A comparative analysis of hepatocellular carcinoma after hepatic resection in young versus elderly patients

Cho Rok Lee

Department of Medicine

The Graduate School, Yonsei University

A comparative analysis of hepatocellular carcinoma after hepatic resection in young versus elderly patients

Directed by Professor Kyung Sik Kim

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Cho Rok Lee

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This certifies that the Master's Thesis
of Cho Rok Lee is approved.

Thesis Supervisor : Kyung Sik Kim

Thesis Committee Member#1 : Young Nyun Park

Thesis Committee Member#2 : Sang Hoon Ahn

The Graduate School

Yonsei University

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It was a great accomplishment of mine that I could broaden my academic knowledge and upgrade my experimental skill while completing the thesis. Based on it, I would like to contribute to the advance of the treatment of hepatocellular carcinoma.

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ABSTRACT

A comparative analysis of hepatocellular carcinoma after hepatic resection in young versus elderly patients

Cho Rok Lee

Department of Medicine
The Graduate School, Yonsei University

(Directed by Professor Kyung Sik Kim)

Purpose: The aim of this study was to investigate the clinical outcomes after surgical treatment of hepatocellular carcinoma (HCC) in the elderly patients compared with younger patients.

Methods: Clinicopathological data and treatment outcomes in 61 elderly (≥70 years old) and 90 younger (≤40 years old) patients with HCC who underwent curative liver resection between 2000 and 2010 were retrospectively collected and compared using various parameters.

Results: The older HCC group was more likely to have hepatitis C virus and non-B non-C hepatitis virus infection, higher values of indocyanine green retention at 15 minutes $(ICGR)_{15}$, more preoperative co-morbidities, and more postoperative complications. There were no significant differences in intraoperative parameters and pathologic features. The recurrence rate, overall survival and disease-free survival rates were similar amongst the two groups.

The only independent prognostic factor of overall survival was postoperative complications.

Conclusion: Our findings suggest that age by itself does not have an adverse effect on operative outcomes, including long-term prognosis. For young and elderly HCC patients, hepatic resection is a safe and effective treatment.

Key words : hepatocellular carcinoma, age, hepatic resection

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I. INTRODUCTION

Hepatocellular carcinoma (HCC) is the fourth most common malignancy and the third most common cause of mortality in the world, and the incidence is gradually increasing.[1,2] Generally, HCC is diagnosed in middle-aged and elderly patients. However, age distribution varies with geographical location.[3] Hepatitis B virus (HBV) is endemic in Korea and the most common and important cause of HCC in Korea. It accounts for approximately 70% of HCC cases.[4] HCC patients infected with HBV are diagnosed at a younger age than those infected with hepatitis C virus (HCV) in endemic areas like Japan and Europe. The peak ages of onset of HCC in Korean patients were in those in their 50s (27.3%), 60s (27.9%), and 70s (19.8%) in 2008.[5] With an increase in

life expectancy, the prevalence of elderly HCC patients has also increased,[6] and with improved screening of HCC in high-risk populations, the prevalence of HCC in younger patients has increased too.[7-10] Several studies have reported a poorer prognosis for elderly HCC patients compared to young patients, whereas others have reported that young patients show a poorer prognosis and a few studies have reported no differences in the outcomes between young and older patients.[7-15]

Hepatic resection is an effective treatment modality for HCC, which may offer a potential cure for patients who have well-preserved liver function.[16] With the improvement of outcomes, transplantation has been established as a durable therapy for HCC patients.[17] Older age is regarded as a high-risk factor for surgical treatment and considered to be responsible for the high incidence of postoperative morbidity[18]. According to the consensus-based treatment guidelines of the Japan Society of Hepatology, the age limitation for transplantation has been restricted to less than 65 years old, and this may cause difficulties in the decision regarding treatment methods.[19]

However, advanced surgical techniques and perioperative management have reduced age-related contraindications for liver surgery. Hepatic resection is an increasingly used treatment strategy for elderly HCC patients and younger HCC patients. There are a few reports comparing the outcomes of younger and elderly HCC patients after hepatic resection and they determined the significance of hepatic resection in the two groups[20,21].

Our retrospective study was designed to characterize patients who develop HCC in old and young age. Due to the increasing incidence of HCC in elderly and younger patients, we sought to compare the outcomes of surgical resection for HCC in patients within the elderly group (≥70 years of age) versus the younger group (≤40 years of age).

II. MATERIALS AND METHODS

1.Patients

From January 2000 to December 2010, a total of 1242 patients were treated at the Department of Surgery inSeverance Hospital located in Seoul, Korea. We defined elderly patients as those over 70 years old because there is a rapid decrease in liver mass and portal blood flow onward from 70 years.[22] The U.S. guidelines for management of HCC suggest screening of Asian males beginning at 40 years of age[23]. We defined younger patients as those less than 40 years old. Amongst all of the treated patients, 66 (5.3%) were ≥70 years old, while 96 (7.7%) were ≤40 years old. Among these 162 patients, 61 met the requirements of the elderly group and 90 met the requirements of the younger group. Only those who were completely followed up were selected for this study. Final diagnoses of HCC were all confirmed by histology.

