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Prognostic Factors of 10-Year Survivors after Initial Treatment for Hepatocellular Carcinoma, Determined in 713 Japanese Patients in Relation to Indication of Liver Transplantation.

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Abstract

Purpose: To clarify the prognostic factors for long-term survival by studying the clinical factors of 10-year survivors after initial treatment for hepatocellular carcinoma (HCC).
Methods: 713 Japanese patients who had received over 10 year's observation after initial treatment for HCC were selected. Differences in clinical factors between 10-year survivors and the remainder were studied. The multiple logistic regression model was used for multivariate analysis.
Results: Significant differences were noted between the groups in age, tumor number, vascular involvement, concordance of Milan Criteria (MC), Japanese tumor-node-metastasis stage, Child-Pugh stage (CP), HCV infection, serum α-fetoprotein level, and modality of initial treatment. Multivariate analysis showed that older age, out of MC, CP-B or -C, and initially treated other than by hepatectomy were independent risk factors for 10-year survival. If patients were within MC and CP-A, the overall 10-year survival rate of those initially treated by hepatectomy was 71%, and 49% for those with HCV infection.
Conclusions: Younger patients with initial HCC within MC and CP-A can expect long-term survival, if surgically resectable. Hepatectomy should be considered especially to HCC patients with HCV infection, if in these categories.

Key words: Milan criteria, Child-Pugh stage, hepatitis C virus infection, hepatectomy

Introduction

Hepatocellular carcinoma (HCC) is a relatively common malignant tumor worldwide, accounting for almost one million deaths annually. Over the past two decades, some newly developed therapeutic options have been applied with varying degrees of success: i.e., hepatectomy [Hx], transcatheter arterial chemoembolization [TACE], and percutaneous ablation therapy [Ablation], including percutaneous ethanol injection, microwave coagulation therapy and radiofrequency ablation. HCC typically presents in association with chronic liver disease or in patients with chronic viral hepatitis. Cirrhosis due to hepatitis B virus

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(HBV) infection carries a seven fold greater risk for HCC. With hepatitis C virus (HCV) infection, there is a four fold greater risk.[1] Thus, to estimate reliably the prognoses of patients with HCC, both hepatic functional reserve and tumor-related factors should be taken into account.[2–4] In recent years, liver transplantation also has been applied to patients with small HCC(s).[5–9] However, graft and patient survival is reduced in liver transplantation recipients with recurrent HCV infection compared to HCV-negative patients.[10–13] A large percentage of patients with HCC develop the tumor on the background of chronic HCV infection. These factors are confusing the therapeutic strategies for HCC patients, especially those with chronic HCV infection. Therefore, discussion of therapeutic intervention for HCC is more difficult than other cancers.

The *Kagoshima Liver Cancer Study Group* was established in 1990, with the aim of performing prospective, therapeutic trials and studies regarding diagnostic and prognostic assessments of HCC .[14–17] Since then, we have recorded prospectively a number of variables in each consecutive patient with HCC in an attempt to investigate these factors further, given that they may affect the prognosis of the disease. In this period, the diagnostic and staging procedure has remained constant and the selection of treatment has been based on uniform criteria.[16]

The purpose of this study is to clarify the prognostic factors for long-term survival by investigation of clinical factors of 10-year survivors after initial treatment for HCC and to discuss the indication and timing of liver transplantation for HCC patients especially with chronic HCV infection.

Methods

Patients and Data Collection

Three hospitals took part in this study. From January 1, 1990 to December 31, 2004, 1343 consecutive patients with primary HCC underwent Hx, Ablation, or TACE as their initial treatment. All were Japanese and included 965 men and 378 women with a median age of 65.3 years (range: 21–88 years). The diagnostic workup was similar in all patients, including a comprehensive clinical and analytic evaluation, chest X-ray, and bone scintigraphy. Intra-abdominal extension was assessed by ultrasonography, dynamic contrast-enhanced computed tomography (CE-CT) and hepatic angiography. Esophagogastric fiberscopy was performed routinely to evaluate the existence of esophagogastric varices.

