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Surgical Outcomes and Prognostic Factors in Elderly Patients (75 Years or Older) with Hepatocellular Carcinoma Who Underwent Hepatectomy

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Abstract

Background: Whether hepatic resection is indicated for elderly patients with hepatocellular carcinoma (HCC) remains controversial.

Methods: This retrospective study evaluated surgical outcomes and prognostic factors in elderly patients with HCC who underwent hepatectomy. Overall survival rates and disease-free survival rates after hepatectomy were compared between 63 patients with HCC who were 75 years or older (elderly group) and 353 patients with HCC who were younger than 75 years (younger group). Prognostic factors in the elderly group were evaluated by means of multivariate analysis with a Cox's proportional-hazards model.

Results: Overall survival rates at 3 and 5 years were respectively 56.2% and 40.2% in the elderly group and 63.4% and 46.6% in the younger group. Disease-free survival rates at these times were 34.9% and 34.9% in the elderly group and 30.8% and 21.5% in the younger group. These differences were not significant. Multivariate analysis revealed a significant association between Child-Pugh class and outcomes (P=0.01).

Conclusions: The safety and survival benefits of hepatectomy in carefully selected elderly patients with HCC are similar to those in younger patients.

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Key words: hepatocellular carcinoma, elderly patients, prognostic factor, survival rate

Introduction

Mean life expectancy has been increasing in many countries, and management of malignancy in the elderly has become a global issue[1–3]. Hepatocellular carcinoma (HCC) is a common malignant tumor with a poor prognosis. The numbers of elderly patients with HCC are expected to increase[4], in part because patients with chronic liver disease are living longer thanks to more effective treatments. Several studies have reported significantly higher rates of morbidity or mortality after hepatectomy for HCC in elderly patients[5–8]. However, recent studies have found that the short-term and long-term outcomes of surgery for HCC in elderly patients are similar to those in younger patients[4,9–12]. Theoretically, liver transplantation is the optimal treatment for HCC because it is the only method that treats both the tumor and the underlying liver cirrhosis. However,

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grafts from elderly donors provide no long-term survival benefit for recipients[13–15]. This lack of survival benefit has been attributed to elderly patients' capacity for liver regeneration being lower than that of younger patients. Whether the indications for hepatic resection are similar in elderly patients and in younger patients has thus been questioned.

We retrospectively compared surgical outcomes between elderly patients and younger patients with HCC to determine whether hepatic resection is indicated for elderly patients. We also studied prognostic factors in elderly patients with HCC, with the ultimate goal of establishing a strategy for managing HCC at our institution.

Materials and Methods

From January 1990 through December 2010, 416 patients with HCC underwent initial curative hepatectomy at the Department of Surgery, Nippon Medical School, Tokyo, Japan. Of these patients, 63 (15.1%) were 75 years or older (elderly group) and 353 patients (84.9%) were younger than 75 years (younger group). Cumulative survival rates and cumulative disease-free survival rates were compared between the groups.

Furthermore, the relations of outcomes to demographic characteristics and factors related to liver function, tumor status, and operation in the elderly group were examined with univariate and multivariate regression analyses.

The indications for surgery were based on a slightly modified version of Makuuchi's criteria, including such factors as the presence or absence of ascites, the serum total bilirubin level, and the indocyanine green retention rate at 15 minutes (ICGR15)[16].

Preoperative imaging studies included chest radiography, abdominal ultrasonography (US), contrast-enhanced or angiographic computed tomography (CT) or both, and selective visceral angiography. A tumor was considered resectable if there was no evidence of extrahepatic metastasis or tumor thrombus in the main portal vein or inferior vena cava and if the entire main tumor and any smaller nodules could be encompassed in the resection, provided that the estimated liver remnant volume was considered adequate. No patient received adjuvant transcatheter arterial embolization or systemic chemotherapy.

Intraoperative US was performed during every resection to detect additional tumor nodules or tumor invasion into major venous branches and to mark the line of parenchymal transection. The liver was transected before 2,000 through a combination of crushing clamp and finger fracture techniques and subsequently through ultrasonic dissection with hepatic inflow occlusion[17]. Operative mortality was defined as death occurring within 30 days after surgery.

