[56]</sup>. The risk factors of this nomogram include age, race, gender, liver primary, coagulopathy, renal failure, congestive heart failure, cardiac arrhythmias, and other major comorbidities. The nomogram was successfully validated by a high-volume center and is the only clinical tool that has been externally validated to predict preoperative mortality after liver resections for malignancy<sup>[57]</sup>.

## CHARACTERISTICS OF ELDERLY HCC PATIENTS WHO UNDERWENT HEPATECTOMY

The characteristics of elderly HCC patients are a higher proportion of females, a lower rate of positive hepatitis B surface antigen (HBs-Ag), better liver functional reserve, and a higher proportion of normal livers<sup>[8,58]</sup> (Table 3).

The hepatic resection rate for elderly HCC patients ranged from 0% to 14%; 12%–28% in younger HCC patients<sup>[8,10,34,58]</sup>. Hepatic resection rates for elderly HCC patients were lower than those for younger HCC patients. Very old patients did not frequently receive surgical treatment and were more likely to receive conservative treatment<sup>[8]</sup>.

A summary of the characteristics of previously reported elderly HCC patients who underwent hepatectomy is shown in Table 3. Similarly to the characteristics of all elderly HCC patients, five studies have shown that the proportion of females in elderly HCC patients is higher than that in younger HCC patients<sup>[10,18,19,21,59]</sup>. Four of those studies were recent. The reasons for the higher proportion of females in elderly HCC patients are that the average life expectancy at birth for females is longer than that of males, and thus the proportion of females is higher than that of males in the elderly population. Moreover, the peak age of occurrence of HCC in females is 5



**Table 2 Risk assessment specific for elderly patients undergoing hepatectomy**

Simple Risk Score		Nomogram	
Physiological parameters	Point		Point
Age		Age	
≤ 55	0	18-54	0
55-75	1	55-70	25
> 75	4	≥ 70	54
Sex		Sex	
Women	0	Women	0
Men	1	Men	19
Hospital type		Race	
Teaching	0	White	0
Nonteaching	3	Non white	21
Charlson comorbidity score		Admission type	
0	0	Elective	8
1	3	Urgent/Emergent	32
2	4	Liver primary	
≥ 3	8	No	0
		Yes	25
		Hypertension	
		Yes	0
		No	61
		Coagulopathy	
		No	0
		Yes	100
		Renal failure	
		No	0
		Yes	87
		Congestive heart failure	
		No	0
		Yes	49
		Cardiac arrhythmias	
		No	0
		Yes	47
		Liver disease	
		No	0
		Yes	41
		Fluid and electrolyte disorders	
		No	0
		Yes	52
		COPD	
		No	0
		Yes	17
		Other neurological disorders	
		No	0
		Yes	95
Operative parameters		Procedure type	
Procedure type		Procedure type	
RFA/enucleation	0	Wedge resection	0
Wedge resection	2	Lobectomy	27
Lobectomy	6		

years older than that in males<sup>[60]</sup>.

Most studies have shown that the rate of positive HBs-Ag was lower in elderly HCC patients than in younger HCC patients<sup>[12,14-17,19,21,23,33,35,61]</sup>. There are many HBV-related HCC patients in China, with lower HBs-Ag rates in elderly HCC patients being reported even in China. On the other hand, the rate of positive HCV antibody (HCV-Ab) is higher in elderly HCC patients than in younger HCC patients<sup>[9,11-13,17,19,33,35,59]</sup>.

Most studies have shown that serum albumin levels are

not different in elderly HCC patients compared to younger HCC patients<sup>[10-13,17,19,20,25,33,62,63]</sup>. Similarly, most studies have shown that the values of indocyanine-green retention rate at 15 min (ICG-R15) are not different in elderly compared to younger HCC patients<sup>[9-11,13,15-17,19,20,24,25,59,62,64]</sup>, while two studies showed that the values of ICG-R15 in elderly HCC patients with hepatectomy were higher than those in younger HCC patients<sup>[21,23]</sup>. Hepatic functional reserve in elderly HCC patients was almost the same as that in younger HCC patients. Surgeons therefore have the same treatment policy for evaluating hepatic functional reserve before hepatectomy in both elderly and younger patients.

Regarding tumor factors, Huang *et al.*<sup>[33]</sup> reported that there was a significantly higher frequency of tumor encapsulation in elderly HCC patients than in younger patients. Tumor encapsulation has been reported to be a favorable prognostic factor for HCC<sup>[65]</sup>. In addition, a higher incidence of tumor encapsulation indicates a higher differentiation of HCC and a lower incidence of vascular invasion<sup>[12]</sup>. It was suggested that a higher frequency of tumor encapsulation might be an indicator of less malignant disease in elderly patients with HCC<sup>[27]</sup>.