Detailed liver function studies were performed routinely. When Hx was acceptable according to the evaluation of liver function, and the tumor type was not

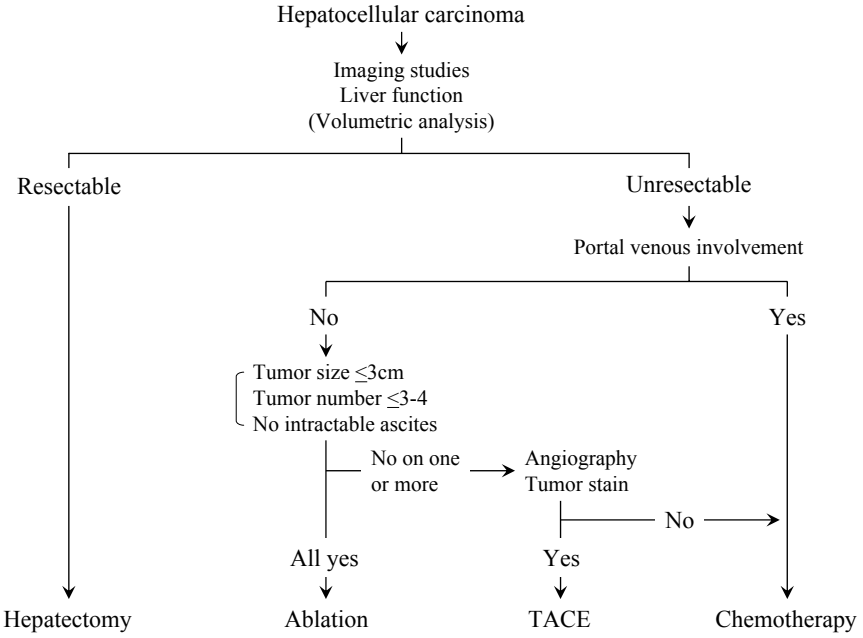

Fig. 1. Patient selection for treatment. Patients who had excessively deteriorated liver function and/or refused therapy received chemotherapy or supportive care; Ablation = percutaneous ablation therapy including percutaneous ethanol injection, microwave coagulation therapy and radiofrequency ablation; TACE = Transcatheter arterial chemoembolization.

Table 1. Definitions of Japanese Tumor-node-metastasis (TNM) stage.

The General Rules for the Clinical and Pathological Study of Primary Liver Cancer (4th edition)	
T factor defined by 3 criteria: single, ≤2cm, or no vascular involvement	
T1	Agree with all 3 criteria
T2	Agree with 2 of 3 criteria
T3	Agree with 1 of 3 criteria
T4	Agree with no criteria
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0
Stage IVa	T4 N0 M0, or Any T N1, M0
Stage IVb	Any T Any N M1

diffuse or massive, volumetric analysis, using CE-CT, was carried out to measure the whole liver volume for the assessment of functional reserve.[18] As far as curative Hx was concerned, the patients were submitted to Hx. When Hx was not feasible because of decreased hepatic reserve and expected liver cell loss due to resection, other therapeutic modalities were utilized, as shown in Fig. 1.[15,16] Patients with HCC(s) less than 3 cm in size and/or four or fewer in number were considered for Ablation. Generally, HCC patients who had complicating main portal branch tumor thrombi were assigned to regional (hepatic arterial) chemotherapy.

Data of tumor size, tumor number and vascular involvement were based on evaluation by CE-CT. Other clinical variables were based on pretreatment diagnostic workup. The quality control of data was made by verifying consistency (e.g. claimed categories of established staging systems were matched with reported values of constituting variables) and possible input errors, as all data entered were checked by two operators. When inconsistencies were found, they were discussed with the single investigator. Tumor-node-metastasis (TNM) stage was according to *The General Rules for the Clinical and Pathological Study of Primary Liver Cancer* (4th edition) summarized in Table 1.[19] Milan criteria were described by Mazaferro et al. as either one tumor ≤5 cm or up to three tumors ≤3 cm.[8]

Analysis of clinical factors for 10-year survival

Patients who were followed up for less than 10 years after initial treatment for HCC (i.e. censoring patients less than 10 years) were excluded from this analysis. Furthermore, patients with distant metastasis of HCC also were excluded. The data of the remaining 713 patients were analyzed. The subjects ranged in age from 30 to 87 years (mean, 63.6 years). The following pretreatment variables were used for the analysis: age, gender of the patient, tumor size, tumor number, vascular involvement, Child-Pugh stage and its constitutive variables (albumin, bilirubin, prothrombin time, ascites, encephalopathy), hepatitis B virus surface antigen (HBsAg), antibodies to hepatitis C virus (anti-HCV), serum α-fetoprotein (AFP) level (ng/ml), serum des-γ-carboxy prothrombin (DCP) level (mAU/ml), and modality of initial treatment (Hx, Ablation or TACE).[18] The patients were then categorized into two groups according to whether they survived 10 years after initial therapy or not. The 10-year survivors were called as Group X, and the non 10-year survivors were called as Group Y.