All patients were followed up monthly by the surgical team during the first year and every 2 months subsequently. During each follow-up visit, serum levels of alpha-fetoprotein (AFP) were measured, and abdominal US was performed. Abdominal CT was performed every 6 months or when AFP levels increased. Diagnosis of recurrence was based on typical imaging findings on CT scans.

All clinicopathological and follow-up data were prospectively entered into a computerized database, with a regular update of any tumor recurrence for each patient after each follow-up examination. All continuous variables are expressed as means ± standard deviation and were compared by means of unpaired *t*-tests. Categorical variables were compared by means of the chi-square test with Yates' correction or Fisher's exact test, as appropriate.

Overall and disease-free survival curves for the elderly group and the younger group were generated with the Kaplan-Meier method, with the date of hepatic resection as a starting point, and were compared with the use of the log-rank test.

Univariate and multivariate analyses were performed to evaluate the prognostic usefulness of the following factors: sex (male vs. female), background liver (no cirrhosis vs. cirrhosis), Child-Pugh classification (A vs. B or C), ICGR15 (≥10% vs. <10%), TNM stage according to the classification of the Liver Cancer Study Group of Japan (I or II vs. III or IV), AFP levels (≥1,000 ng/mL vs. <1,000 ng/

Table 1 Comparison of clinicopathological features, operative procedures, and outcomes in patients with HCC in the elderly group and the younger group

	Elderly group (n=63)	Younger group (n=353)	P value
Sex (male : female)	39 : 24	271 : 82	0.087
Age (years)	75–87 (76.0)	25–74 (62.7)	<0.001
Background liver (LC : non-LC)	28 : 35	185 : 168	0.292
Child-Pugh classification (A : B : C)	56 : 07	265 : 84 : 4	0.341
ICGR15 (%)	15.0 ± 11.7	19.1 ± 13.0	0.181
TNM stage (Ⅰ : Ⅱ : Ⅲ : Ⅳ)	8 : 31 : 16 : 8	49 : 136 : 103 : 65	0.433
AFP (ng/mL)	1,938 ± 8,446	26,246 ± 23,272	0.625
Presence of multiple tumors (yes : no)	20 : 43	149 : 204	0.156
Presence of macro venous invasion (yes : no)	17 : 46	124 : 229	0.266
Tumor size (mm) (≥20 : <20)	54 : 9	273 : 80	0.321
Operative time (min)	105–728 (312)	90–760 (326)	0.596
Blood loss (mL)	60–12,730 (1,300)	30–16,900 (839)	0.974
Operative procedure (partial resection : anatomic resection)	30 : 33	150 : 203	0.623
(≥lobectomy : <lobectomy)	13 : 50	78 : 275	0.926
Morbidity	19 (30.2%)	81 (22.9%)	0.265
Mortality	4 (6.3%)	10 (2.8%)	0.297

HCC, hepatocellular carcinoma; LC, liver cirrhosis; ICGR15, indocyanine green retention at 15 minutes; Stage, TNM stage according to the Liver Cancer Study Group of Japan; AFP, alpha-fetoprotein.

mL), presence of multiple tumors (yes vs. no), presence of macroscopic venous invasion (yes vs. no), tumor size (≥20 mm vs. <20 mm), operation time (≥ 300 minutes vs. <300 minutes), and blood loss (≥800 mL vs. <800 mL).

Postoperative complications were defined as follows. Pleural effusion was defined as discharge of >100 mL per day from the chest drain persisting for more than 1 week or, in patients without a chest drain, the need for chest drainage to manage respiratory insufficiency. Intractable ascites was defined as discharge of >200 mL per day from the abdominal drain persisting for more than 1 week or the need for abdominal drainage to treat abdominal distension after drain removal. Surgical site infection was defined as intra-abdominal or abdominal wall abscess requiring drainage. Bile leakage was defined as obvious bile discharge from the drain lasting for more than 5 days. Pneumonia and ileus were diagnosed on the basis of clinical signs and radiographic findings. Hyperbilirubinemia was defined as a serum total bilirubin level of >10 mg/dL. Postoperative bleeding was defined as a considerable amount of bloody discharge from a drain necessitating blood transfusion or the need for surgical or interventional procedures to stop the bleeding. Liver failure was defined as a serum total bilirubin level of >10 mg/dL, a prothrombin time of <20%, or uncontrollable ascites.

