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年々進歩する消化器領域の最新情報と治療方針を隔年ごとに整理し，簡潔にまとめた最新版．巻頭トピックスでは，「B型慢性肝炎に対する新しい抗ウイルス薬」「小腸内視鏡治療の進歩」ほか，最近注目の話題について解説．各論として，疾患ごとに診断確定後の基本的治療方針，処方の実際から生活指導までを詳述．各疾患の治療に関する最新トピックスも紹介し，臨床現場で常に手元において確認できる一冊．

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Hepatectomy for Hepatocellular Carcinoma in Elderly Patients Aged 75 Years or More

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Abstract

Background The aim of this study was to clarify the characteristics of elderly hepatocellular carcinoma (HCC) patients aged 75 years or more who underwent hepatectomy and to clarify whether elderly patients with HCC benefit from hepatectomy.

Methods Between January 1990 and December 2006, 570 patients underwent curative hepatectomy for HCC. Elderly patients were defined as those aged 75 years or more. Clinicopathological data and outcomes after hepatectomy for 64 elderly and 502 younger patients were prospectively collected and compared.

Results The proportion of elderly patients with chronic viral infection was less than that of younger patients ($p<0.001$). Cirrhotic patients in the elderly group were less than those in the younger group ($p=0.03$). The elderly patients had better liver function than did the younger patients ($p=0.007$) but had more advanced HCC with microscopic vascular invasion than did the younger patients ($p=0.04$). There was no operative mortality in the elderly patients and there was no significant difference in postoperative complication rates and long-term survival after hepatectomy between the two groups.

Conclusions Hepatectomy for elderly patients with resectable HCC is safe and feasible. Selected elderly patients with HCC might benefit from hepatectomy.

Keywords Hepatocellular carcinoma · Hepatectomy · Elderly

Introduction

The average life expectancy at birth has been increasing in many countries. Japan had the highest life expectancy worldwide in 2006. The average life expectancy in Japan is the longest in the world, life expectancy at birth for males being 79 years and that for females being 86 years.[1] The number of patients with hepatocellular carcinoma (HCC) has been increasing,[2] and elderly HCC patients have been getting older.[3] With the increase in average lifetime, the age at which a person is considered elderly is rising. Clarification of the optimal treatment strategy for extremely elderly patients with HCC has thus become an urgent necessity. With advances in surgical treatment for HCC, hepatectomy for elderly HCC patients has become safer. There have been many reports on hepatectomies for elderly HCC patients.[4–11] However, most studies were for patients aged 70 years or more. There have been few reports on the safety and feasibility of hepatectomy for HCC patients aged 75 years or more and whether HCC patients aged 75 years or more benefit from hepatectomy. The aim of this study was to identify the characteristics of elderly HCC patients aged 75 years or more who underwent hepatectomy in comparison with those of younger HCC patients and to clarify whether HCC patients aged 75 years or more benefit from hepatectomy.

This work originated from the Department of Surgery, Division of Frontier Medical Science, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan.

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Methods

Patients' data were collected prospectively from 1986 in our program. Between January 1990 and December 2006, 570 consecutive HCC patients underwent curative hepatectomy in Hiroshima University Hospital. Curative hepatectomy was defined as the removal of all recognizable tumors. Data for four patients whose outcomes during the follow-up period were uncertain were excluded from the analysis. Data for the remaining 566 HCC patients were included in the analysis.

The patients included 429 men (76%) and 137 women (24%). The mean age at operation was 63.5 years (range, 23 to 86 years). In this study, elderly patients were defined as those aged 75 years or more. Sixty-four patients were in the elderly group and 502 patients were younger than 75 years of age (younger group). The mean age of patients in the elderly group was 77.5±2.4 years (range, 75 to 86 years) and that of the younger patients was 61.7±8.7 years (range, 23 to 74 years).

Only elderly patients whose general condition fulfilled the American Society of Anesthesiologists' Physical Status Score class I or class II were considered for hepatectomy.[12] The indication and procedure for hepatectomy were the same as those described previously.[13,14] Briefly, Child–Pugh class C was regarded as contraindication for hepatectomy. The selection of type of hepatectomy was made on the basis of liver function and tumor extent. Liver function was assessed by Child–Pugh classification and the indocyanine green retention rate at 15 min (ICGR15). In patients without ascites and with a normal bilirubin level, ICGR15 became the main determinant of resectability. For example, right hemihepatectomy could be tolerated if ICGR15 was in the normal range. One third of the liver parenchyma could be resected for patients with ICGR15 of 10% to 19%, segmentectomy was possible with ICGR15 of 20% to 29%, and limited resection was possible with ICGR15 of 30% or more.[15] Hepatectomy was indicated when it was judged by preoperative imaging studies that all tumors could be resected with sufficient hepatic functional reserve. However, when the HCC tumors were hypovascular, suggesting that the tumors were well-differentiated HCC, and were 2 cm or less in size and the number of tumors was three or less, percutaneous ablation therapies were preferable despite hepatectomy also being feasible, depending on the tumor location in the liver, irrespective of the patient's age.[16] There was no difference between the indication for hepatectomy for younger patients and that for hepatectomy for elderly patients throughout the period of the present study. Resections of two segments or more according to Couinaud's segmentation were defined as major hepatectomy. For patients undergoing multiple resections, the most important procedure was considered to be the main type of hepatectomy. There is a tendency to select limited resection in cases of severe cirrhosis or tumors located on the surface of the liver.

Clinicopathological findings were recorded according to the criteria of the Liver Cancer Study Group in Japan.[17] Liver cirrhosis was confirmed by histological examination of a resected specimen. A modification of the Clavien classification was used to grade the severity of postoperative complications.[18] Grade I complications were defined as deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions. This grade also includes wound infections opened at the bedside. Grade II complications were defined as those requiring pharmacological treatments with drugs. Blood transfusions and total parenteral nutrition are also included. Grade III complications were defined as those requiring surgical, endoscopic, or radiological intervention. Grade IV complications were life-threatening complications requiring intermediate care/intensive care unit management. Grade V complications were those that resulted in death of a patient. Operative mortality was defined as death within 30 days after surgery. In-hospital mortality was defined as death occurring within the period of hospitalization.

Follow-up evaluation after the operation consisted of clinical physical examinations, blood chemistry tests, and measurements of levels of tumor markers, including alpha-fetoprotein and des-gamma-carboxy prothrombin, every month for 2 years. After 2 years, the patients were assessed every 3 months. Patients were examined by abdominal ultrasonography every 3 months and by computed tomography every 6 months during the follow-up periods. Our follow-up protocol included evaluation by hepatologists of not only cancer recurrence but also progress of chronic hepatitis or liver cirrhosis. When recurrence was indicated by any of these examinations, patients underwent hepatic angiography (Fig. 1). The patients were regularly followed up until June 30, 2007 and every patient was followed up for at least 6 months.

Statistical analyses were performed using the unpaired Student's t test and the chi-square test with Fisher's exact

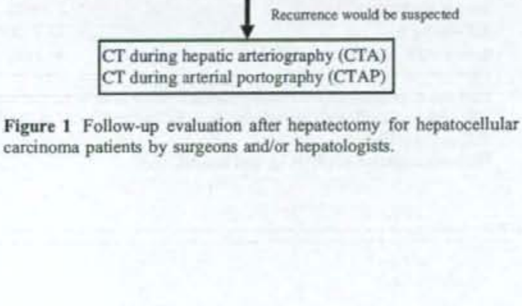

Figure 1 Follow-up evaluation after hepatectomy for hepatocellular carcinoma patients by surgeons and/or hepatologists.

test. Survival and disease-free survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test. Disease-free survival was calculated by considering any death or recurrence as an event. A p value of less than 0.05 was considered to be statistically significant. Statistical analysis was carried out using the software of StatView for Windows (Version 5.0; SAS Institute, Cary, NC, USA).

Results

The mean follow-up period for all survivors was 4.4± 3.4 years (range, 0.5 to 17.0 years). Operative mortality and in-hospital mortality rates in all patients were 0.4% (n=2) and 0.7% (n=4), respectively. Characteristics of patients in the two groups are shown in Table 1. One (2%) of the 64 patients in the elderly group had positive hepatitis B surface antigen (HBsAg), whereas 119 (24%) of the 502 patients in the younger group had positive HBsAg ($p<0.001$). The numbers of patients without either hepatitis B virus (HBV) or hepatitis C virus (HCV) infections in the elderly group and the younger group were 17 (27%) and 51 (10%), respectively ($p<0.001$). The incidence of cirrhosis in the elderly group was 31%, whereas that in the younger group was 52% ($p=0.03$). Preoperative laboratory tests showed that the elderly group had better liver function than did the younger group as assessed by prothrombin time (PT) ($p=0.007$), aspartate aminotransferase (AST) ($p=0.02$), and alanine aminotransferase (ALT) ($p<0.001$).