Survival analysis

In order to demonstrate the significance of Hx and discuss indication and timing of liver transplantation, a total 244 of patients within Milan criteria and initially treated by Hx were selected from the original 1343 patients. These 244 patients included the censored 159 patients followed up for less than 10 years after Hx. The number of patients with Child-Pugh stage A was 221 and 23 had Child Pugh stage B or C. Subgroup analysis was performed in relation to the presence of anti-HCV.

Statistical analysis

Continuous variables except AFP or DCP were expressed as the mean ± the standard deviation and compared by an unpaired *t* test. Because AFP and DCP had lognormal distributions, these were expressed as the geometric mean and compared by an unpaired *t* test based on the geometric mean. Categorical variables were compared using a χ^2 test. The multiple logistic regression model was used for multivariate analysis. The Kaplan-Meier method was used for survival analysis. A *P* value of less than 0.05 was considered statistically significant. The *P* values in this study were two sided. All statistical analyses were done using the software package StatView version 5.0 (Abacus Concepts, Berkeley, CA).

Results

Analysis of clinical factors for 10-year survival

Forty-one patients had survived 10 years after initial

Table 2. Characteristics of the 713 patients included in the analysis of clinical factors for 10-year survival.

Variable	Total (n = 713)	Group X (10-year survivor) (n = 41)	Group Y (non 10-year survivor) (n = 672)	*P*
Age(years)	30-87			0.0012*
Mean ± SD	63.6 ± 8.9	59.3 ± 9.0	63.9 ± 8.8	
Gender				0.8445
Male	531 (74.5%)	30 (73.2%)	501 (74.6%)	
Female	182 (25.5%)	11 (26.8%)	171 (25.4%)	
Tumor size				0.2254
≤ 2 cm	145 (20.3%)	12 (29.3%)	133 (19.8%)	
2cm < ≤ 5cm	384 (53.9%)	22 (53.6%)	362 (53.8%)	
5cm < ≤ 10cm	144 (20.2%)	7 (17.1%)	137 (20.4%)	
10cm <	40 (5.6%)	0 (0.0%)	40 (6.0%)	
Tumor number				<0.0001*
Uninodular	295 (41.4%)	33 (80.5%)	262 (39.0%)	
Multinodular	418 (58.6%)	8 (19.5%)	410 (61.0%)	
Vascular involvement				0.0077*
Negative	585 (82.0%)	40 (97.6%)	545 (81.1%)	
Positive	128 (18.0%)	1 (2.4%)	127 (18.9%)	
Milan criteria				0.0003*
Within	328 (46.0%)	30 (73.2%)	298 (44.3%)	
Out of	385 (54.0%)	11 (26.8%)	374 (55.7%)	
Japanese TNM stage				<0.0001*
Stage I	91 (12.8%)	10 (24.4%)	81 (12.0%)	
Stage II	223 (31.3%)	25 (61.0%)	198 (29.5%)	
Stage III	304 (42.6%)	5 (12.2%)	299 (44.5%)	
Stage IVa	95 (13.3%)	1 (2.4%)	94 (14.0%)	
Child-Pugh stage				0.0004*
A	502 (70.4%)	39 (95.1%)	463 (68.9%)	
B or C	211 (29.6%)	2 (4.9%)	209 (31.1%)	
HBsAg				0.2653
Negative	573 (81.6%)	30 (75.0%)	543 (82.0%)	
Positive	129 (18.4%)	10 (25.0%)	119 (18.0%)	
Unknown	11	1	10	
Anti-HCV				0.0101*
Negative	185 (26.8%)	17 (44.7%)	168 (25.7%)	
Positive	506 (73.2%)	21 (55.3%)	485 (74.3%)	
Unknown	22	3	19	
AFP value (ng/ml)	1.0 - 255720	2.0 - 4010	1.0 - 255720	0.0066*
Geometric mean	91.6	33.6	97.6	
DCP value (mAU/ml)	2.0 -7430000	8.0 - 112000	2.0 - 7430000	0.1312
Geometric mean	320.9	158.4	333.3	
Modality of initial treatment				<0.0001*
Hx	166 (23.3%)	26 (63.4%)	140 (20.8%)	
Ablation	157 (22.0%)	7 (17.1%)	149 (22.2%)	
TACE	390 (54.7%)	8 (19.5%)	383 (57.0%)	