## SHORT-TERM OUTCOME OF HEPATECTOMY FOR ELDERLY HCC PATIENTS

The mortality rate after hepatectomy for elderly HCC patients ranged from 0% to 42.9% (Table 4). However, due to recent advances in surgical procedures and peri-operative management, most recent studies have shown that mortality rates after hepatectomy in both elderly and younger patients are similar<sup>[14-17,20,21,24,25,33,35,59,61,63,64]</sup>. Child-Pugh B and C are risk factors of operative death for elderly HCC patients<sup>[66]</sup>. Regarding major hepatectomy, although the degree of liver regeneration at one month after right lobectomy in elderly patients is not different from that in younger patients, the incidence of hospital death due to hepatic failure after right lobectomy in elderly HCC patients is extremely high<sup>[62]</sup>. It is possible that remnant liver regeneration immediately after major hepatectomy in elderly patients is impaired<sup>[67]</sup> (Table 4).

The morbidity rate after hepatectomy for elderly HCC patients ranged from 9% to 51%. Despite the high rate of comorbidity disease in elderly patients, as mentioned above, most studies have shown that morbidity rates of elderly patients are not different from those in younger patients. On the other hand, Ferrero *et al.*<sup>[13]</sup> reported that postoperative morbidity rate was lower in elderly HCC patients. Moreover, Kondo *et al.*<sup>[14]</sup> reported that the frequency of pneumonia is the only difference in postoperative complications.

Meanwhile, the mortality and morbidity rates after hepatectomy in elderly patients with colorectal liver metastasis (CLM) range from 0% to 8% and 14.2% to 52.5%, respectively. The rates in elderly patients with CLM are not different from those in elderly patients with HCC<sup>[68]</sup>.

**Table 3** Characteristics of elderly hepatocellular carcinoma patients

Ref.	Year	Country	Age	Number of patients		Sex (male) (%)		HBV (%)		HCV (%)		Child-Pugh (B) (%)		Alb (g/dL)		ICG-R15 (%)	
				Y	E	Y	E	Y	E	Y	E	Y	E	Y	E	Y	E
Takenaka <i>et al</i> <sup>[9]</sup>	1994	Japan	70	229	39	81	69	18	5	59	88 <sup>1</sup>	24	13	NA	NA	17.4	18.7
Yamamoto <i>et al</i> <sup>[62]</sup>	1997	Japan	70	40	7	87.5	71.4	10	29	77	71	NA	NA	3.9	4.0	13.6	11.2
Poon <i>et al</i> <sup>[10]</sup>	1999	China	70	299	31	86	67.7 <sup>1</sup>	85.9	51.6	NA	NA	4.7	3.2	4.1	4.1	12.6	14.0
Wu <i>et al</i> <sup>[23]</sup>	1999	Taiwan	80	239	21	79.5	90.5	58.5	28.6 <sup>1</sup>	NA	NA	18.8	23.8	NA	NA	14.2	17.7 <sup>1</sup>
Hanazaki <i>et al</i> <sup>[11]</sup>	2001	Japan	70	283	103	78.4	68.9	23.7	18.4	40.7	55.4 <sup>1</sup>	20.1	26.2	3.7	3.7	21.0	21.0
Yeh <i>et al</i> <sup>[12]</sup>	2004	Taiwan	70	398	34	77.9	79.4	74	25.8 <sup>1</sup>	31.8	63.2 <sup>1</sup>	23.6	33.3	3.8	3.6	13.3	22.6
Ferrero <i>et al</i> <sup>[13]</sup>	2005	Italy	70	177	64	81.9	73.4	21.4	10.9	38.9	60.9 <sup>1</sup>	22.0	15.6	3.7	3.6	7.2	9.3
Zhou <i>et al</i> <sup>[61]</sup>	2006	China	65	125	54	85.6	88.9	84.8	59.3 <sup>1</sup>	NA	NA	4.8	14.8 <sup>1</sup>	NA	NA	NA	NA
Kondo <i>et al</i> <sup>[14]</sup>	2008	Japan	70	210	109	75.7	72.4	41	11.9 <sup>1</sup>	45.7	54.1	6.1	9.2	NA	NA	NA	NA
Kaibori <i>et al</i> <sup>[15]</sup>	2009	Japan	70	333	155	80.7	76.8	20.1	9.7 <sup>1</sup>	693	71.6	9.3	10.3	3.6	3.7 <sup>1</sup>	18.7	19.8
Oishi <i>et al</i> <sup>[16]</sup>	2009	Japan	75	502	64	76	75	24	2 <sup>1</sup>	66	70	15.0	8.0	3.8	3.7	17.7	18.7
Huang <i>et al</i> <sup>[33]</sup>	2009	China	70	268	67	82.8	86.6	88.8	65.7 <sup>1</sup>	1.1	7.5 <sup>1</sup>	4.1	6.0	4.1	4.0	NA	NA
Mirici-Cappa <i>et al</i> <sup>[34]</sup>	2010	Italy	70	142	43	81.7	74.4	15	7.1	47.1	57.1	31.3	27.4	NA	NA	NA	NA
Tsujita <i>et al</i> <sup>[17]</sup>	2010	Japan	75	77	23	67.5	73.9	22	0 <sup>1</sup>	65	91 <sup>1</sup>	4.0	0.0	4.0	4.0	18.0	19.0
Portolani <i>et al</i> <sup>[35]</sup>	2011	Italy	70	276	175	82.2	72	30.8	17.1 <sup>1</sup>	31.9	45.1 <sup>1</sup>	8.3	6.9	NA	NA	NA	NA
Yamada <i>et al</i> <sup>[24]</sup>	2012	Japan	80	267	11	77	55	27	36	58	56	8.0	22.0	3.7	3.3 <sup>1</sup>	17.6	19.4
Tsujita <i>et al</i> <sup>[25]</sup>	2012	Japan	80	385	23	65.7	65.2	23.1	8.7	70.6	87	31.7	21.7	3.9	4.0	17.0	16.5
Nishikawa <i>et al</i> <sup>[19]</sup>	2013	Japan	75	206	92	78.1	66.3 <sup>1</sup>	17.5	4.3 <sup>1</sup>	56.3	66.3 <sup>1</sup>	3.9	2.2	4.0	3.8	13.9	14.6
Hirokawa <i>et al</i> <sup>[59]</sup>	2013	Japan	70	120	100	82	69 <sup>1</sup>	NA	NA	50	68 <sup>1</sup>	18.0	12.0	NA	NA	14.3	15.1
Ide <i>et al</i> <sup>[20]</sup>	2013	Japan	75	192	64	82	67	22	13	65	69	13.0	11.0	3.9	3.9	15.7	19.1
Ueno <i>et al</i> <sup>[21]</sup>	2013	Japan	75	186	66	81	65 <sup>1</sup>	20	2 <sup>1</sup>	55	56	9.0	9.0	4.0	3.9 <sup>1</sup>	13.0	14.0 <sup>1</sup>
Taniai <i>et al</i> <sup>[64]</sup>	2013	Japan	75	353	63	77	62	NA	NA	NA	NA	24.0	11.0	NA	NA	19.1	15.0
Wang <i>et al</i> <sup>[63]</sup>	2014	China	70	152	56	79	71	98.7	96.5	1.3	3.6	20.0	14.0	3.9	3.9	NA	NA