If possible, hepatic resection was offered to patients with resectable tumors. All patients were medically fit for major laparotomy. Resectability was assessed by ultrasonography, computed tomography (CT), magnetic resonance imaging (MRI), hepatic angiogram and positron emission tomography (PET). Liver function was assessed using a combination of Child's grading, liver biochemistry tests and indocyanine green (ICG) clearance.

2. Clinicopathological parameters, surgical data and postoperative survival

Clinical factors analyzed included age, gender, body mass index (BMI), co-morbid diseases, indocyanine green retention rate at 15 minutes ($ICGR_{15}$), viral hepatitis status, serum α-fetoprotein, MELD and MELD-Na score and the Barcelona Clinical Liver Cancer (BCLC) staging classification. The pathological parameters reviewed include, tumor number, tumor size, resection margin, gross classification, satellite nodules, Edmondson-Steiner grading, liver cirrhosis, macro and micro vascular invasion and tumor, node, and metastasis (TNM) staging. We analyzed intraoperative and postoperative outcomes using operative time, intraoperative blood loss, intraoperative blood transfusion, type of resection and complications. Following the Couinaud classification, major hepatic resection was defined as the involvement of more than three segments. Minor resection was defined as fewer than two segments - including partial resection. Tumor size was measured by determining the greatest dimension of the largest tumor.

3. Follow-up

The follow-up duration was calculated from the operation date to either the day of death of the day of last follow-up. After discharge, all patients were checked for recurrence by imaging (ultrasonography, CT) and laboratory data (tumor markers such as alpha fetoprotein(AFP), prothrombin induced by vitamin K absence or antagonist II(PIVKA-II)). The median follow-up was

39.9 months (range, 0 – 131 months).

4. Statistical analysis

Statistical analysis was performed using SPSS 16 software (SPSS, Chicago, IL, USA). Patient characteristics were analyzed using the Wilcoxon test for continuous variables and the χ-square test for independent variables. Cumulative survival rate was calculated using the Kaplan-Meier technique, and differences between the curves were tested using the log-rank test. Independent risk factors associated with survival time were determined using a stepwise Cox regression analysis. A two-sided P value of less than 0.05 was considered statistically significant.

III. RESULTS

1. Patients clinical characteristics

Clinical characteristics of the elderly and younger groups are shown in Table 1. The mean age of the two groups was 72.6 ± 2.4 years (range, 70 to 81 years) and 35.1 ± 4.1 years (range, 8 to 40 years), respectively. The elderly group included 48 men and 13 women. The elderly group had a similar gender distribution to the younger group, which included 75 men and 15 women (p=0.525). Mean BMI values of the two groups was not significantly different (p=0.079). However, $ICGR_{15}$ was higher in the elderly group (p=0.001). The prevalence of Hepatitis B antigen positivity was significantly higher in the younger group. Conversely, HCV Ab positivity was significantly higher in the elderly group (p=0.001). No significant differences were found for alpha-fetoprotein (AFP), model for end stage liver disease (MELD) score, MELD-Na score and BCLC stage between the two groups. Compared with younger HCC patients, elderly patients had a significantly higher incidence of preoperative comorbidities (p=0.000) and postoperative complications (p=0.042) (Table 1).

Table 1. Comparison of patients clinical characteristics between younger and older patients with hepatocellular carcinoma

Variables	Elderly group (n=61)	Younger group (n=90)	P value
Age (years)	72.6 (± 2.4)	35.1 (± 4.1)	**0.000**
Gender			**0.525**
Male	48 (78.6%)	75 (83.3%)	
Female	13 (21.4%)	15 (16.7%)	
Etiology of liver disease			**0.001**
HBV*	35 (57.4%)	83 (92.2%)	
HCV†	11 (18.0%)	2 (2.2%)	
HBV*+HCV†	2 (3.3%)	0 (0%)	
Non-B and non-C	13 (21.3%)	5 (5.6%)	
BMI			**0.079**
< 25	42 (68.8%)	67 (74.4%)	
≥ 25	19 (31.2%)	23 (25.6%)	
$ICGR_{15}$ (%)‡	13.9 (± 8.7)	6.6 (± 4.5)	**0.001**
AFP§ (IU/mL) (median ± SD)	2456.7 (± 8553.6)	2387.7 (± 9080.1)	**0964**
< 400	42 (71.2%)	51 (60.7%)	**0.340**
≥400	19 (28.8%)	38 (39.3%)	
MELD score (median,range)	7.0 (6~12)	6.9 (6~15)	**0.481**
<8	45 (73.8%)	73 (81.1%)	
8-11	15 (24.6%)	15 (16.7%)	
>11	1 (1.6%)	2 (2.2%)	
MELD-Na score (median,range)	8.8 (3~18)	8.1 (3~21)	**0.721**
<8	29 (47.5%)	48 (53.3%)	
8-11	22 (36.1%)	27 (30.0%)	
>11	10 (16.4%)	15 (16.7%)	