HBsAg, hepatitis B virus surface antigen. Anti-HCV, antibody to Hepatitis C virus. AFP, serum α-fetoprotein level. DCP, serum des-γ-carboxy prothrombin level. Hx, hepatectomy. Ablation, percutaneous ablation therapy including percutaneous ethanol injection, microwave coagulation therapy and radiofrequency ablation. TACE, transcatheter arterial chemoembolization.

Table 3. Multivariate analysis of clinical factors for 10-year survival.

Variable	Relative risk ratio 95% confidence interval			*P*	Likelihood ratio *P*
Gender (female / male)		1.776		0.2616	0.2725
	0.651	-	1.776		
Age		1.065		0.0133*	0.0136*
	1.013	-	1.119		
Miran criteria (within / out of)		2.810		0.0457*	0.0386*
	1.020	-	7.741		
Child-Pugh stage (A / B or C)		6.803		0.0135*	0.0026*
	1.488	-	31.250		
Anti-HCV (Negative / Positive)		1.919		0.2077	0.2181
	0.696	-	1.919		
AFP level (<400 / ≥400)		0.894		0.8603	0.8613
	0.257	-	3.113		
DCP level (<100 / ≥100)		2.428		0.1035	0.0939
	0.834	-	7.066		
Modality of initial treatment					0.0063*
(Hx / Ablation)		3.584		0.0196*	
	1.227	-	10.417		
(Hx / TACE)		4.878		0.0034*	
	1.689	-	14.085		

Anti-HCV, antibody to hepatitis C virus. AFP, serum α-fetoprotein level. DCP, serum des-γ-carboxy prothrombin level. Hx, hepatectomy. Ablation, percutaneous ablation therapy including percutaneous ethanol injection, microwave coagulation therapy and radiofrequency ablation. TACE, transcatheter arterial chemoembolization.

treatment and called as Group X. Twenty one patients in Group X were without relapse of HCC during the 10 years after initial treatment. Of the remaining 20 patients, all had relapsed HCC in the liver and one also had metachronous pulmonary metastasis. All 672 patients who were not 10-year survivors (Group Y) had died due to relapsed HCC, hepatic failure, gastrointestinal breeding, including rupture of esophageal varices, or initial treatment-related complications. Five hundred and forty three patients in Group Y had relapsed HCC within 10 years of initial treatment. The characteristics of the patients in this study are summarized in Table 2. Patients in Group X were significantly younger than those in Group Y (P=0.0012) but there were no significant differences in gender, tumor diameter or HBsAg. Significant differences were noted between the groups in tumor number, vascular involvement, concordance of Milan Criteria, Japanese TNM stage, Child-Pugh stage, anti-HCV, and modality of initial treatment (P<0.0001, P=0.0077, P=0.0003, P<0.0001, P=0.0004 P=0.0101 and P<0.0001, respectively). Group X had lower AFP levels than Group Y (P=0.0066), but no significant difference in DCP levels. The majority (63.4%) of Group X was treated by Hx, but the most common treatment of Group Y was by TACE.

Table 3 shows multivariate analysis of clinical factors related to 10-year survival. Multivariate analysis showed that older age, out of Milan criteria and Child-Pugh stage B or C, and initially treated other than by Hx were independent risk factors for 10-year survival (P=0.0133, P=0.0457, P=0.0135, P=0.0196 [Hx vs. Ablation] and P=0.0034 [Hx vs. TACE], respectively).

Survival analysis

Figure 2 shows overall survival curves of the patients initially treated by Hx within Milan criteria. Five- and ten-year survival rates were 70% and 53%, respectively. Figure 3 shows subgroup analysis of survival of the patients initially treated by Hx within Milan criteria in relation to Child-Pugh stage. Five- and ten-year survival rates of the patients with Child-Pugh stage A were 75% and 56%, respectively. The five-year survival rate of the patients with Child-Pugh stage B or C was 36%. Figure 4 shows the subgroup analysis of survival of the patients initially treated by Hx within Milan Criteria and Child-Pugh stage A, in relation to the presence of anti-HCV. Five- and ten-year survival rates of anti-HCV negative patients were 83% and 66%, respectively, and those of the anti-HCV positive patients were 71% and 49%, respectively.