A multivariate stepwise Cox regression analysis was performed to identify significant contributors that were independently associated with death on univariate analysis. The level of significance was set at $P<0.05$. All statistical analyses were performed with a statistical software package (Stat View 5.0; SAS Institute Inc., Cary, NC).

Results

Of the 416 subjects, 63 (15.1%) were 75 years or older (elderly group); 53 of these patients (12.7%) were aged 75 to 79 years, and 10 (2.4%) were aged 80 to 87 years. The younger group comprised 353 patients (84.9%). The elderly group and the younger group did not differ significantly in terms of sex ratio or hepatic factors, such as Child-Pugh score and ICGR15. Tumor-related factors and surgical factors also did not differ significantly between the

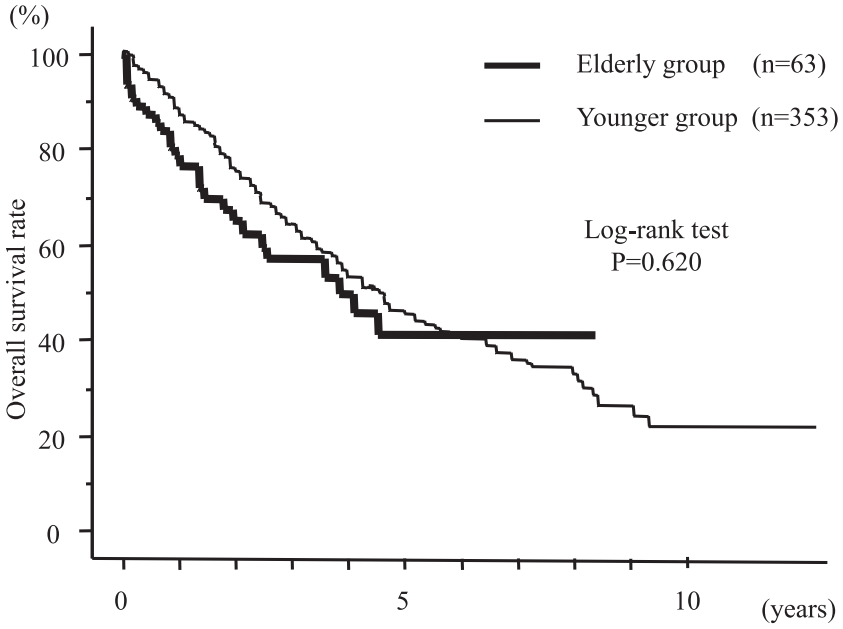

Fig. 1 Overall survival curves of patients with hepatocellular carcinoma in the elderly group and the younger group.

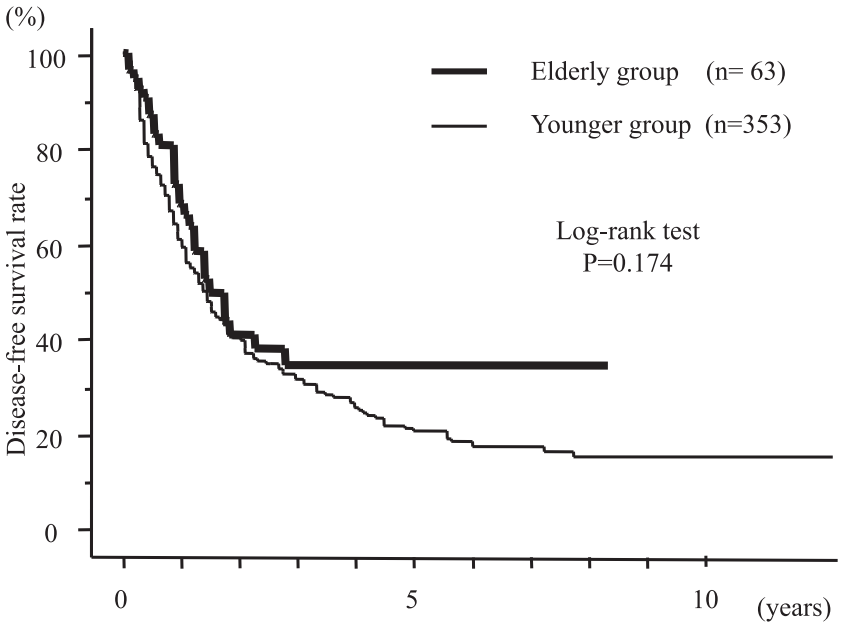

Fig. 2 Disease-free survival curves of patients with hepatocellular carcinoma in the elderly group and the younger group.