BCLC[**] stage			**0.960**
0	5 (8.2%)	8 (8.9%)	
A	31 (50.8%)	45 (50.0%)	
B	12 (19.7%)	18 (20.0%)	
C	13 (21.3%)	19 (21.1%)	
Preoperative co-morbidities			**0.000**
No	19 (31.1%)	88 (97.8%)	
Yes	42 (68.9%)	2 (2.2%)	
Postoperative complication	17 (27.9%)	13 (14.4%)	**0.042**
General complications	9 (13.1%)	8 (8.9%)	
Hepatic complications	8 (14.8%)	5 (5.5%)	
Postoperative hospital stay	15.36(±16.9)	13.33(±8.9)	**0.352**

Abbreviations: HBV*: hepatitis B virus; HCV[†]: hepatitis C virus; ICGR 15 (%)[‡]: indocyanine green retention rate at 15 minutes; AFP[§]: α-fetoprotein; TACE[‖]:transarterial chemoembolization; RFA[¶]: radiofrequency ablation; BCLC[**]: Barcelona Clinic Liver Cancer

2. Intraoperative data

There were no significant differences in operation time, intraoperative blood loss, and intraoperative blood transfusion between the elderly and younger group. Although elderly patients had a higher major resection rate than younger patients, the difference was not statistically significant (p=0.068) (Table 2).

Table 2. Intraoperative data of the two groups.

Variables	Elderly group (n=61)	Younger group (n=90)	P value
Operation time (min) (median, range)	311.3 (130-660)	329.1 (125-690)	**0.356**
Intraoperative blood loss (ml) (median, range)	760.0(40~3200)	718.3(50~3400)	**0.713**
Intraoperative blood transfusion (n)	20(32.8%)	22 (24.4%)	**0.174**
Type of resection			**0.068**
Major resection	35 (57.4%)	37 (41.1%)	
Minor resection	26 (42.6%)	53 (58.9%)	

3. Pathologic features

For tumor size, resection margin, gross classification, tumor number, Edmondson-Steiner grading, liver cirrhosis rates, macro and microscopic vascular invasion, and pTNM staging, there were no significant differences between the two groups (Table 3).

Table 3. Pathologic features of the two groups.

Variables	Elderly group (n=61)	Younger group (n=90)	P value
Tumor size (median, range)	4.48 (1.5~12)	4.32 (1~15)	**0.721**
<5cm	41 (67.2%)	61 (67.8%)	
≥ 5cm	20 (32.8%)	29 (32.2%)	
Margin of resection			**0.488**
< 1cm	24 (40.0%)	30 (33.3%)	
≥ 1cm	37 (60.0%)	60 (66.7%)	
Gross classification			**0.501**
Infiltrative type	5(6.8%)	9 (10%)	
Expanding type	20 (33.9%)	39 (43.4)	
Multinodular confluent type	24 (40.7%)	31 (34.4)	
Single nodular with perinodular extension type	12 (18.6%)	11 (12.2)	
Tumor number			**0.203**
Single	52(85.2%)	69 (76.7%)	
Multiple	9 (14.8%)	20 (23.7%)	
Edmondson-Steiner grading system			**0.347**
I	2 (3.3%)	5(5.6%)	
II	25 (40.9%)	35 (38.9%)	
III	30 (49.2%)	46 (51.1%)	
IV	4 (6.6%)	4 (4.4%)	
Liver cirrhosis			**0.236**
Absent	22(36.1%)	41 (45.6%)	
Present	39 (63.9%)	29 (54.4%)	
Macroscopic vascular invasion			**0.648**
Absent	53 (86.9%)	75 (83.3%)	
Present	8 (13.1%)	15 (16.7%)	
Microscopic vascular invasion			**0.136**
Absent	28 (45.9%)	53 (58.9%)	
Present	33 (54.1%)	37 (41.1%)	
pTNM stage			**0.768**
I	18 (29.5%)	32 (35.6%)	
II	29 (47.5%)	38 (42.2%)	
IIIa	2 (3.3%)	6 (6.7%)	
IIIb	9 (4.9%)	10 (11.1%)	
IIIc	3 (3%)	4 (4.4%)	