<sup>1</sup>Represents significant difference. Y: Younger patients; E: Elderly patients; Alb: Albumin; ICG: Indocyanine-green retention rate at 15 min; HCV: Hepatitis C virus; HBV: Hepatitis B virus; NA: Not available.

## LONG-TERM OUTCOME OF HEPATECTOMY FOR ELDERLY HCC PATIENTS

Overall survival rates after hepatectomy in elderly HCC patients at 5 years ranged from 26% to 75.9%, whereas those in younger HCC patients ranged from 31.4% to 68%<sup>[9-13,15,16,19,20,23-25,33,34,59,61,64]</sup>. Most reports demonstrated that overall survival rates after hepatectomy at 5 years are not different in elderly patients compared to younger patients<sup>[9-13,15,16,19,20,23-25,34,59,61,63,64]</sup>. Only one study showed better overall survival rates after hepatectomy at 5 years in elderly patients<sup>[33]</sup>. In that study, the overall 5-year survival rates after hepatectomy were 43.2% in the elderly group and 31.4% in the younger group, whereas 5-year disease-free survival rate in the elderly group was not significantly different from that in the younger group. Thus, it was suggested that elderly patients with HCC possibly had longer tumor-bearing survival than that of younger patients because HCC in the elderly patients was less advanced and less aggressive<sup>[27]</sup> (Table 4).

Since the majority of elderly patients have various comorbidities, deaths unrelated to HCC may have affected the survival rate in the elderly group. However, long-term results for elderly HCC patients who underwent hepatectomy were almost the same as those for younger patients. One possible explanation is that elderly patients who undergo hepatectomy might be strictly selected before referring to hospitals because hepatectomy is a more invasive procedure than other gastrointestinal surgeries.

Postoperative recurrence of HCC is the most important factor affecting survival of patients who have undergone radical resection. Repeated hepatectomy has been suggested to be the most effective treatment for recurrent HCC<sup>[69]</sup>. Even for elderly patients with recurrent HCC, repeated hepatectomy has been recommended to achieve better survival if the tumors are resectable and hepatic functional reserve is preserved<sup>[11]</sup>. Tsujita *et al*<sup>[17]</sup> reported that the criteria of initial therapy for recurrent HCC are identical to those of initial treatment for primary HCC, even in elderly patients.