Tumor characteristics and intra- or postoperative results in both groups are shown in Table 2. Tumors in the elderly group tended to be larger than those in the younger group ($p=0.057$). The incidence of microscopic vascular invasion in the elderly group was significantly higher than that in the younger group ($p=0.04$). Major hepatectomies were performed more frequently in the elderly group than in the younger group ($p=0.008$). Blood loss during the operation, perioperative blood transfusion rate, operative mortality rate, in-hospital mortality rate, and postoperative complication rate were not significantly different between the two groups. The incidences of complications that occurred after hepatectomy according to grade were comparable. The 14 complications that occurred in the elderly group were categorized as grade I in seven patients, grade II in four patients, grade III in one patient, and grade IV in two patients.

Overall survival rates after hepatectomy in the elderly group at 3, 5, and 10 years were 77%, 58%, and 32%, respectively, whereas those in the younger group were 81%, 64%, and 33%, respectively (Fig. 2). Disease-free survival rates in the elderly group at 3, 5, and 10 years were 43%, 30%, and 0%, respectively, whereas those in the younger group were 46%, 28%, and 14%, respectively (Fig. 3). There were no significant differences between the two groups in overall survival rates and disease-free survival rates.

The patterns of cancer recurrence and the details of treatments for the recurrences in both groups are shown in Table 3. Thirty-three (49%) of the patients in the elderly group and 304 (61%) of the patients in younger group had HCC recurrences after hepatectomy. The patterns of

Table 1 Backgrounds in Both Groups

Characteristics	Group		p value
	Younger (n=502)	Elderly (n=64)	
Age at operation (years)	61.7±8.7	77.5±2.4	<0.001
Sex: male (%)	381 (76)	48 (75)	N.S.
HBsAg: positive (%)	119 (24)	1 (2)	<0.001
Anti-HCVAb: positive (%)	330 (66)	45 (70)	N.S.
Non-B and non-C (%)[a]	51 (10)	17 (27)	<0.001
Liver cirrhosis (%)	261 (52)	20 (31)	0.03
Child–Pugh grade A (%)	427 (85)	59 (92)	N.S.
Platelet count (/μL)	13.7±13.5	13.7±6.1	N.S.
Prothrombin time (%)	85±20	93±19	0.007
Total bilirubin (mg/dL)	0.8±0.3	0.8±0.3	N.S.
Aspartate aminotransferase (IU/L)	50±28	41±18	0.02
Alanine aminotransferase (IU/L)	52±33	39±22	<0.001
Serum albumin (g/dL)	3.8±0.5	3.7±0.5	N.S.
ICG-R15 (%)	17.7±9.6	18.7±10.8	N.S.
Serum AFP (ng/mL) >400 (%)	94 (19)	15 (23)	N.S.

Data are expressed as the means±standard deviations or as the number of patients (percentage of total patients)

HBsAg hepatitis B surface antigen, *Anti-HCVAb* anti-HCV antibody, *AFP* alpha-fetoprotein, *ICGR15* indocyanine green retention rate at 15 min, *N.S.* not significant

[a] Patients negative for HBsAg and anti-HCVAb

Table 2 Tumor Characteristics and Intra- or Postoperative Results in Both Groups

Tumor characteristics and results	Group		*p* value
	Younger (*n*=502)	Elderly (*n*=64)	
Mean tumor size (cm)[a]	3.3±2.2	3.9±2.3	0.057
Number of tumors: multiple (%)	155 (31)	12 (19)	N.S.
Tumor stage: I, II/III, IV	370/132	48/16	N.S.
Tumor differentiation: mod. or por. (%)	398 (85)	54 (89)	N.S.
Capsule formation: positive (%)	403 (81)	54 (84)	N.S.
Microscopic vascular invasion: positive (%)	145 (29)	27 (42)	0.04
Operative procedure: major hepatectomy (%)	79 (15)	19 (30)	0.008
Blood loss (mL)[a]	430±438	356±381	N.S.
Blood transfusion: yes (%)	27 (5)	5 (8)	N.S.
Operative mortality: yes (%)	2 (0.4)	0 (0)	N.S.
Hospital mortality: yes (%)	5 (1)	1 (2)	N.S.
Postoperative complications[b]: yes (%)	97 (19)	14 (22)	N.S.
Grade I	35 (7)	7 (11)	N.S.
Grade II	36 (7)	4 (6)	
Grade III	16 (3)	1 (2)	
Grade IV	8 (2)	2 (3)	
Grade V	2 (0.3)	0 (0)	

N.S. not significant, *mod.* moderately differentiated, *por.* poorly differentiated

[a] Values are presented as the means±standard deviations

[b] Postoperative complication was defined as any event satisfying the criteria advocated by Dindo et al.[17]

recurrence, the proportions of patients who could receive treatment for recurrence, and the modalities of treatments used were not different in the two groups.

The causes of death in both groups are shown in Table 4. There was no significant difference in the distribution of causes of death between the two groups. Deaths unrelated to cirrhosis or HCC in the elderly group included death from cardiovascular disease in five patients and death from malignant diseases other than HCC in two patients.

Discussion

The present study showed a difference in etiology of HCC in elderly patients and that in younger patients. The positive rate for HBsAg was significantly lower in the elderly group. The proportion of patients negative for HBsAg and anti-HCV antibody was clearly larger in the elderly group. These findings agree with the results of previous studies.[19–21] HBV-related chronic liver disease results from a vertical transmission during the perinatal period or a horizontal

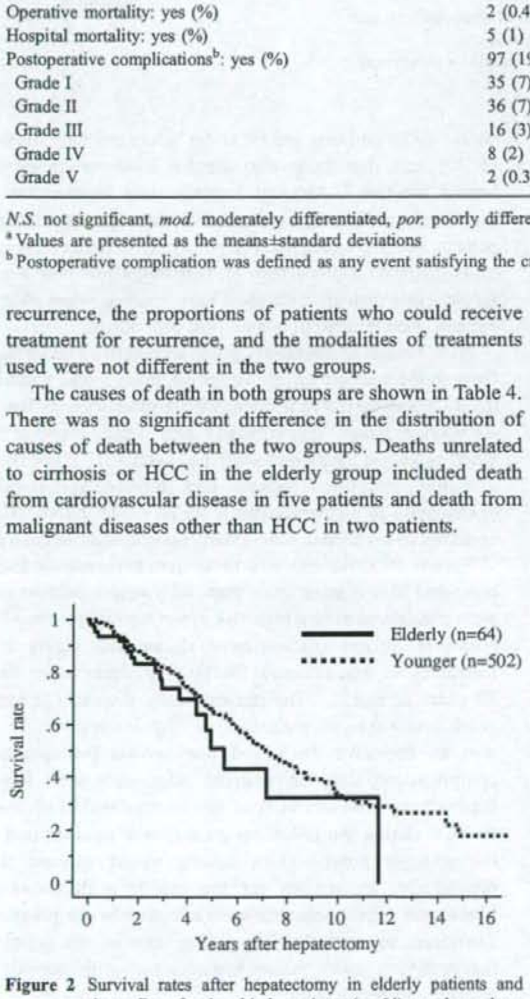

Figure 2 Survival rates after hepatectomy in elderly patients and younger patients. Data for the elderly patients (n=64) are shown by a *thick line* and data for the younger patients (n=502) are shown by a *dotted line*. There was no significant difference between the two groups in survival rate.

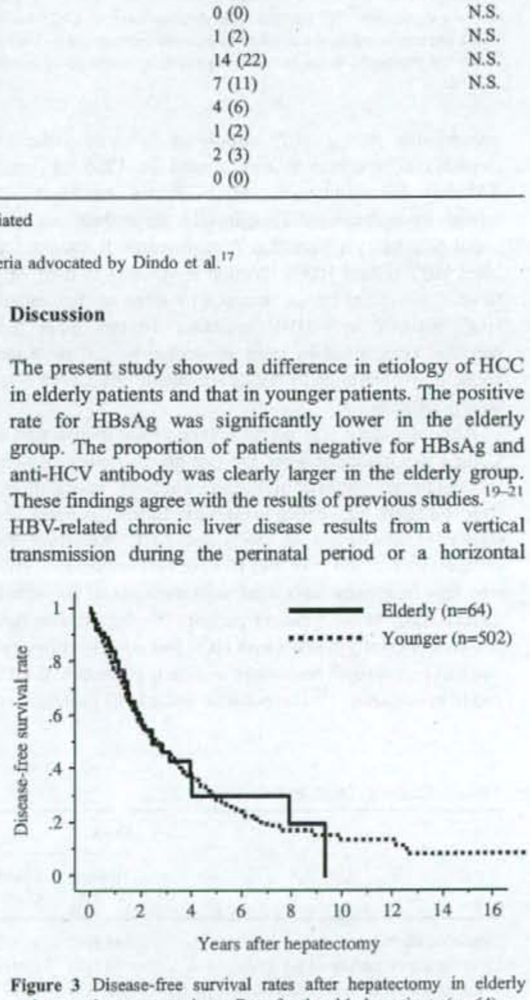

Figure 3 Disease-free survival rates after hepatectomy in elderly patients and younger patients. Data for the elderly patients (n=64) are shown by a *thick line* and data for the younger patients (n=502) are shown by a *dotted line*. There was no significant difference between the two groups in disease-free survival rate.