4. Postoperative follow-up results

The recurrence rate in the elderly group was 41.0% (25/61) and tended to be lower than that of the younger group (48.9%, 44/90); however, the difference was not statistically significant (p=0.329). In elderly patients, intrahepatic, extrahepatic, and both types of recurrences were detected in 21 (34.4%), three (4.9%), and one (1.6) patients, respectively. In younger patients, intrahepatic, extrahepatic and both types of recurrences were detected in 29 (32.2%), seven (7.8%), and eight (8.9%) patients. The extrahepatic recurrence sites were lung, brain and bone. Eleven patients (47.8%) in the elderly group and 23 patients (53.5%) in the younger group presented with a recurrence within one year after surgery (p=0.661). Patients with recurrent HCC were treated with transarterial chemoembolization, repeated hepatic resection, systemic chemotherapy, radiofrequency therapy, and wedge resection for lung metastasis. The treatment method used for recurrent HCC patients was not different between the two groups (Table 4). In the elderly group, 32 patients (52.5%) were alive and recurrence-free, while 13 patients (21.3%) were alive and had a recurrence of HCC. In the younger group, 44 patients (48.9%) were alive and recurrence-free, while 19 patients (21.2%) were alive and had a recurrence of HCC. The mortality rate was 26.2% (16/61) in for the elderly group and 30.0% (27/90) for the younger group, with no significant difference. Six patients (37.5%, 6/16) in the elderly group and five patients (18.5%, 5/27) in the younger group expired within 1 year of the surgery. Although the

younger group showed more mortality within 1 year, the difference was not no significant. One patient died of postoperative bleeding.

Table 4. Postoperative results of the two groups.

	Elderly group (n=61)	**Younger group (n=90)**	**P value**
Recurrence	25 (41.0%)	44 (48.9%)	**0.329**
Time to recurrence			**0.661**
>1year after operation	11(47.8%)	23(53.5%)	
≤1year after operation	14 (42.2%)	21 (46.5%)	
Recurrence location			**0.262**
Intrahepatic	21(84%)	29(65.9%)	
Extrahepatic	3(12%)	7(7.8%)	
Both	1(4%)	8(8.9%)	
Recurrence treatment			**0.309**
Hepatic resection	2	4	
Systemic Chemotherapy	2	9	
Radiofrequency therapy	4	4	
Extrahepatic resection	1	3	
Supportive care	2	0	
Status at last follow-up			**0.146**
Alive without recurrence	32(52.5%)	44(48.9%)	
Alive with recurrence	13(21.3%)	19(21.1%)	
Dead	16 (26.2%)	27 (30.0%)	
Time to mortality	6(37.5%)	5(18.5%)	**0.095**
>1year after operation	6(37.5%)	5(18.5%)	
≤1year after operation	10(62.5%)	22(81.5%)	

5. Survival

The overall and disease-free survival curves are shown in Figure 1a and 1b. The median overall survival of the elderly and younger groups was 108.0 (0~119) months and 109.7 (4~131) months, respectively. The overall survival rates after hepatectomy at 1, 3 and 5 years was 86.5%, 75.1%, and 62.3%, respectively, in the elderly group and 94.4%, 75.1%, and 69.1%, respectively, in the younger group. The median disease-free survival of the elderly and younger groups was 31.7 (1~96) and 49.8 (3~100) months, respectively. The disease-free survival rate after hepatectomy at 1, 3, and 5 years was 78.6%, 51.7%, and 48.0% in the elderly group, respectively, and 75.5%, 57.5%, and 45.6% in the younger group, respectively. The overall and disease-free survival rates after hepatic resection did not differ significantly between the elderly and younger groups(Fig 1-A,B).

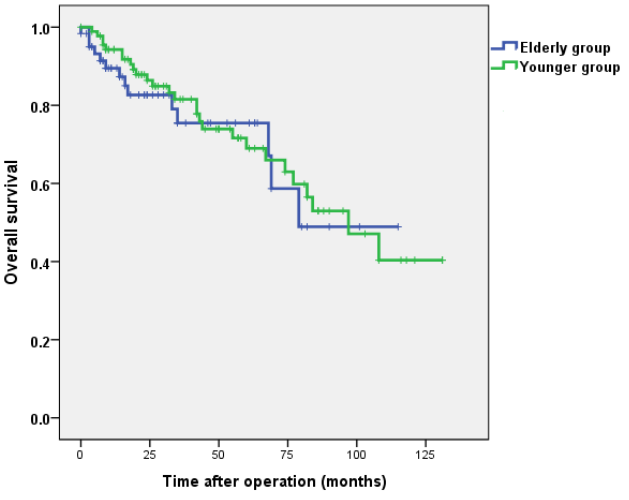

Figure 1(A). Overall survival (p=0.485)