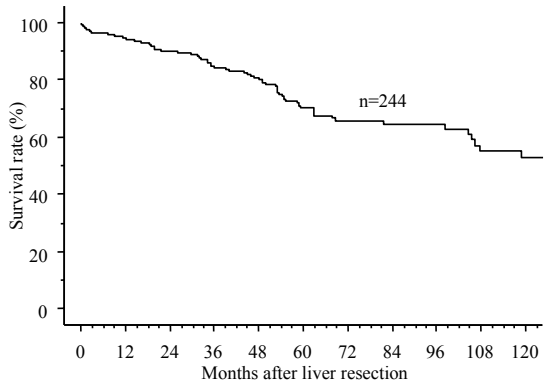

Fig. 2. Survival curves of the patients within Milan criteria and treated by hepatectomy. Five- and ten-year survival rate was 70% and 53%, respectively.

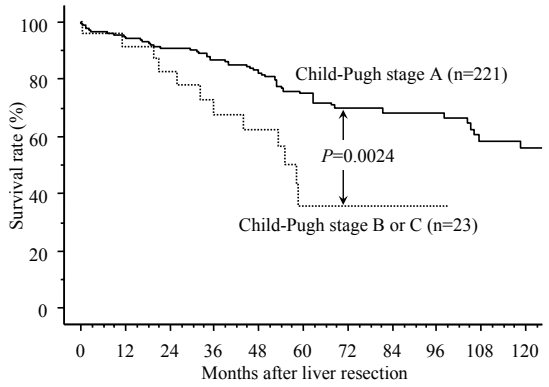

Fig. 3. Subgroup analysis of Fig. 2. The solid line shows the survival curves of the patients within Milan criteria and Child-Pugh stage A, and treated by hepatectomy (5-year survival rate: 75% 10-year survival rate: 56%). The broken line shows the survival curves of the patients within Milan criteria and Child-Pugh stage B or C (5-year survival rate: 36%).

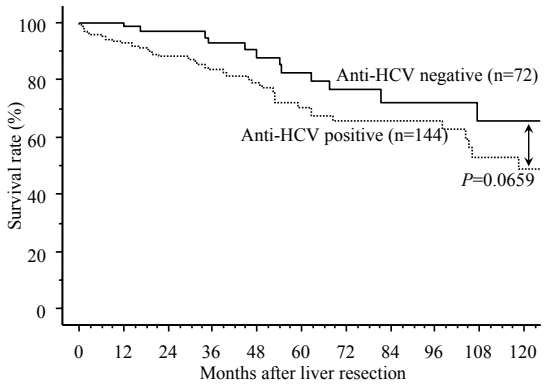

Fig. 4. Subgroup analysis of the patients within Milan criteria and Child-Pugh stage A, and treated by hepatectomy. The solid line shows the survival curves of those who were anti-HCV negative (5-year survival rate: 83% 10-year survival rate: 66%). The broken line shows the survival curves of those who were anti-HCV positive (5-year survival rate: 71% 10-year survival rate: 49%). Five patients were not examined for anti-HCV; Anti-HCV = antibody to hepatitis C virus.

Discussion

In this study, we investigated the clinical prognostic factors of 10-year survival after initial treatment for HCC. There were significant differences in age, tumor number, vascular involvement, Child-Pugh stage, and presence of anti-HCV between 10-year survivors (Group X) and the remainder (Group Y). In addition, there were also significant differences in concordance of Milan criteria and TNM stage that integrated the tumor number and vascular involvement. Our findings are in agreement with other recent studies.[21, 22] However, in those studies, there was significant correlation between tumor diameter and the prognosis, whilst here there were no significant differences in tumor diameter between 10-year survivors and the remainder.[21, 22] Some studies mentioned that higher AFP levels and/or higher DCP levels correlate with poor prognosis.[21–24] In this study, the geometric mean of AFP level was significantly lower in 10-year survivors than the remainder, but no significant difference was noted in DCP levels.

Multivariate analysis revealed that younger age, within Milan criteria, and Child-Pugh stage A were independent factors contributing to long-term survival. These results accorded with recent studies.[21, 23, 25] In some recent articles, it was suggested that higher AFP levels were independent risk factors for long-term survival.[23] However, in this study, an AFP level above ≥400ng/dl was not an independent risk factor.