Table 3 Cancer Recurrence After Hepatectomy and Treatments for Recurrent HCC

		Younger (n=502)	Elderly (n=64)	p value
Cancer recurrence[a]: yes		304 (61)	33 (49)	N.S
Pattern of recurrence[b]	Remnant liver	256 (84)	25 (76)	N.S.
	Distant organ	12 (4)	4 (12)	
	Remnant liver+distant organ	36 (12)	4 (12)	
Treatments for recurrence[b]: yes		257 (85)	25 (76)	N.S.
Main treatment for recurrence[b]	Repeat hepatectomy	77 (30)	4 (16)	N.S.
	Liver transplantation	9 (4)	0	
	PAT	85 (33)	12 (48)	
	TACE	72 (28)	9 (36)	
	Others	14 (5)	0	

N.S. not significant, *PAT* percutaneous ablation therapy, *TACE* transarterial chemoembolization

[a] Data are expressed as the number of patients (percentage of total patients)

[b] Data are expressed as the number of patients (percentage of patients who had a recurrence)

transmission during early childhood in most patients.[22] Hepatitis B vaccination was started in 1986 in Japan. Although the numbers of HBV-infected newborns and infants have decreased dramatically since then, no adult population has yet benefited from hepatitis B vaccination. Most HBV-related HCCs develop in patients in their early fifties. This might be the reason why there are few elderly HCC patients with HBV infection. Factors other than hepatitis virus infection such as alcohol or genetic disturbance may contribute to the development of HCC in some elderly patients.

Although there was no difference in the distribution of Child–Pugh grades between the two groups, elderly patients showed higher values of prothrombin activity, indicating that liver function was better preserved. Elderly patients also showed lower levels of AST and ALT, indicating that inflammation of the liver was less active. Furthermore, HCC was less frequently associated with cirrhosis in the elderly patients than in the younger patients. Several studies have shown that elderly patients with HCC had good liver function and that only a small percentage of elderly patients with HCC had liver cirrhosis.[19,23] It is possible that a large proportion of patients with cirrhosis and HCC die before reaching the age of 70 years that those who survive have well-preserved hepatic function.[20] Although indications for hepatectomy in the elderly patients were similar to those in the younger patients in our program according not only to tumor stage but also to hepatic functional reserve, there might have been a bias for selecting patients with good liver function when elderly patients were referred to our surgical department.

HCC tumors in the elderly group tended to be larger than those in the younger group. Moreover, microscopic vascular invasion occurred more frequently in the elderly group than in the younger group. Approximately 30% of the patients in the elderly group in the present study had neither HBV nor HCV infection, and these patients had not received regular examination as high-risk patients for HCC. Therefore, HCC could not be detected in some elderly patients at an early stage.

Elderly HCC patients who underwent hepatectomy had a comorbid illness more often than did younger patients and were considered to be a high-risk group for hepatectomy.[4,24] However, recent studies have shown the safety and feasibility of hepatectomy for HCC patients older than 70 years of age.[8–10] The present study showed the same good results even for patients aged 75 years or more. There was no operative death and few serious postoperative complications even in patients who underwent major hepatectomy. The incidence of deaths unrelated to cirrhosis or HCC during the follow-up periods was equal to that in the younger group. These results might indicate that preoperative evaluations for the elderly with comorbid illness and patient selection were adequate in our program. Therefore, selected elderly patients have no disadvantage for receiving even major hepatectomy with regard to tolerance to hepatectomy.

The present study for the elderly (75 years of age or more) revealed that the overall 5-year survival rate and 5-year disease-free survival rate were 58% and 30%,

Table 4 Causes of Death in Both Groups

	Group	
	Younger (n=235)	Elderly (n=26)
Cancer death (%)	148 (63)	16 (62)
Liver failure or rupture of EV (%)	42 (18)	3 (12)
Death unrelated to liver cirrhosis or HCC (%)	39 (17)	7 (27)
Unknown causes (%)	4 (2)	0
Operative mortality (%)	2 (1)	0

EV esophageal varices, *HCC* hepatocellular carcinoma respectively, similar to the results of recent studies for elderly HCC patients (70 years of age or more). The prognosis of elderly HCC patients after hepatectomy was equal to that of younger HCC patients despite the fact that the elderly patients had more advanced HCC than did the younger patients and required major hepatectomy more frequently than did the younger patients. These disadvantages of the elderly group for prognosis after hepatectomy might be diminished by the better hepatic function of this group. In Japan, 75-year-old males and females have average life expectancies of 11.3 years and 15.0 years, respectively.[25] Selected elderly patients aged 75 years or more might benefit from hepatectomy by avoiding early death from HCC.

Recently, radiofrequency ablation (RFA) has been developed as a new alternative therapy for early-stage HCCs. Not only younger patients but also elderly patients with early-stage HCC might benefit from this modality, which is less invasive than hepatectomy. Our policy for the treatment of early-stage HCC has been that, when the HCC tumors were 2 cm or less in size and the number of tumors was three or less, percutaneous ablation therapies were indicative despite hepatectomy also being feasible, depending on the tumor location in the liver, irrespective of the patient's age. However, not only long-term outcomes of RFA for elderly patients with HCCs but also the safety and feasibility of RFA for the elderly remain unclear and should be confirmed by a prospective study.

Conclusion

HCC patients aged 75 years or more who underwent hepatectomy had better liver function but had more advanced tumors than did the younger HCC patients. However, hepatectomy for HCC patients with preserved liver function was feasible and safe, and the prognosis after hepatectomy for the elderly patients was comparable to that for the younger patients. Selected elderly patients with HCC might benefit from hepatectomy.

Conflict of interest None.

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Comparative study of the Japan Integrated Stage (JIS) and modified JIS score as a predictor of survival after hepatectomy for hepatocellular carcinoma

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Background. The purpose of the study was to compare the abilities of the JIS and modified JIS (m-JIS) scores to predict survival after hepatectomy for hepatocellular carcinoma (HCC). ***Methods.*** Data for patients who underwent hepatectomy for HCC at Hiroshima University Hospital between 1986 and 2006 were included. The overall survival and disease-free survival were calculated by the Kaplan-Meier method, and differences between groups were tested by the log-rank test. The statistics of the Akaike information criterion (AIC) were used to show the more appropriate model. ***Results.*** A total of 626 patients were included (male/female, 468/158; mean age, 63.4 ± 9.6 years; Child-Pugh class A/B, 524/102; liver damage grade A/B/C, 356/261/9). Mean survival and disease-free survival were 8.04 ± 0.39 and 4.69 ± 0.32 years, respectively. There was a significant difference in the overall survival rate between JIS scores 1 and 2, and 2 and 3 ($P < 0.05$), but not between scores 0 and 1, or 3 and 4 ($P > 0.05$). Except between m-JIS scores 0 and 1, there was excellent discriminatory ability in overall survival rate between other consecutive groups. Concerning disease-free survival, a significant difference was found only between JIS scores 1 and 2. However, the disease-free survival rate could be well differentiated between m-JIS scores 1 and 2, and 3 and 4. The m-JIS score had a higher discriminatory ability, indicated by a linear trend analysis, and a higher homogeneity likelihood ratio, and lower AIC statistics, than the original JIS score in predicting both overall and disease-free survival. ***Conclusions.*** The modified-JIS scoring system using liver damage grade is better than the original JIS scoring system in predicting survival after hepatectomy for HCC in Japan.