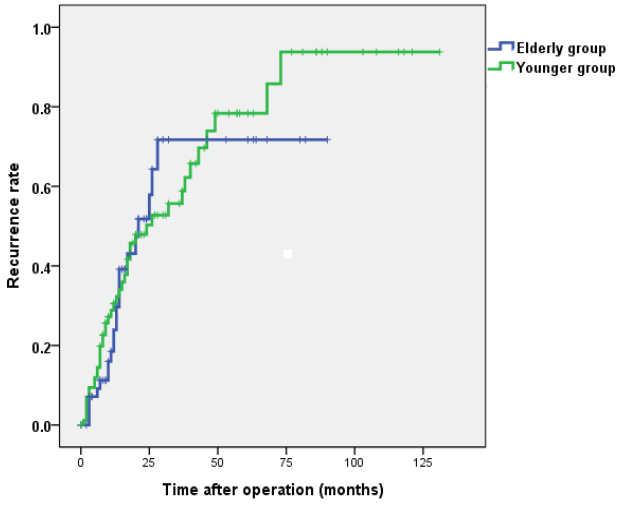

Figure 1(B). Disease free survival (p=0.825)

6. Prognostic factors of the survival

In the univariate Cox regression analysis of the all the HCC patients, age was not a significant prognostic factor. However, the variables that were associated with survival included postoperative complications, tumor number, microvascular invasion, and TNM stage. In the multivariate analysis of the HCC patients, only postoperative complications emerged as an independent predictor of overall survival (Table 5).

Table.5. Univariate and multivariate analyses associated with overall and disease-free survival after hepatic resection in HCC patients .

	Overall survival			Disease-free survival		
Variables	**Univariate P value**	**Multivariate P value**	**Relative hazard (95% CI)**	**Univariate P value**	**Multivariate P value**	**Relative hazard (95% CI)**
Age	0.485	NS		0.609	NS	
Postoperative complications	0.001	0.000	0.332 (0.202~ 0.547)	0.288	NS	
Satellite nodules	0.025	NS		0.050	NS	
Microvascular invasion	0.016	NS		0.064	NS	
pTNM stage	0.010	NS		0.024	NS	

IV. DISCUSSION

There are various kinds of treatment methods for HCC. Local therapies such as transarterial chemoembolization (TACE) and radiofrequency ablation (RFA) have widely been used as non-surgical treatment modalities for HCC. However, hepatic resection is the primary treatment method for HCC patients in whom hepatic resection is possible.[16] Hepatic resection is an increasing treatment strategy for elderly HCC patients, similar to the strategy for younger HCC patients. Advanced surgical techniques and perioperative management have reduced age-related contraindications to liver surgery. Recently in Korea through the advantages in preoperative tests, surgical techniques and through the improvement of postoperative management, hepatic resection mortality has decreased to less than 1-3% and the 5-year survival rate has increased by 50% or more[24]. With modern medical technology developments and improved quality of life, the average life expectancy has increased, while the size of the elderly population is also increasing. Therefore, older aged patients are increasingly more prevalent amongst HCC patients.[6] With increased HCC screening of high-risk populations, the population of younger HCC patients has increased, too.[7-10] Age of the elderly is regarded as an important risk factor when considering surgical treatment due to the high incidence of postoperative morbidity. The age of the patient at the time of diagnosis of some types of cancer can also be a prognostic value. For example, papillary thyroid and

bladder cancer show good survival outcomes in young patients. However, breast and gastric cancers show poor survival outcomes in young patients.[25-28] There are still some controversies regarding whether age influences the prognosis of HCC patients. Several studies have reported a poorer prognosis for younger patients compared to elderly patients. However, the opposite has been reported or no difference in the outcome between the two groups has been previously found. [7-15]Therefore, in this study, we evaluated only the two age groups who underwent curative liver resection for HCC, particularly patients in the elderly group (≥70 years of age) versus the young group (≤40 years of age). Some studies have defined young HCC patients as those from 15 to 50 years old. These varying ages may provide an explanation for the differences reported in the prognosis for young HCC patients. The U.S. guidelines for management of HCC suggest that screening of Asian males begin at 40 years of age[23]. Therefore, we defined young patients as those below this age guideline. The determination of the cut-off age for elderly HCC patients has also varied in the literature.[29-32] Zoli et al. reported that portal blood velocity and flow were significantly decreased in older patients (>70 years old)[22]. The age at which a person becomes elderly depends on social, environmental, and individual factors. In textbooks, elderly patients are often defined as those over 70 years old. Therefore, we defined elderly patients over those 70 years old or more because thereafter there is a rapid decrease in liver mass and portal blood flow.

In our study here, in both of the two groups, men were more susceptible to HCC than women, with a men to women ratio of 3.6:1 in the elderly group and 5.0:1 in the younger group. The proportion of female patients in elderly group was higher than in the younger group. Mohamed et al. have reported that in almost all countries males have a higher rate of HCC incidence than females.[33]

Younger patients showed a higher positive rate for hepatitis B (92.2% of the younger group versus 57.4% of the elderly group), and elderly patients showed a higher positive rate for hepatitis C (2.2% of the younger group and 18.0% of the elderly group). Although HBV was the main cause of HCC in both, HCV and non-B non-C etiology was significantly more common in the elderly group than the younger group. In Chinese and black African populations, hepatitis B virus infection accounts for up to 80% of HCC cases, and the age at which HCC is diagnosed is lower than in hepatitis C-endemic areas.[33] HBV is the most prevalent risk factor for HCC in Korea. About 65-70% of HCC patients are HBsAg positive, and most HBV positive patients acquire HBV vertically.[4] HCC risk in those with chronic HBV infection appears to increase the severity of liver disease. Since almost all of the young patients were infected at birth, HBV cirrhosis develops earlier than other causes of HCC. HCV is the most important risk factor for HCC in Western Europe, North America, and Japan[34]. HCV-infected HCC patients are older than HBV-infected HCC patients because HCV infection is acquired usually in

adult life. HCC development has been shown to occur decades after initial infection.