Overall survival rates at 5 years in elderly patients with CLM are 16% to 38%. The outcomes for elderly patients undergoing hepatectomy for HCC are better than those for elderly patients undergoing hepatectomy for CLM<sup>[68]</sup>.

## CONCLUSION

The average life expectancy at birth and number of elderly HCC patients have been increasing worldwide. Thus, the necessity of invasive treatments including hepatectomy for elderly patients has been increasing. Hepatectomy can now be performed safely for strictly selected elderly patients. With strict preoperative evaluation, both short-term and long-term results after hepatectomy for elderly HCC patients are almost the same as those for younger patients. Considering physiological characteristics and the high prevalence of comorbid disease in elderly patients, it is important to assess patients more meticulously and to plan an elective operation in detail for elderly patients scheduled to undergo major hepatectomy.

**Table 4** Outcome of hepatectomy for elderly hepatocellular carcinoma patients

Ref.	Year	Country	Age	Number of patients		Mortality rate (%)		Morbidity rate (%)		OS at 5 years (%)	
				Y	E	Y	E	Y	E	Y	E
Takenaka <i>et al</i> <sup>[9]</sup>	1994	Japan	70	229	39	1	5	50	51	51.6	75.9
Yamamoto <i>et al</i> <sup>[62]</sup>	1997	Japan	70	40	7	5	42.9 <sup>1</sup>	NA	NA	NA	NA
Poon <i>et al</i> <sup>[10]</sup>	1999	China	70	299	31	6	10	40	48	51	58
Wu <i>et al</i> <sup>[23]</sup>	1999	Taiwan	80	239	21	2.1	0	15.5	14.3	59.3	40.9
Hanazaki <i>et al</i> <sup>[11]</sup>	2001	Japan	70	283	103	6	9.7	23.3	28.2	40	42.2
Yeh <i>et al</i> <sup>[12]</sup>	2004	Taiwan	70	398	34	7.7	10.5	NA	NA	32.1	39.6
Ferrero <i>et al</i> <sup>[13]</sup>	2005	Italy	70	177	64	9.6	3.1	42.4	23.4 <sup>1</sup>	32.3	48.6
Zhou <i>et al</i> <sup>[61]</sup>	2006	China	65	125	54	2.4	0	NA	NA	38.6	50.1
Kondo <i>et al</i> <sup>[14]</sup>	2008	Japan	70	210	109	2.9	3.7	43.8	41.3	NA	NA
Kaibori <i>et al</i> <sup>[15]</sup>	2009	Japan	70	333	155	4	3	19	18	57.3	54.6
Oishi <i>et al</i> <sup>[16]</sup>	2009	Japan	75	502	64	1	2	19	22	64	58
Huang <i>et al</i> <sup>[33]</sup>	2009	China	70	268	67	1.1	1.5	4.5	9	31.4	43.2 <sup>1</sup>
Mirici-Cappa <i>et al</i> <sup>[34]</sup>	2010	Italy	70	142	43	NA	NA	NA	NA	32.4	44.8
Tsujita <i>et al</i> <sup>[17]</sup>	2010	Japan	75	77	23	1	0	NA	NA	83 <sup>2</sup>	70 <sup>2</sup>
Portolani <i>et al</i> <sup>[35]</sup>	2011	Italy	70	276	175	4.3	3.4	16.7	16	NA	NA
Yamada <i>et al</i> <sup>[24]</sup>	2012	Japan	80	267	11	0	0	3.3 (LF)	0 (LF)	43	26
Tsujita <i>et al</i> <sup>[25]</sup>	2012	Japan	80	385	23	0.8	4.3	NA	NA	84.8	95.7
Nishikawa <i>et al</i> <sup>[19]</sup>	2013	Japan	75	206	92	NA	NA	15.5	16.3	64.4	43
Hirokawa <i>et al</i> <sup>[59]</sup>	2013	Japan	70	120	100	2	2	35	32	64	56
Ide <i>et al</i> <sup>[20]</sup>	2013	Japan	75	192	64	3.1	3.1	29	33	68	59
Ueno <i>et al</i> <sup>[21]</sup>	2013	Japan	75	186	66	1	0	19	26	NA	NA
Taniai <i>et al</i> <sup>[64]</sup>	2013	Japan	75	353	63	2.8	6.3	22.9	30.2	46.6	40.2
Wang <i>et al</i> <sup>[63]</sup>	2014	China	70	152	56	1.3	3.6	47.4	53.6	NA	NA

<sup>1</sup>Represents significant difference; <sup>2</sup>Represents OS at 3 years. Y: Younger patients; E: Elderly patients; OS: Overall survival rate; NA: Not available; LF: Liver failure.

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**P- Reviewer:** Abdul-Wahed NM, De Nardi P, Zezos P  
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ISSN 1007-9327



9 771007 932045