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Key words: hepatocellular carcinoma, TNM stage, JIS score, Child-Pugh classification, liver damage grade

Introduction

Although some new therapeutic modalities have been developed and proven to be effective in the treatment of hepatocellular carcinoma (HCC), hepatectomy remains the main radical treatment method.[1] The outcome of hepatectomy has been greatly improved in recent years by the use of more rational selection criteria, better surveillance, and improved surgical techniques. In Japan, the 5-year survival rate of patients with HCC who underwent hepatectomy increased from less than 40% in the 1980s to more than 50% in the 1990s.[2]

There are now several staging systems for hepatocellular carcinoma, and those taking into account both liver function and tumor progression are considered to have better predictive value. For the past 30 years, the Child-Pugh classification system has been widely used to assess a patient's liver functional reserve, owing to its simplicity of use, the ease with which its parameters can be measured, and its effectiveness in providing prognostic information. It has also been incorporated into some staging systems, such as the Cancer of Liver Italian Program (CLIP)[3] and the Barcelona Clinic Liver Cancer (BCLC) staging system.[4] The JIS scoring system was first proposed by Kudo et al. in 2003 and was soon accepted by many institutions in Japan because of its simplicity and validity.[5,6]

However, the JIS scoring system was developed on the basis of all HCC patients. The liver function of most candidates for hepatectomy was Child-Pugh A, or even Child-Pugh B, without encephalopathy, ascites, or significant hyperbilirubinemia. Therefore, surgeons do not consider it much superior to TNM stage for predicting the survival of patients who undergo hepatic resection for HCC.

The liver damage grade classification proposed by the Liver Cancer Study Group of Japan (LSCGJ) has been shown to be better for evaluating the liver functional reserve, especially for surgical candidates.[7] The m-JIS scoring system, which takes into account the liver damage grade for HCC, was proposed by Nanashima et al.[8] and has been shown to be a useful predictor of prognosis for HCC patients receiving hepatic resection.[9] However, the number of cases was relatively small. The purpose of this study was to determine the relative abilities of JIS and m-JIS to predict both overall survival and disease-free survival after hepatectomy for HCC performed in a single institute.

Materials and methods

Patients

Data for 806 consecutive patients who underwent hepatic resection for HCC by a single team for the first time between January 1986 and December 2006 were collected at the Department of Surgery, Division of Frontier Medical Science, Programs for Biomedical Research, Graduate School of Biomedical Science at Hiroshima University. Patient data were collected prospectively from 1986 in our program. Data for three patients who underwent emergent operations due to rupture of the tumors were not included in the analysis because of the incompleteness of their data. In addition, data for 177 patients with remnant tumors after hepatectomy were excluded. TNM stage, Child-Pugh classification, and liver damage grade prior to surgical treatment were obtained according to the criteria shown in Tables 1–3.[10] TNM stage was assessed by preoperative image examination and confirmed by clinical findings during the operation and examination of resected specimens.

The indication and procedure for hepatectomy and follow-up protocol was the same as previously described.[11,12] Briefly, Child-Pugh class C was regarded as a contraindication for hepatectomy. The selection of type of hepatectomy was made on the basis of liver function and tumor extent. Liver function was assessed by Child-Pugh classification and the indocyanine green retention rate at 15 min (ICGR15). In patients without ascites and with a normal bilirubin level, ICGR15 became the main determinant of resectability. For example, right hemihepatectomy could be tolerated if ICGR15 was in the normal range. One-third of the liver parenchyma could be resected for patients with ICGR15 of 10% to 19%, segmentectomy with ICGR15 of 20% to 29%, and limited resection with ICGR15 of 20% to 29%.[13] Hepatectomy was indicated when all tumors

Table 1. Definition and criteria of TNM stage for HCC according to LCSGJ

Factors	Factor score	Determination
T factors	T1	Fulfilling all three factors
1. Solitary tumor	T2	Fulfilling two factors
2. Maximum tumor size ≤2 cm	T3	Fulfilling one factor
3. No vessel invasion (portal vein, hepatic vein or bile duct)	T4	Fulfilling none of the factors
N factor	N0	Absent
Lymph node metastasis	N1	Present
M factor	M0	Absent
Distant metastasis	M1	Present
Stage I		T1 N0 M0
Stage II		T2 N0 M0
Stage III		T3 N0 M0
Stage IV-A		T4 N0 M0 or T1–T4, N1M0
Stage IV-B		T1-4, N0 or 1, M1

LCSGJ, Liver Cancer Study Group of Japan; HCC, hepatocellular carcinoma

Table 2. Definition and criteria of Child-Pugh classification

Points	A	B	C
Encephalopathy	None	Minimal	Advanced (coma)
Ascites	Absent	Controlled	Refractory
Serum bilirubin (mg/dl)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dl)	>3.5	2.8–3.5	<2.8
Prothrombin activity (%)	>70	40–70	<40

Total scores: 5–6, Child-Pugh class A; 7–9, Child-Pugh class B; 10–15, Child-Pugh class C

Table 3. Definition and criteria of liver damage grade classification according to LCSGJ

Grade	A	B	C
Serum bilirubin (mg/dl)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dl)	>3.5	3.0–3.5	<3.0
Prothrombin activity (%)	>80	50–80	<50
ICGR15 (%)	<15	15–40	>40
Ascites	Absent	Controlled	Refractory

If more than one grade is applicable to the patient, the highest grade with most involved variables should be recorded
ICGR15, indocyanine green retention rate at 15 min

Table 4. Definition and criteria of JIS score[6]

Child-Pugh class	TNM stage	Value assigned
A	I	0
B	II	1
C	III	2
	IV	3

JIS score = (Child-Pugh class) + (TNM stage)
JIS, Japan Integrated Stage

Table 5. Definition and criteria of m-JIS score[8]

Liver damage grade	TNM stage	Value assigned
A	I	0
B	II	1
C	III	2
	IV	3

m-JIS score = (Liver damage grade) + (TNM stage)
m-JIS, modified Japan Integrated Stage

could be resected within the hepatic functional reserve. The operative procedures included limited resection in 359 (57.3%) cases, segmentectomy in 149 (23.8%), sectionectomy in 71 (11.3%), hemihepatectomy in 40 (6.4%), and extended hemihepatectomy in 7 (1.1%). For patients undergoing multiple resections, the most important procedure was considered to be the main type of hepatectomy. There is a tendency to select limited resection in cases of severe cirrhosis or tumors located on the surface of the liver. The patients were regularly followed-up until 30 June 2007, and every patient was followed for at least 6 months.

The study conformed to the tenets of the Declaration of Helsinki of the World Medical Association and was approved by the Ethics Review Board of Hiroshima University Hospital.

Methods

Overall survival time and disease-free survival time were computed from the day of the operation to the most recent follow-up. Surviving patients and those who died from causes other than liver disease were censored. Patients receiving liver transplantation for postoperative liver failure were also censored on the day prior to the transplantation. The JIS score comprised the sum of points for the two variables of the Japanese TNM classification and Child-Pugh classification (Table 4).[6] Similarly, the m-JIS score is the sum of points for the Japanese TNM classification and liver damage grade (Table 5).[8]

Statistical analysis

Disease-free survival and overall survival were calculated according to the Kaplan-Meier method, and differences between groups were tested for significance using the log-rank test. The relation between the two indexes was analyzed by Pearson's correlation test. The Cox proportional hazard model was used to calculate the likelihood ratio (LR) χ^2 to determine homogeneity (small differences in survival among patients at the same stage within each system). The likelihood was also expressed as an Akaike information criterion (AIC) statistic. The AIC statistic was defined as AIC = $-2\log$ maximum likelihood + 2 × the number of parameters in the model. A smaller AIC value indicated a more desirable model for predicting outcome. The linear trend χ^2 was then used to measure the discriminatory ability of each staging system. A two-tailed *P* value of <0.05 was considered statistically significant. Statistical analysis was carried out by using SPSS version 13.0 (SPSS, Chicago, IL, USA) and SAS statistical software (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 626 patients were included in the analysis (468 men, 158 women; mean age, 63.4 ± 9.6 years; range 23–86 years). The profiles of the patients are shown in Table 6. Among the patients, 367 (58.6%) tested posi-

Table 6. Patient profiles

Variables	Patients in study (%)	Variables	Patients in study (%)
Sex		Recurrent site	
Male	468 (74.8)	Intrahepatic	290
Female	158 (25.2)	Extrahepatic	26
Age (years)	23–86	Intrahepatic and extrahepatic	43
Mean ± SD	63.4 ± 9.6	Child-Pugh classification	
Underlying liver disease		A	524 (83.7)
Hepatitis C	367 (58.6)	B	102 (16.3)
Hepatitis B	108 (17.3)	Liver damage grade	
Hepatitis B and C	17 (2.7)	A	356 (56.9)
Non-B and non-C	91 (14.5)	B	261 (41.7)
Undetermined (HCV or HBV)	53 (8.5)	C	9 (1.4)
Background liver abnormalities		TNM staging	
Chronic hepatitis	274 (43.8)	I	118 (18.8)
Liver cirrhosis	344 (55.0)	II	242 (38.7)
Normal range	8 (1.3)	III	195 (31.2)
Number of tumors		IV	71 (11.3)
single	457 (73.0)	JIS score	103 (16.5)
2	121 (19.3)	0	224 (35.8)
≥3	48 (7.7)	1	187 (29.9)
Tumor size (cm)		2	101 (16.1)
≤2.0	171 (27.3)	3	11 (1.8)
2.1–3.0	190 (30.4)	4	
3.1–5.0	175 (28.0)	Modified-JIS score	
>5.0	90 (14.4)	0	66 (10.5)
Macroscopic vascular invasion		1	190 (30.4)
Yes	69 (11.0)	2	212 (33.9)
No	557 (89.0)	3	122 (19.5)
Recurrence		4	36 (5.8)
Yes	359 (57.4)	Operative procedures	
No	206 (32.9)	Limited resection	359 (57.3)
Unknown	61 (9.7)	Segmentectomy	149 (23.8)
Number of recurrent tumors		Sectionectomy	71 (11.3)
Single	162	Hemihepatectomy	40 (6.4)
2–3	110	Extended hemihepatectomy	7 (1.1)
≥4	78		
Unknown	9		