In agreement with previous reports[35,36], our study showed a higher rate of comorbidity (such as cardiovascular, pulmonary or renal disease, diabetes mellitus, hypertension, etc.) in the elderly group. However, in the younger group, only two patients had a preoperative comorbidity. Regarding postoperative short-term outcomes, the overall complication rate was 27.9% and 14.4% in elderly group and younger group, respectively, with hepatic problems (for example, ascites, pleural effusion, bile leakage, and postoperative bleeding) and general problems (for example, postoperative wound seroma, and psychiatric problems). The concomitance of medical disease in elderly patients could influence postoperative complications. In the multivariate analyses, postoperative complication was the only independent prognostic factor related to overall survival. Making a cautious decision about appropriate patient selection for hepatic resection and maximal preservation of remnant liver is the most important matter in the elderly group. Surgical technique refinement should be advanced to prevent postoperative complications. In this study there was one case of hospital mortality in the elderly group. Huang et al. reported that liver function preservation is one independent predictor of hospital mortality[37]. Postoperative liver failure is an important cause of death after hepatic resection. Precise assessment of hepatic function is one of the most important issues in hepatic resection. After

exhaustive evaluation of the preoperative general condition and assessment of hepatic reserve, appropriate patients can be selected and such selection may decrease postoperative complications and mortality.

Our data showed that the mean $ICGR_{15}$ was higher in the elderly group than in the younger group. Bae et al. reported that $ICGR_{15}$, tumor multiplicity, and TNM stage are independent prognostic factors for overall survival.[38] However, in Bae et al's study, $ICGR_{15}$ was not a prognostic factor of survival outcome. It is possible that hepatectomy was performed only on patients with well-preserved liver function and that the overall intraoperative parameters and tumor pathologic characteristics of both groups were not different.

Our study showed similar long-term prognoses in elderly and younger patients with HCC after hepatectomy. Postoperative recurrence of HCC was the most important factor affecting the survival of patients who underwent hepatic resection. Kim et al. reported that HBeAg positivity and recurrence was a significant factor for the overall survival rate after curative hepatectomy of HCC patients[39]. In our study, there were no significant differences in recurrence of HCC between the two groups and the recurrence rate within a year after operation was similar for the two groups. However, about half of the recurrent events were diagnosed within a year. Therefore more frequent follow-ups of patients in the early postoperative period are suggested. Most of the patients with recurrent HCC underwent palliative treatments like TACE, RFA, and systemic chemotherapy because of low functional reserve of the

remnant liver. Intrahepatic recurrence was the most common site in the two groups. Six patients underwent a repeated hepatectomy in this study. Sugimachi et al. suggested that repeated hepatectomy is the most effective treatment for recurrent HCC.[40] Even for elderly patients with recurrent HCC, a repeated hepatectomy was also recommended to achieve better survival if the tumors were resectable.[35]

Some studies have shown a similar long-term survival in the elderly and the younger patients with HCC. [14,20,41] In this study, there was also no difference in the overall survival and the disease- free survival rate. However, there are some differences between our study. We compared the long-term outcome of the elderly and young HCC patients who underwent curative hepatic resection. These results suggested that age was not an independent prognostic factor in HCC patients after curative hepatic resection. However, the importance of age in patients selection for surgery should be considered carefully.

V. CONCLUSION

In conclusion, postoperative outcomes of curative resection of HCC were similar in elderly and young patients, even though elderly patients had a higher incidence of preoperative comorbidities and postoperative complications. Improvements in operative safety have also allowed hepatectomy for HCC to be performed in elderly patients. Age itself should not be a contraindication to hepatic resection, but it suggests that a more stringent selection of elderly patients should be used when considering surgery.