Regarding modality of initial treatment, Hx was significantly correlated with achievement of 10-year survival. Furthermore, multivariate analysis showed that initial treatment by Hx, rather than Ablation or TACE, was an independent prognostic factor for long-term survival. Our study suggested that younger patients within Milan criteria and Child-Pugh stage A might expect long-term survival, if Hx is applicable.

Recently, liver transplantation was established as a therapeutic option for patients with small HCC(s). Habib et al. reported the long-term outcome of adult cadaveric liver transplantation performed at the Thomas E. Starzl Transplantation Institute, University of Pittsburgh. Five- and ten-year patient survival rates were 72% and 58%, respectively, and graft survival rates were 65% and 53%, respectively.[26] However, the 5- and 10-year survival rates of our patients initially treated by Hx within Milan criteria and Child-Pugh stage A were 75% and 56%, respectively. Although the studies are not directly comparable, this suggests that there is no great difference between Hx and cadaveric liver transplantation.

Furthermore, in most studies, a reduction in patient and graft survival in HCV-positive, compared to HCV-negative liver recipients, was found to be associated with recurrence of HCV infection after liver transplantation. The natural history of chronic HCV disease after liver transplantation often is accelerated compared to patients with HCV disease who were not transplant recipients. Reports indicated that 20% to 40% of liver transplant recipients with recurrent HCV disease progress to allograft cirrhosis within 5 years, compared to less than 5% of non-transplanted patients with chronic HCV disease.[11, 12] Ghobrial et al.[12] reported that the 5-and 10-year patient survival rates of adult cadaveric liver transplantation for anti-HCV positive recipients were 68% and 60%, respectively, and graft survival rates were 56% and 49%, respectively. These survival data are in agreement with a report by Forman et al.[13] and valid. The 5-and 10-year survival rates of our patients initially treated by Hx within Milan criteria and Child-Pugh stage A, and with chronic HCV infection were 71% and 49%, respectively. Although the studies are not strictly comparable, this suggests that there is no great difference between Hx and cadaveric liver transplantation in patients with chronic HCV infection. Furthermore, preliminary evidence suggests that recurrent HCV infection may occur earlier and may be more severe in living donor liver transplant (LDLT) recipients.[27]

In conclusion, Hx should be considered as initial treatment in anti-HCV positive patients with resectable HCC and within Milan criteria and Child-Pugh stage A even if LDLT is available. Conversely, if HCC patients progress to Child B or further, 10-year survival after initial treatment other than liver transplantation becomes almost impossible. It is suggested that delayed the timing of liver transplantation as far possible is beneficial to the long term survival of such patients. In case of LDLT, recurrent HCV infection may occur earlier and may be more severe, but the timing of transplantation may be more flexible than cadaveric transplantation. Thus, timing of liver transplantation must be well considered carefully, especially in the case of LDLT.

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邦人肝細胞癌初回治療713例中における10年生存例の臨床予後因子の検討 ～肝移植の適応との兼ね合い～

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【目的】肝細胞癌治療後の長期生存に関係する予後因子を明らかにするために，初回治療後10年以上の生存を得ている症例の臨床因子を検討した．
【方法】初回治療後10年以上の経過観察が可能であった肝細胞癌患者713例を対象とし，10年以上の生存群とそれ以外の間での臨床因子の違いを検討した．多変量解析は多重ロジスティック解析を用いて行った．
【結果】年齢，腫瘍数，脈管侵襲，ミラノ基準内外，取り扱い規約上の進行度，Child-Pugh分類，HCV感染，血清α－フェトプロテイン値および初回治療の治療法について，10年以上の生存群とそれ以外の間で有意差が認められた．多変量解析では，高齢，ミラノ基準外，Child-Pugh分類B以上および肝切除以外の初回治療が10年以上の長期生存に対する危険因子であった．ミラノ基準内，Child-Pugh分類Aで初回治療として肝切除を受けた場合の10年生存率は，HCV陰性であれば71％，陽性であれば49％であった．
【結論】ミラノ基準内およびChild-Pugh分類Aを満たす若年のHCC患者においては，肝切除による治療が可能であれば長期生存が期待できる．特にこれらの区分に属するHCV陽性の肝細胞癌患者においては肝切除が推奨される．