HCV, hepatitis C virus; HBV, hepatitis B virus

tive for hepatitis C virus antibody (HCVAb), 108 (17.3%) were positive for hepatitis B surface antigen (HBsAg), 17 (2.7%) were positive for both HCVAb and HBsAg, 91 (14.5%) were negative for both HCVAb and HBsAg, and 53 (8.5%) were not tested. Background liver abnormalities were diagnosed by histopathological examination and included chronic viral hepatitis in 274 (43.8%) of the patients and cirrhosis in 344 (55.0%), with normal ranges in only eight (1.3%) patients. According to the TNM staging system, 118 (18.8%) cases were stage I, 242 (38.7%) stage II, 195 (31.2%) stage III, and 71 (11.3%) stage IV. As shown in Fig. 1, the patients had a more even distribution according to the m-JIS score than according to the JIS score.

Relationship between Child-Pugh classification and liver damage grade

According to the Child-Pugh classification, 524 (83.7%) of the patients had Child-Pugh A and 102 (16.3%)

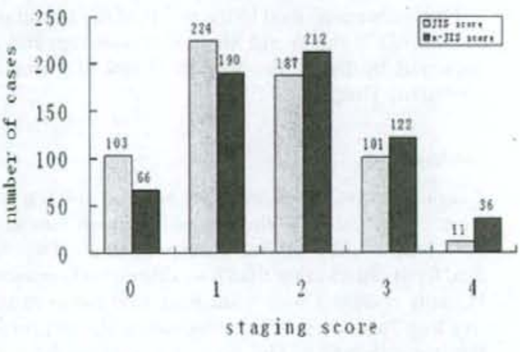

Fig. 1. Comparison of the distribution of patients by the Japan Integrated Stage (*JIS*) score and modified JIS (*m-JIS*) score. The m-JIS score tended to be significantly higher than the original JIS system score ($P = 0.000$)

Table 7. Relationship between the liver damage grade and Child-Pugh classification

Child-Pugh classification		Liver damage grade		
		A	B	C
A	524	353 (53.3%)	171 (27.3%)	0
B	102	3 (0.5%)	90 (14.4%)	9 (1.4%)

Child-Pugh B disease. No patient had Child-Pugh C disease, which was considered to be a contraindication for surgery. According to liver damage grade, 356 (56.9%) patients were grouped in A, 261 (41.7%) in B, and 9 (1.4%) in C. Analysis by Pearson's correlation test showed a significant relationship between Child-Pugh classification and liver damage grade (Pearson's correlation coefficient = 0.515, P = 0.000) (Table 7). Although 67.7% of the patients were evaluated as having the same grade of both liver damage and Child-Pugh classification, 28.8% were underevaluated by the Child-Pugh classification. In other words, these patients were further divided into two groups according to liver damage grade, especially Child-Pugh A patients.

Overall survival after hepatic resection

The overall mean and median survival times were 8.04 ± 0.39 and 6.48 years, respectively. The overall 1-, 3-, 5- and 10-year survival rates after hepatic resection were 92.0%, 77.5%, 59.9%, and 29.1%, respectively, for all patients. No significant difference was found between groups undergoing different operative procedures. There was no significant difference between TNM stages I and II or between stages III and IV, but significant differences were found between stages II and III (Fig. 2A). In our study, only two patients did not have ICGR15 results, but their liver damage grade could be determined according to the criteria shown in Table 3. There were 263, 133, and 228 patients in groups with ICGR15 levels of <14%, 14%–20%, and >20%, respectively. Although the overall survival rate tended to decrease as the ICGR15 level increased, no significant difference was found between the overall survival rates of patients with ICGR15 of <14% and those with ICGR15 of 14%–20%. However, patients with ICGR15 of >20% had a significantly decreased overall survival rate.

Although the overall survival rate could be well discriminated between groups classified by either Child-Pugh or liver damage grade, the latter had a better discriminatory ability, as mentioned above. According to the JIS scoring system, there was a significant difference between scores 1 and 2, and scores 2 and 3, but no significant differences could be found between scores 0 and 1, or scores 3 and 4 (Fig. 2B). The modified-JIS scoring system showed excellent discriminatory ability between consecutive scores, except between scores 0 and 1 (Fig. 2C).

Disease-free survival after hepatectomy

During the follow-up, 359 (57.4%) patients had recurrence of HCC, and in 290 of these patients the recurrence was intrahepatic only (Table 6). The recurrence rate was 62.5% in Child-Pugh A (295/472) patients and 68.8% (64/93) in Child-Pugh B patients. Although the recurrence rate tended to increase from Child-Pugh A to B, no significant difference was found ($P > 0.05$). According to liver damage grade, the recurrence rate was 58.6% (187/319), 70.2% (167/238), and 62.5% (5/8) in patients with liver damage grade A, B, and C, respectively. The recurrence rate increased significantly from liver damage grade A to B ($P < 0.05$). No significant difference was found in the recurrence rate between groups receiving different kinds of hepatectomy. The mean and median disease-free survival times were 4.69 ± 0.32 days and 2.65 years, respectively. The 1-, 3-, 5-, and 10-year disease-free survival rates after hepatic resection was 78.1%, 46.0%, 29.5%, and 14.1%, respectively, for all patients. Survival differed significantly between TNM stages II and III, but not between stages I and II or stages III and IV (Fig. 3A). In contrast to the overall survival rate, no significant difference was found between patients with ICGR15 14%–20% and >20%, but the disease-free survival rate in these two groups was decreased significantly compared with that in patients with ICGR15 of <14%.

Patients with Child-Pugh class A disease had a better disease-free survival rate than those with Child-Pugh class B disease. Similarly, patients with liver damage grade A had a better disease-free survival rate than those with grade B, but there was no significant difference between patients with grade B and those with grade C. According to the JIS score, we found a significant difference in survival only between patients with scores 1 and 2 (Fig. 3B). By the modified-JIS score, the disease-free survival rate could be well differentiated between patients with scores 1 and 2 and those with scores 3 and 4 (Fig. 3C).

Comparison of suitability of the models

According to our results (Table 8), the m-JIS score had a higher discriminatory ability, indicated by linear trend, and homogeneity likelihood ratio, and lower AIC statistics, than the original JIS score in predicting both overall and disease-free survival.