REFERENCES

1. HB E-s. Hepatocellular carcinoma : an epidemiologic view. J Clin Gastroenterol 2002;35:72-8.
2. Parkin D. Global cancer statistics in the year 2000. Lancet Oncol 2001;2:533-43.
3. Shiratori Y, Yoshida H, Omata M. Different clinicopathological features of hepatocellular carcinoma in relation to causative agents. J Gastroenterol 2001;36(2):73-8.
4. Kwon SY, Lee CH. Epidemiology and prevention of hepatitis B virus infection. Korean J Hepatol 2011;17(2):87-95.
5. The Korea Central Cancer Registry, National Cancer Center. Annual report of cancer statistics in Korea in 2008, Ministry of Health and Welfare, 2010.
6. Dohmen K, Shirahama M, Shigematsu H, Irie K, Ishibashi H. Optimal treatment strategy for elderly patients with hepatocellular carcinoma. J Gastroenterol Hepatol 2004;19(8):859-65.
7. Cho S, Yoon J, Hwang S, Lee H. Do young hepatocellular carcinoma patients with relatively good liver function have poorer outcomes than elderly patients? J Gastroenterol Hepatol 2007;22(8):1226-31.
8. Chen C, Chang T, Cheng K, et al. Do young hepatocellular carcinoma patients have worse prognosis? The paradox of age as a prognostic factor in the survival of hepatocellular carcinoma patients. Liver int 2006;26(7):766-73.
9. Ng IO, Ng MM, Lai EC, Fan ST. Pathologic features and patient survival in hepatocellular carcinoma in relation to age. J Surg Oncol 1996;61(2):134-7.
10. Lam CM, Chan AO, Ho P, Ng IO, Lo CM, Liu CL, et al. Different

presentation of hepatitis B-related hepatocellular carcinoma in a cohort of 1863 young and old patients - implications for screening. Aliment Pharmacol Ther 2004;19(7):771-7.

11. Aramaki M, Kawano K, Sasaki A, Ohno T, Tahara K, Kai S, et al. Hepatocellular carcinoma in young adults. Hepatogastroenterology 2005;52(66):1795-7.
12. Yamazaki Y, Kakizaki S, Sohara N, Sato K, Takagi H, Arai H, et al. Hepatocellular carcinoma in young adults: the clinical characteristics, prognosis, and findings of a patient survival analysis. Dig Dis Sci 2007;52(4):1103-7.
13. Chang P, Ong W, Lui H, Tan C. Is the prognosis of young patients with hepatocellular carcinoma poorer than the prognosis of older patients? A comparative analysis of clinical characteristics, prognostic features, and survival outcome. J Gastroenterol 2008;43(11):881-8.
14. Kaibori M, Matsui K, Ishizaki M, Saito T, Kitade H, Matsui Y, et al. Hepatic resection for hepatocellular carcinoma in the elderly. J Surg Oncol 2009;99(3):154-60.
15. Yamamoto K, Takenaka K, Matsumata T, Shimada M, Itasaka H, Shirabe K, et al. Right hepatic lobectomy in elderly patients with hepatocellular carcinoma. Hepatogastroenterology 1997;44(14):514-8.
16. Huang J, Li B, Chen G, Li JQ, Zhang YQ, Li GH, et al. Long-term outcomes and prognostic factors of elderly patients with hepatocellular carcinoma undergoing hepatectomy. J Gastrointest Surg 2009;13(9):1627-35.
17. Facciuto ME, Koneru B, Rocca JP, Wolf DC, Kim-Schluger L, Visintainer P, et al. Surgical treatment of hepatocellular carcinoma beyond Milan criteria. Results of liver resection, salvage transplantation, and primary liver transplantation. Ann Surg Oncol 2008;15(5):1383-91.

18. Lui WY, Chau GY, Wu CW, King KL. Surgical resection of hepatocellular carcinoma in elderly cirrhotic patients. Hepatogastroenterology 1999;46(26):640-5.
19. Kudo M, Okanoue T. Management of hepatocellular carcinoma in Japan: consensus-based clinical practice manual proposed by the Japan Society of Hepatology. Oncology 2007;72 Suppl 1:2-15.
20. Nanashima A, Abo T, Nonaka T, Fukuoka H, Kidaka S, Takeshita H, et al. Prognosis of patients with hepatocellular carcinoma after hepatic resection: are elderly patients suitable for surgery? J Surg Oncol 2011;104(3):284-91.
21. Takeishi K, Shirabe K, Muto J, Toshima T, Taketomi A, Maehara Y. Clinicopathological features and outcomes of young patients with hepatocellular carcinoma after hepatectomy. World J Surg 2011;35(5):1063-71.
22. Zoli M, Iervese T, Abbati S, Bianchi GP, Marchesini G, Pisi E. Portal blood velocity and flow in aging man. Gerontology 1989;35(2-3):61-5.
23. Bruix J, Sherman M. Management of hepatocellular carcinoma. Hepatology 2005;42(5):1208-36.
24. Kim KS. Current status of hepatic surgery in Korea. Korean J Hepatol Dec 2009;15 Suppl 6:S60-4.
25. Adami HO, Malker B, Holmberg L, Persson I, Stone B. The relation between survival and age at diagnosis in breast cancer. N Engl J Med 1986;315(9):559-63.
26. Wan J, Grossman HB. Bladder carcinoma in patients age 40 years or younger. Cancer 1989;64(1):178-81.
27. Shaha AR, Shah JP, Loree TR. Risk group stratification and prognostic factors in papillary carcinoma of thyroid. Ann Surg Oncol 1996;3(6):534-8.