groups. The groups were similar with respect to morbidity (elderly group, 30.2%, vs. younger group, 22.9%; P=0.265) and mortality (6.3% vs. 2.8%, P=0.297) (**Table 1**). The median follow-up period was 28.6 months (range, 1–110 months) in the elderly group and 25.0 months (range, 1–249 months) in the younger group. Overall survival rates at 3 and 5 years were respectively 56.2% and 40.2% in the elderly group and 63.4% and 46.6% in the younger group (**Fig. 1**). Disease-free survival rates at 3 and 5 years were respectively 34.9% and 34.9% in the elderly group and 30.8% and 21.5% in the younger group (**Fig. 2**). None of these differences were significant.

Table 2 shows the survival statistics calculated according to patient characteristics, tumor features,

Table 2 Significant prognostic factors, on univariate analysis, for overall survival in patients with HCC in the elderly group

	P value	Relative risk	95% CI
Sex (male vs. female)	0.7354	0.875	0.403–1.899
Background liver (noncirrhosis: cirrhosis)	0.0401	0.218	0.063–0.754
Child-Pugh classification (A vs. B or C)	0.0122	0.361	0.163–0.801
ICGR15 (≥10% vs. <10%)	0.5065	0.668	0.203–2.197
Stage (I or II vs. III or IV)	0.0188	0.407	0.193–0.862
AFP (≥1,000 ng/mL vs. <1,000 ng/mL)	0.2295	1.796	0.691–4.666
Presence of multiple tumors (Yes vs. No)	0.4042	0.711	0.318–1.586
Presence of macro venous invasion (Yes vs. No)	0.0577	0.346	0.116–1.085
Tumor size (mm) (≥20 mm vs. <20 mm)	0.9832	0.989	0.341–2.862
Operative time (≥300 min vs. <300 min)	0.0441	0.408	0.171–0.977
Blood loss (≥ 800 mL vs. : <800 mL)	0.2025	1.711	0.749–3.911

LC, liver cirrhosis; ICGR15, indocyanine green retention at 15 minutes; Stage, TNM stage according to the Liver Cancer Study Group of Japan; AFP, alpha-fetoprotein; CI, confidence interval.

Table 3 Significant prognostic factors, on multivariate analysis, for overall survival in patients with HCC in the elderly group

	P value	Relative risk	95% CI
Background liver (noncirrhosis vs. cirrhosis)	0.6691	1.311	0.370–4.539
Child-Pugh classification (A vs. B or C)	0.0450	0.275	0.061–1.252
Stage (I or II vs. III or IV)	0.7413	1.312	0.262–6.562
Operative time (≥360 min vs. <360 min)	0.3016	0.358	0.051–2.516

Stage, TNM stage according to the Liver Cancer Study Group of Japan; CI, confidence interval.

and operative procedures. Background liver (relative risk [RR]=0.218, 95% confidence interval [CI]=0.063–0.754, P=0.040), Child-Pugh classification (RR=0.361, 95% CI=0.163–0.801, P=0.012), TNM stage (RR=0.407, 95% CI=0.193–0.862, P=0.019), and operation time (RR=0.408, 95% CI=0.171–0.977, P=0.044) were the only factors significantly associated with outcomes on univariate analyses. On multivariate analysis, only Child-Pugh classification (RR=0.275, 95% CI=0.061–1.252, P=0.045) was significantly related to overall survival (**Table 3**).

Postoperative complications were similar in the groups, except for a higher rate of pneumonia in the elderly group than in the younger group (**Table 4**).

Discussion

Aging is associated with gradual decreases in liver volume and blood flow[18]. General markers of liver function, such as aminotransferase levels, serum total bilirubin levels, and alkaline phosphatase levels, are largely unaffected by aging. In contrast, serum levels of albumin, some amino acids, and some coagulation factors, including fibrinogen, prothrombin, and thromboplastin, decrease[19]. Several studies in old rodents have suggested that aging compromises the regenerative capacity of the liver in terms of both the rate of regeneration and the extent to which the organ's original volume is restored after hepatectomy or ligation of the portal vein[20,21]. On the other hand, several studies in humans have claimed that liver regeneration after portal vein embolization is unaffected by aging[22]. Whether or not aging limits liver regeneration thus remains controversial clinically. In liver transplantation, donor age is a prognostic factor for recipients[13–15]. The finding that younger donor age is associated with better outcomes suggests that livers of elderly patients have less capacity for regeneration than do those of younger patients.