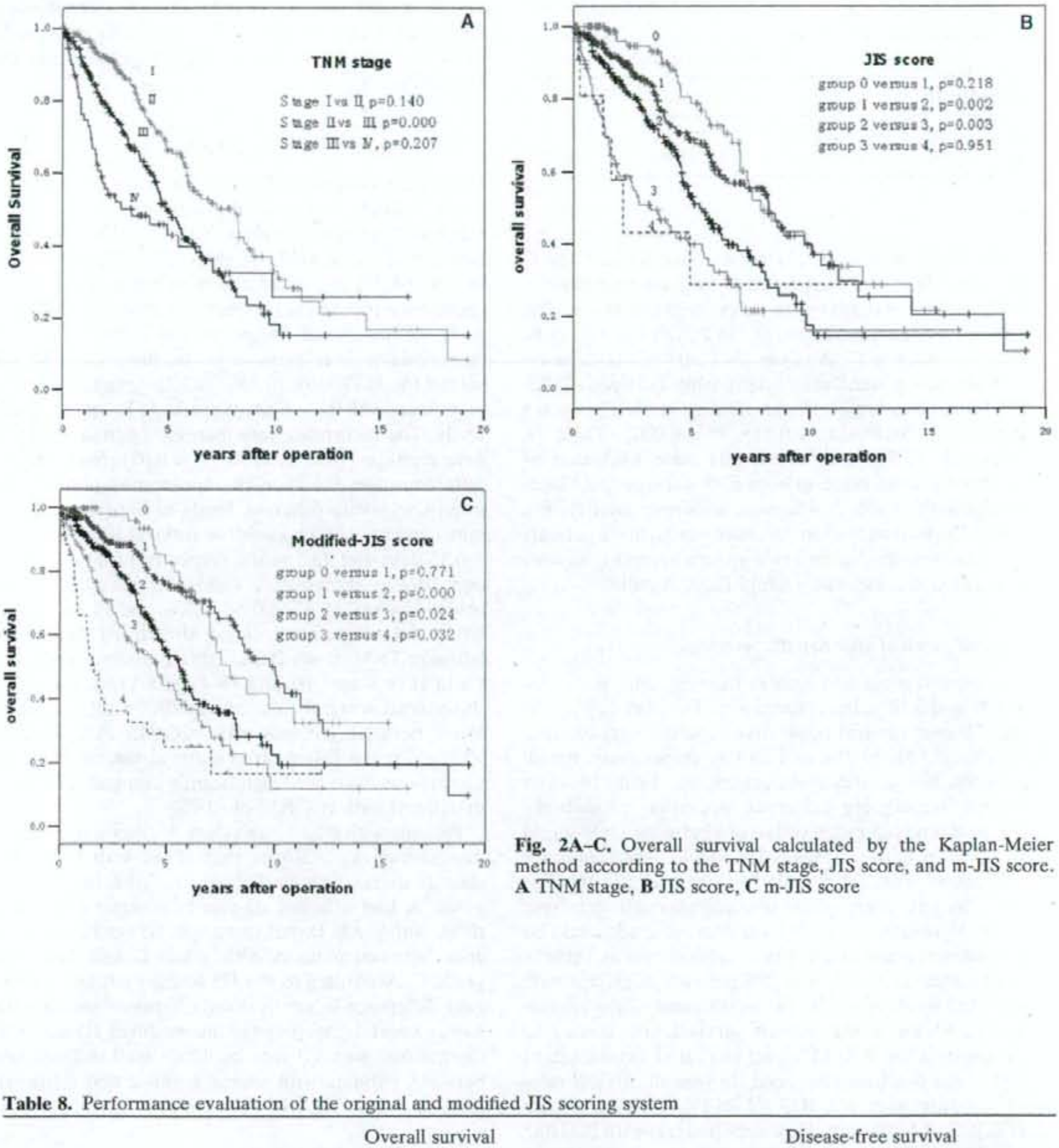

Fig. 2A–C. Overall survival calculated by the Kaplan-Meier method according to the TNM stage, JIS score, and m-JIS score. **A** TNM stage, **B** JIS score, **C** m-JIS score

Table 8. Performance evaluation of the original and modified JIS scoring system

	Overall survival			Disease-free survival		
Scoring system	Linear trend χ^2	LR χ^2	AIC	Linear trend χ^2	LR χ^2	AIC
CP	10.6	15.7	2557.6	5.2	8.9	3843.6
Liver damage grade	23.8	29.9	2412.5	13.8	24.0	3617.6
TNM	17.8	29.9	2152.1	6.7	13.0	3221.5
JIS score	25.9	41.5	2088.5	10.8	19.7	3141.4
Modified JIS score	37.0	56.3	2051.3	16.9	32.2	3086.6

Higher discriminatory ability (linear trend χ^2) and homogeneity LR χ^2 test values, and lower AIC statistics, were associated with better performance of the scoring system

CP, Child-Pugh classification; JIS, Japan integrated stage; LR, likelihood ratio; AIC, Akaike information criterion

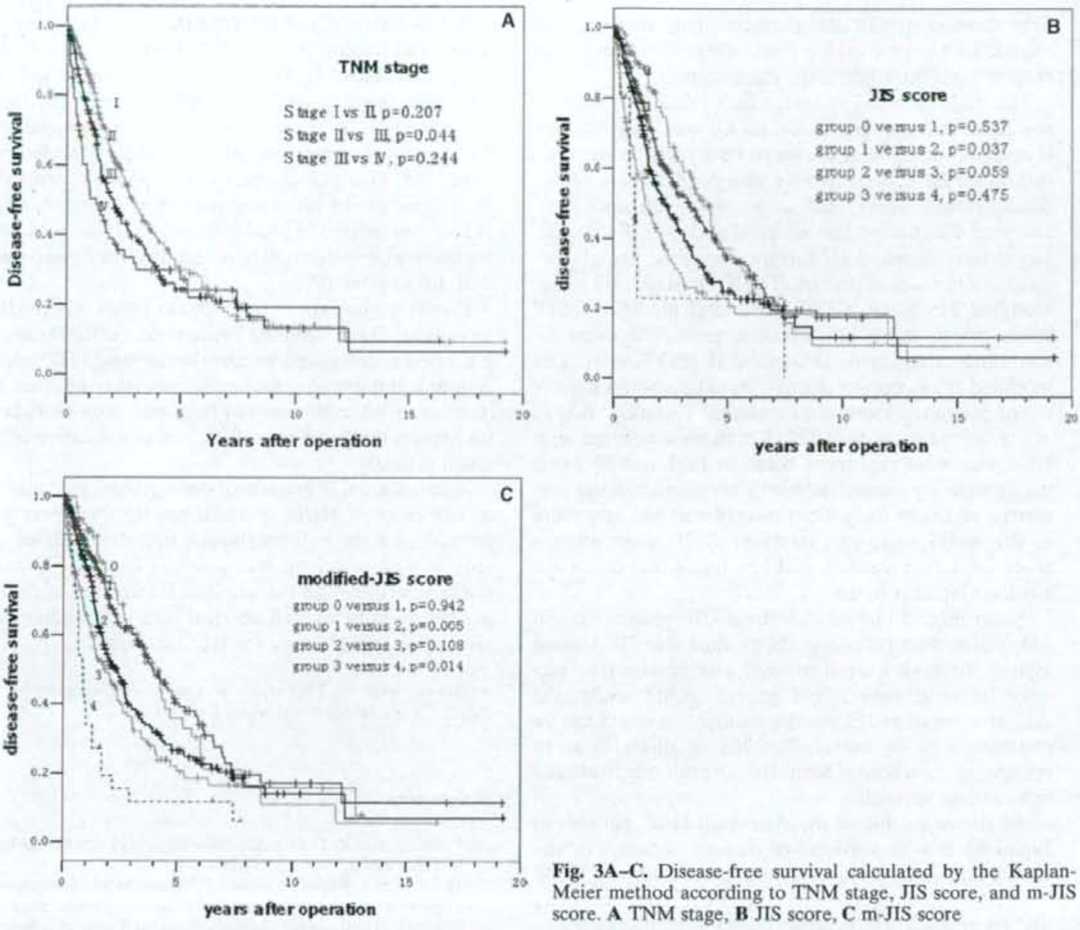

Fig. 3A–C. Disease-free survival calculated by the Kaplan-Meier method according to TNM stage, JIS score, and m-JIS score. **A** TNM stage, **B** JIS score, **C** m-JIS score

Discussion

The prognosis of HCC patients after hepatectomy has been shown to be affected by several factors, including tumor staging, liver functional reserve, perioperative care, strict follow-up, and hospital volume.[14] It is critical to select the best therapeutic modality before the operation, and only about 20%–30% of patients are indicated for hepatectomy.

The JIS scoring system was first proposed by Kudo et al.[6] in 2003 and was soon adopted by many institutions in Japan for its simplicity and effectiveness. Several studies have compared staging systems for HCC. The CLIP and JIS scoring systems were shown to be suitable for patients in Japan with HCC, and the former seemed to be more suitable before 1991 and the latter to be better in the era of early detection and treatment of HCC that began after 1990.[15] Chen et al.[16] concluded that the CLIP system should be used for staging major hepatectomy patients and that the JIS system could be used for staging minor hepatectomy patients.

However, as shown in our data, most patients who underwent hepatectomy had Child-Pugh A liver function. Approximately 30% of Child-Pugh A patients were classified as having liver damage grade B liver function. Patients regarded as having the same grade of liver function by the Child-Pugh classification can be further divided into two groups on the basis of their liver damage grade classification. This method was shown to be stricter for evaluating liver functional reserve than the Child-Pugh classification.

The m-JIS scoring system, which takes into account the liver damage grade for HCC, was proposed by Nanashima et al.[8] and shown to be a useful prognostic system for HCC patients who underwent hepatic resection. In their study, 101 cases were retrospectively analyzed for disease-free survival and overall survival. Later, Nanashima et al.[9] further compared overall survival of 230 cases as predicted by TNM stage, JIS score, modified JIS score, CLIP score, and modified CLIP score, which takes into account protein induced by vitamin K absence or antagonist II (PIVKA-II). The modified JIS score was also shown to be a better predictor of prognosis than other systems.[9] Recently, Ikai et al.[17] analyzed records of 42269 patients diagnosed with HCC who were registered between 1992 and 1999 in a nationwide Japanese database. They compared the predictive accuracy for patient overall survival according to the m-JIS score and modified CLIP score using a cross-validation method, and concluded that the m-JIS scoring system is better.