28. Katai H, Sasako M, Sano T, Maruyama K. Gastric carcinoma in young adults. Japanese J Clin Oncol 1996;26(3):139-43.
29. Jing Lin X, Sharma D, Bing Hui Y, Bo-Heng Z, Zeng-Chen M, Zhi-Quan W, et al. Analysis of the clinicopathological features of hepatocellular carcinoma in elderly patients. J Nepal Med Assoc 2008;47(171):132-5.
30. Saneto H, Kobayashi M, Kawamura Y, et al. Clinicopathological features, background liver disease, and survival analysis of HCV-positive patients with hepatocellular carcinoma: differences between young and elderly patients. J Gastroenterol 2008;43(12):975-81.
31. Su CW, Lei HJ, Chau GY, Hung HH, Wu JC, Hsia CY, et al. The Effect of Age on the Long-term Prognosis of Patients With Hepatocellular Carcinoma After Resection Surgery: A Propensity Score Matching Analysis. Arch Surg 2012;147(2):137-44.
32. Hanazaki K, Kajikawa S, Adachi W, Amano J. Hepatocellular carcinoma in the elderly: result of surgical management. The American J Gastroenterol 2000;95(4):1109-10.
33. Shariff MI, Cox IJ, Gomaa AI, Khan SA, Gedroyc W, Taylor Robinson SD. Hepatocellular carcinoma: current trends in worldwide epidemiology, risk factors, diagnosis and therapeutics. Expert Rev Gastroenterol Hepatol 2009;3(4):353-67.
34. Shepard CW, Finelli L, Alter MJ. Global epidemiology of hepatitis C virus infection. Lancet Infect Dis 2005;5(9):558-67.
35. Tsujita E, Utsunomiya T, Ohta M, et al. Outcome of repeat hepatectomy in patients with hepatocellular carcinoma aged 75 years and older. Surgery 2010;147(5):696-703.
36. Aldrighetti L, Arru M, Catena M, Finazzi R, Ferla G. Liver resections in over-75-year-old patients: surgical hazard or current practice? J

Surg Oncol 2006;93(3):186-93.

37. Huang Z, Xu L, Yang T, et al. Hepatic resection: an analysis of the impact of operative and perioperative factors on morbidity and mortality rates in 2008 consecutive hepatectomy cases. Chinese Med J 2009;122(19):2268-77.

38. Bae Ts, Kim SB, Park SH, Choi DW. Outcome of Hepatic Resection for Hepatocellular Carcinoma Patients. J Korean Surg Soc 2003;64(6):480-6.

39. Kim SH, Choi SB, Lee JG, et al. Prognostic factors and 10-year survival in patients with hepatocellular carcinoma after curative hepatectomy. J Gastroint Surg 2011;15(4):598-607.

40. Sugimachi K, Maehara S, Tanaka S, Shimada M. Repeat hepatectomy is the most useful treatment for recurrent hepatocellular carcinoma. J Hepatobiliary Pancreat Surg 2001;8(5):410-6.

41. Lee SH, Choi HC, Jeong S, et al. Hepatocellular carcinoma in older adults: clinical features, treatments, and survival. J Am Geriatr Soc 2011;59(2):241-50.

ABSTRACT

젊은 연령 및 고령 환자에서 발생한 원발성 간암의 간절제술후 성적비교 연구

<지도교수 김 경 식>

연세대학교 대학원 의학과

이 초 록

목적 : 본 연구의 목적은 고령과 젊은연령의 간암환자에서 간절제술후의 성적을 비교함에 있다.

방법 : 2000년부터 2010년까지 본원에서 간암으로 진단받고 간절제수술을 받은 70세 이상의 고령환자 61명과 40세 이하의 젊은연령 환자 90명의 임상병리학적 결과, 치료후 성적등을 비교하였다.

결과 : 고령환자군이 젊은환자군에 비해서 C형간염 또는 B형이나 C형이 아닌간염의 비율이 높았고, $ICGR_{15}$의 수치가 높았다. 또한 수술전 다른 내과적 질병을 동반한 경우가 많았고, 수술후 합병증의 비율도 높았다. 그러나 두환자군간에 수술중 결과나 수술후 조직학적 결과에서는 통계적으로 유의한 차이가 없었다. 재발율,

생존율도 두군간에 차이가 없었다. 수술후 합병증여부가 전체생존율에 영향을 미칠 수 있는 예후인자였다.

결론 : 본 연구의 결과 연령자체는 간암환자의 간절제 수술직후의 결과나 장기간의 예후에 영향을 미치지는 않는것으로 나타났다. 따라서 고령이나 젊은연령의 간암환자에게 있어서 간절제술은 안전하고 효과적인 치료방법이라고 할 수 있을 것이다.

핵심되는 말 : 간세포암, 연령, 간절제