Table 4 Postoperative complications in patients with HCC in the elderly group and the younger group

	Elderly group (n=63)	Younger group (n=353)	P value
Pleural effusion	7 (11.1%)	33 (9.3%)	0.837
Ascites	6 (9.5%)	45 (12.7%)	0.609
Surgical site infection	8 (12.7%)	22 (6.2%)	0.118
Intra-abdominal abscess	4 (6.3%)	10 (2.8%)	0.295
Abdominal wall abscess	4 (6.3%)	12 (3.4%)	0.443
Bile leakage	6 (9.5%)	30 (8.5%)	0.981
Pneumonia	5 (7.9%)	5 (1.4%)	0.007
Ileus	2 (3.2%)	5 (1.4%)	0.640
Hyperbilirubinemia	2 (3.2%)	8 (2.3%)	0.664
Intra-abdominal bleeding	1 (1.6%)	4 (1.1%)	0.760
Liver failure	4 (6.4%)	12 (3.4%)	0.443

Recent studies have found that short-term and long-term outcomes of surgery for HCC are similar in elderly and younger patients[4,9–12]. Long-term outcomes of present patients were generally consistent with those of previous studies. In the present study rates of morbidity and mortality were slightly higher, but not significantly higher, in elderly patients than in younger patients. Perioperative care for elderly patients is essential for improving short-term outcomes of surgery. Elderly patients have lower preoperative serum albumin levels and poorer renal function than do younger patients. Consequently, pleural effusion, ascites, or both cannot be controlled by diuretics in some elderly patients. Such patients are at high risk for hepatic or renal failure (or both) if massive loss of plasma proteins or dehydration (or both) continues. Perioperative care of elderly patients with HCC who undergo hepatectomy should therefore include the provision of adequate infusion volumes and appropriate doses of diuretics to avoid severe complications[23]. In Japan, the procedure for hepatectomy is usually decided according to Makuuchi's criteria[16]. When treating HCC many hepatic surgeons prefer anatomic resection to nonanatomic resection, because anatomic resection has been reported to yield better results[24]. Anatomic resection, if feasible, is the procedure of choice for elderly patients with HCC in most hospitals. In the present study, the rate of anatomic resection did not differ significantly between elderly patients and younger patients. The rate of major resection also did not differ significantly between the groups.

Many prognostic factors for overall survival in elderly patients have been reported, including alcohol abuse, AFP levels, serum albumin levels, and tumors larger than 5 cm in diameter[4,9]. In the present study, only the Child-Pugh classification was significantly related to overall survival rates. This finding suggests that the decision to perform hepatectomy in elderly patients with Child-Pugh class B cirrhosis should be carefully considered.

Many series have found similar morbidity rates in elderly patients and younger patients[4,10,11,26]. However, some studies have found lower morbidity rates in elderly patients[9,25], because younger patients, in hope of cure, usually undergo more aggressive procedures, which are associated with and higher rates of complications.

Aggressive surgery increases the risk of postoperative liver failure[9]. In the present study, elderly patients had a significantly higher incidence of pneumonia. We attribute this higher rate to our performing aggressive surgery, such as anatomic or major resection, in both elderly patients and younger patients. Respiratory function decreases with age, and elderly patients generally have a higher risk of pneumonia than do younger patients. Kondo et al. have reported that pneumonia is the most frequent complication in elderly patients, and preventative measures against pneumonia are essential[10]. Recently, we recommend that elderly patients undergo intensive preoperative respiratory training to improve ventilatory function.

Conclusions

Some elderly patients with HCC, excluding those with Child-Pugh class B cirrhosis, can safely undergo hepatectomy with good outcomes similar to those in younger patients. Further studies are needed to address issues, such as the characteristics of patients for whom surgery is contraindicated.

Conflict of Interest: We have no personal or financial interests to declare. Nor have we received any financial support from commercial sources for the research presented herein.

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