According to our results, the m-JIS scoring system has better discriminatory ability than the JIS scoring system for both overall survival and disease-free survival between consecutive groups. Additionally, the AIC statistic of m-JIS was the smallest, so m-JIS can be considered to be better than the original JIS score system in predicting both the overall survival and disease-free survival.

As shown in this study, almost all HCC patients in Japan have a background of chronic hepatitis or cirrhosis, and about 60% patients are infected with HCV. Coexisting cirrhosis is associated with a higher mortality and recurrence rate, possibly owing to multicentric carcinogenesis, which limits the efficacy of hepatic resection.[18,19] As liver damage grade had better discriminatory ability than the Child-Pugh classification in predicting the recurrence of HCC after hepatic resection, the m-JIS score had a higher stratifying ability of disease-free survival, even in surgery patients.

Radiofrequency ablation (RFA) is an effective local ablation therapy for HCC with favorable long-term outcome, and there has been a remarkable increase in its use recent years.[20-22] The tumor stage and Child-Pugh classification have been found to be significantly related to survival rate after RFA therapy.[23] There has been a major controversy about the first choice of treatment for HCC that is both small and resectable and treatable by RFA. Comparison of the prognosis of HCC patients who have undergone RFA with the prognosis of those who have undergone hepatectomy according to the m-JIS scoring system might help resolve controversy.

In this study, 225 of the enrolled patients were diagnosed and treated before 1997. These patients tended to have advanced TNM stage disease and a worse prognosis than those treated after 1997, mainly because after 1997 surgical techniques, perioperative management, therapy of recurrent cancer, and imaging techniques improved. The indications for an operation remained unchanged in our team, and the better ability of the m-JIS scoring system in predicting survival was seen both for those who underwent hepatectomy before and those that did so after 1997.

However, the data were limited to Japan, where HCC screening has been routine nationwide. Further research is needed to determine whether the modified JIS scoring system is suitable for other countries. Also, because the number of the cases was not large and only candidates for hepatectomy were enrolled, further validation of the result is needed.

In conclusion, the results of our retrospective analysis of 626 cases of HCC in which hepatectomy was performed by a single team showed that the modified JIS scoring system taking into account the liver damage grade is better than the original JIS scoring system in predicting both overall survival and disease-free survival after hepatectomy for HCC in Japan.

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Original Paper

Rapid Recovery of Postoperative Liver Function after Major Hepatectomy using Saline-linked Cautery

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ABSTRACT

Background/Aims: The exact effect of heat injury in the residual liver on postoperative liver function is not totally understood. The purpose of this study was to compare postoperative liver function after major liver resection using an argon laser beam coagulator (AR) and that using saline-linked cautery (SLC) for vessels and bile duct sealing.

Methodology: Between January 2001 and December 2005, thirty patients were analyzed in this study retrospectively. The inclusion criteria were that the patients received hemihepatectomy without vascular and biliary reconstruction in a non-cirrhotic liver. Operative variables and liver functions were compared between the AR method and the SLC method.

Results: The clinical profiles of the two groups were almost identical, including preoperative hepatic function. Although there was no difference in most of the intraoperative variables between them, warm ischemic time in the SLC group was shorter than in the AR group (46.53 + 25.42 min vs. 70.47±11.48 min: $p=0.003$). Albumin and bilirubin levels at 7 days after hepatectomy were not significantly different between the two groups, but low-density lipoprotein (LDL) and apolipoprotein B (ApoB) levels in the SLC group at 7 days after hepatectomy were significantly higher than in the AR group (84.27 ± 14.38 mg/dl vs. 60.21 ± 14.27 mg/dl: $p=0.001$; 69.53 ± 17.18 mg/dl vs. 55.87 ± 9.56 mg/dl: $p=0.012$, respectively).

Conclusion: SLC reduces warm ischemic time during hepatectomy. Furthermore, the rapid recovery of LDL and ApoB levels in the SLC group indicates that the SLC method has potential benefits for postoperative hepatic function.

KEY WORDS:
Liver Regeneration; Liver Function; Saline-linked Cautery; Low-density Lipoprotein; Apolipoprotein

ABBREVIATIONS:
Argon laser beam coagulator (AR); Saline-linked cautery (SLC); How-density lipoprotein (HDL); Low-density lipoprotein (LDL); Apolipoprotein (Apo); Cavitron Ultrasonic Surgical Aspirator (CUSA); Dissecting sealer (DS); Floating ball (FB); Indocyanin green retention rate at 15 min. ($ICGR_{15}$); Retinol binding protein (RBP); Albumin (ALB); Prothrombin time (PT); Gamma glutamyl transferase (GGT); Analysis of variance (ANOVA).

INTRODUCTION

Liver resection for malignant liver tumors has improved dramatically due to the development of novel surgical techniques and devices. Mortality in the 1980s was reported to be approximately 10% for major hepatectomy (1, 2), but has now been reduced to only a few percent in modern hepatic surgery (3-5). Various techniques and devices are now used for liver transection such as the clamp crush method (6), finger fracture method (7), various ablation methods (8-10), with or without a Cavitron Ultrasonic Surgical Aspirator (CUSA™) (11), ultrasonic scalpel (12), and Ligasure™ (13). The saline-linked cautery (SLC), also known as a dissecting sealer (DS3.0™ or DS3.5C™, TissueLink Medical, Dover, NH) (14, 15), can be used for liver parenchymal transection and with an improved design compared to the previously developed floating ball (FB3.0™) (16). SLC coagulates the liver parenchyma by keeping the temperature at 100°C or less to obtain optimal sealing of vessels 5 mm in diameter or smaller and bile ducts up to 1 mm (17) in size; therefore it controls blood loss and shortens operative time without unnecessary clipping or tying of small vessels during liver transection. On the other hand, the major concern about the SLC method has been whether there is any harmful heat injury to the residual liver that might affect postoperative liver function (16,18). However, the exact effects of heat injury and necrosis in the residual liver on the postoperative liver function are not totally understood.

Serum lipid alteration has been proved to represent recovery of residual liver function (19,20). The residual liver function is dependent on the type of liver resection and severity of liver disease (5). The serum hyaluronic acid level can be a predictive factor for postoperative liver dysfunction (5), as it is correlated with the other hepatic functional markers such as type IV collagen and indocyanin green retention rate at 15 min ($ICGR_{15}$). Rapid turnover proteins such as retinol binding protein (RBP) and pre-albumin (ALB) were tested to evaluate the nutritional condition of the patient, which was associated with liver function, within a few weeks prior to surgery. Although these indicators could evaluate liver function before hepatectomy, they did not represent alteration of the liver function during liver regeneration. The recovery of liver function during liver regeneration could be difficult to evaluate after modern hepatectomy. Classic hepatic markers cannot be used for subtle hepatic dysfunction because they are almost stable in recent cases. No critical liver failure was seen

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in any of our recent hemihepatectomized cases; therefore, we need to evaluate subcritical liver dysfunction by monitoring other indicators to assess new surgical devices. Combinations of serum cholesterol and apolipoprotein (Apo) levels also represent liver function; high-density lipoprotein (HDL) and ApoAI could be tested for chronic liver function (19,21), whereas LDL and ApoB can be evaluated for acute liver function (20). Among the lipids, LDL and ApoB represent recovery of liver function within one week after hepatectomy (20). Although the mechanism of the liver dysfunction after major hepatectomy is not completely understood, LDL and ApoB can be indicators representing recovery of liver function.

To assess the effect of SLC on postoperative liver function, we reviewed patients who underwent hemihepatectomy within five years. Then we compared the methods used to coagulate vessels and bile ducts, i.e. use of the AR or the SLC. The purpose of our study was to examine the effect of SLC on residual liver function after major hepatectomy.

METHODOLOGY

We examined 30 patients who received hemihepatectomy in a single institute from January 2001 and December 2005 and were eligible using the following criteria: 1. A Child-Pugh score with Pugh's modification before surgery of five points. 2. A body mass index between 18 and 25. 3. No vascular and biliary reconstruction. Hemihepatectomy was carried under hepatic inflow occlusion (Pringle's maneuver; 10 min occlusion and 5 min perfusion) with a CUSA™. Hemostasis was obtained either by AR or SLC after skeletonizing liver parenchymal tissues. The major technical difference between the hemostatic devises was that the precoagulation on the superficial liver parenchyma within 5 mm was obtained using SLC before liver parenchymal skeletonize. We compared the clinical and intraoperative variables of the AR group and SLC group. The surface of the resected liver in all patients was cut in the midplane of the liver.

Blood loss was calculated by the nursing staff in the operating room, and included ascites and/or the saline used in conjunction with SLC during the operation. The timing of blood transfusion was determined by the anesthesiologist. The study design conformed to the ethical guidelines of the Declaration of Helsinki as reflected by prior approval of the institution's Human Research Committee.

Assessment of the liver function

Laboratory tests for ALB, bilirubin, prothrombin time (PT), blood cell counts, AST, ALT, gamma glutamyl transferase (GGT), choline esterase, RBP, preALB, HDL, LDL, ApoAI, ApoB, hyaluronic acid, type IV collagen and the $ICGR_{15}$ were evaluated before hepatectomy. Intraoperative data and any complications during the first 7 postoperative days wère recorded. The liver function was assessed at 3 and 7 days after operation and all laboratory tests were performed in the early morning on the day of assessment.

Statistical analysis

For statistical analysis, demographic and perioperative laboratory tests, were extracted from the database and the differences between the groups were compared using the χ^2 test followed by the post-hoc 2 x 2 Fisher exact test and analysis of variance (ANOVA) using the StatView 5.0 software package (Abacus Concepts Inc., Berkeley, CA) when needed. All results are expressed as mean values ± SD. $P < 0.05$ was considered to be statistically significant.

RESULTS

We studied all patients underwent hemihepatectomy for various liver tumors. The patients in this study were a homogeneous population that should have exhibited the same perioperative course to recover liver function if there were no technical errors during the operation. The demographic profile of the patients is shown in **Table 1.** There was no significant difference between the AR group and SLC group. Although there was no significant difference in the complication rate between the groups, no bile leakage was seen in the SLC group. None of the patients were admitted in the ICU and no postoperative bleeding or death was seen. All patients could take meals at 2 or 3 days after hepatectomy and all nourishment was taken orally by 7 days at the time of the evaluation.

Blood laboratory tests were evaluated before hepatectomy. All the patients received hemihepatectomy with good liver function. None of the markers or serum levels were significantly different between the groups before hepatectomy (**Table 2**). The surgical procedure was almost the same for both groups, except for the use of an AR or SLC. Intraoperative data are shown in **Table 3**. There was no significant difference in operating time, blood loss or blood transfusion between the groups, whereas warm ischemic time in the SLC group was significantly shorter than in the AR group (46.53 ± 25.42 min vs. 70.47 ± 11.48 min: $P = 0.003$).

We compared albumin, bilirubin and lipid levels at 3 days and 7 days after hepatectomy (**Figure 1**). There was no significant difference in the albumin, bilirubin, HDL and ApoAI levels between the groups. On the other hand, LDL and ApoB levels in the SLC group at 7 days after operation were significantly higher than in the AR group (84.27 ± 14.38 mg/dl vs. 60.21 ± 14.27 mg/dl: $p=0.001$; 69.53 ± 17.18 mg/dl vs. 55.87 ± 9.56 mg/dl: $p=0.012$, respectively).

DISCUSSION

Novel surgical procedure for liver surgery

Various techniques have been employed for liver parenchymal transection (6). Small vessels less than 1 mm in diameter may be sealed with normal diathermy, whereas large vessels should be ligated or clipped. The SLC is a novel device for liver resection (14, 15, 18) that results in optimal vessel and bile duct sealing. The vessels, composed of endovascular cells and muscular cells, are surrounded by connective tissue, which is considered to play an important role in achieving complete sealing permanently. The optimal temperature and time to seal the connective tissue were estimated to be about 60 ℃ to 100 ℃ for a few seconds. Mild heat around 60 ℃ ruptures the hydrogen bonds that crosslink and stabilize the triple helix structure of banded, fibrillar collagen (Types I and III) found in the walls of blood vessels and bile ducts, resulting in shrinkage of up to 60% (22). Excessively high temperatures generated by the conventional electrocautery or the AR cause carbonization within a certain period to prevent energy penetration deep inside the tissue and can not obtain firm collagen shrinkage to seal the vessels and bile ducts (17). On the other hand, the lower temperature penetrates deep into the tissue within certain period of time to cause a good thermal effect and sealing (17). Therefore, using SLC during the procedure resulted in good bleeding control that saved time for hemostasis; however, the total operating time was no different due to the time taken to obtain optimal sealing. We did not see any time benefit using SLC during the operations, though we did not observe any bile leakage or postoperative bleeding in this study. Therefore, a further large multicenter trial must be designed to clarify the SLC effect reducing postoperative morbidity after hepatectomy.

Best device for liver transection

Recently, two randomized trials to determine the effect of SLC on hepatectomy were reported with contrary results (15, 18). Aloia et al. (15) reported that SLC reduced inflow occlusion time, blood loss, and operative time. The liver function after hepatectomy was comparable with and without SLC. In contrast, Arita et al. (18) reported that SLC did not contribute any benefit compared to the conventional clamp crush method, although they reported results irreconcilable with their previous preliminary report (16). It is reasonable for there to be no difference in blood loss between the groups only if hepatic blood flow is properly controlled during hepatectomy. SLC can avoid unnecessary inflow occlusion in the early procedure of hepatectomy as we have seen in this study. Based on our criteria for applying the Pringle maneuver, it was thought that, initially, a few Pringle maneuvers could be skipped in the SLC group and in fact; two patients in the SLC group underwent the hemihepatectomy without the Pringle's maneuver and blood transfusion. The peripheral liver surface up to 5 mm in depth and the edge of the liver along the midplane could be dissected by any means without any bleeding as long as proper precoagulation has done using SLC. The different results between their studies and ours may be due to different techniques of hepatectomy and the study design itself. Our technique for liver dissection using SLC is always ablation first and subsequent dissection with either CUSA™ or Frazier suction. The order of the procedure is very important

TABLE 1 Clinical Characteristics of the Patients

	AR (n=15)	SLC (n=15)	p value
Age	55.6±7.9	62.3±10.3	0.055
Male:Female	9:6	2:13	0.099
Left hepatectomy	7	8	
Right hepatectomy	8	7	0.715
HCC (HBV)	6	7	
CCC	4	2	
Metastatic cancer	1	4	
Others	4	2	0.337
Wound infection	2	2	
Bile leakage	2	0	
Pleural effusion	2	2	
Ascites	1	2	0.664
ICU stay (day)	0	0	0.999

Data are expressed as mean ± standard deviation.
ST: standard method using CUSA and argon beam coagulator; SLC: saline-linked cautery; HCC: hepatocellular carcinoma; HBV: hepatitis B virus; CCC: cholangiocellular carcinoma; ICU: intensive care unit.

TABLE 2 Laboratory Evaluation before Hepatectomy

	AR (n=15)	SLC (n=15)	p value
ALB (g/dl)	3.91±0.37	3.91±0.47	0.999
Bilirubin (mg/dl)	0.98±0.55	0.67±0.35	0.075
PT (%)	105.25±12.70	103.32±14.41	0.702
Platelets ($10^4/\mu l$)	19.05±4.95	23.53±7.42	0.062
AST (IU/L)	38.01±20.11	37.07±22.67	0.906
ALT (IU/L)	35.61±19.24	37.41±25.02	0.827
GGT (IU/L)	221.67±200.29	135.41±89.37	0.139
RBP (ng/ml)	2.73±0.98	3.35±1.35	0.166
Pre-ALB (ng/ml)	20.81±5.61	22.49±8.11	0.512
HDL (mg/dl)	47.01±16.32	45.07±8.37	0.686
LDL (mg/dl)	110.61±13.45	123.93±32.32	0.151
ApoA (mg/dl)	115.93±29.88	119.73±19.55	0.683
ApoB (mg/dl)	86.27±13.76	98.03±21.91	0.091
Hyaluronate (ng/ml)	99.22±88.52	68.04±41.77	0.227
Type IV Collagen (ng/ml)	8.06±5.81	5.64±1.96	0.137
$ICGR_{15}$ (%)	9.98 ± 6.75	8.04±4.57	0.364

Data are expressed as mean ±standard deviation.
AR: argon beam coagulator; SLC: saline-linked cautery; ALB: albumin;
PT: prothrombin time; AST: aspartate transaminase; ALT: alanine transaminase; GGT: gamma glutamyl transferase; CholE: choline esterase; RBP: retinol-binding protein HDL, high-density lipoprotein; LDL, low-density lipoprotein;
Apo: apolipoprotein; ICG: indocyanine green retention rate at 15 minutes.

TABLE 3 Intraoperative Data of Patients undergoing Hemihepatectomy

	AR (n=15)	SLC (n=15)	p value
Operative time (min)	447.67±118.09	422.41±130.61	0.583
Blood loss (ml)	758.67±374.09	659.33±328.82	0.447
Warm ischemic time (min)	70.47±11.48	46.53±25.42	0.003*
Packed red blood cells (ml)	128.08±162.24	58.64±122.72	0.198

Data are expressed as mean ± standard deviation.
*Asterisk represents a significant difference ($p < 0.05$).