Hiroshima J. Med. Sci.
Vol. 47, No.3, 99~104, September, 1998
HIJM 47-14

Factors Affecting Postoperative Prognosis in the Solitary-nodule Type of Hepatocellular Carcinoma: Experience of 132 Cases in our Institute

Toshimasa ASAHARA[1], Kiyohiko DOHI[1], Koji KATAYAMA[1], Toshiyuki ITAMOTO[1], Yuzo OKAMOTO[1], Hideki NAKAHARA[1], Eiji ONO[1], Keizo SUGINO[1], Seiji MARUBAYASHI[1], Hiroshi YAHATA[1], Mikiya KITAMOTO[2], Toshio NAKANISHI[2], Kazuyoshi AZUMA[3], Katsuhide ITO[3] and Fumio SHIMAMOTO[4]

1) Second Department of Surgery, Hiroshima University School of Medicine
2) First Department of Internal Medicine, Hiroshima University School of Medicine
3) Department of Radiology, Hiroshima University School of Medicine
4) Department of Pathology, Hiroshima University Hospital

ABSTRACT

A retrospective analysis of clinical and pathological factors was performed on 132 surgical cases with solitary-nodule type HCC in our hospital. The overall cancer-free survival rates after 1, 3 and 5 years were 82.2%, 42.3% and 26.5%, respectively. With univariate analysis, the significant prognostic factors for survival were tumor size, cancer cell infiltration of the fibrous capsule of the tumor (fc-inf), invasion into portal vein (vp), and intrahepatic metastasis (im), while significant prognostic factors for non-recurrence were tumor size, fc-inf, vp, im, Edmondson-Steiner's classification and perioperative blood transfusion. With multivariate analysis for recurrence, significant factors were vp, clinical stage (CS), and perioperative blood transfusion. Therefore, prognostic factors for long-term survival in surgical cases of HCC are thought to be good hepatic function, absence of portal invasion, and avoidance of perioperative blood transfusion if possible.

Key words: *Hepatocellular carcinoma, Hepatectomy, Prognostic factor*

Hepatocellular carcinoma (HCC) is one of the most common cancers in the world and Japan is no exception. There are many options for the treatment of HCC, such as hepatic resection, percutaneous ethanol injection (PEI), transcatheter arterial embolization (TAE), and microwave coagulation therapy (MCT). Hepatic resection is the most reliable procedure for tumor ablation and long-term, tumor-free survival. However, the long-term prognosis for HCC treated by curative resection is still unsatisfactory because of the high incidence of recurrence in the remnant liver after hepatic resection. This study was designed to clarify the significance of various clinicopathological factors for long-term survival.

MATERIALS AND METHODS

From 1986 to 1994, 264 patients with HCC underwent various types of hepatectomy in our hospital. There were 209 men and 55 women and the age of the patients ranged from 36 to 83 years old (mean: 59 years). The patients were observed over a 3-year period. Specimens were examined macroscopically and histologically, and the patients were followed up in our hospital. Periodic examinations for recurrence of HCC were performed (tests for tumor markers, such as α-fetoprotein (AFP), protein induced by Vitamin K deficiency and antagonist II (PIVKA-II) and ultrasonography (US) were conducted every 3 months; computed tomography (CT) or magnetic resonance imaging (MRI) was performed every 6 months). Recurrence in the remnant liver was diagnosed by a combination of serum AFP, PIVKA-II level, US, CT, MRI and hepatic angiography.

Patients who had died within 1 month after surgery and who had received an absolutely non-curative operation, defined as macroscopic tumor left in the remnant liver, were excluded from this study.

Using univariate analysis on data from 132 patients (96 men and 36 women), we assessed the relationship between clinicopathological factors and prognosis of solitary-nodule type HCC. The solitary-nodule type was selected for analysis because the relationship among the various prognostic factors, such as intrahepatic metastasis, tumor multicentricity, and tumor-related factors

Address: 1–2–3 Kasumi, Minami-ku, Hiroshima 734–8551, Japan
TEL: +81–82–257–5221, FAX: +81-82-257-5224

of each individual tumor of the multiple-nodule type are considered very complex.

STATISTICS: Cumulative survival and non-recurrence rates were calculated by the method of Kaplan and Meier[13], and statistical analysis was performed by the generalized Wilcoxon test. Each of the clinicopathological factors was evaluated by Cox multiregression analysis[19]. $p<0.05$ was considered significant. There were several unknown data that were excluded from this study; these included tumor size (5 cases), fc (1 case), portal invasion (1 case), Edmondson's grade (18 cases) and blood transfusion (1 case).

RESULTS

Figure 1 shows the overall cancer-free survival curve. We calculated the 1-, 2-, 3- and 5-year cancer-free survival rates to be 82.2%, 60.1%, 42.3% and 26.5%, respectively.

Table 1 reveals the relationship between the patients' background, including gender, age, hepatitis B virus surface antigen (HBsAg), hepatitis C virus antibody (HCV), clinical stage (CS) (the grade of the clinical severity of liver cirrhosis defined by the Liver Cancer Study Group of Japan), and prognosis. With regard to gender, no significant differences were observed in the recurrence and survival rates. Age was divided into 4 groups, 40–49, 50–59, 60–69 and 70 or more years old. No significant differences were found in the survival rates among the 4 groups, but the patients of 70 or more years old had a significantly lower recurrence rate than the 50–59 and 60–69 year old groups. The study population was divided into 2 groups based on hepatitis viral infection status as follows: 17 patients were positive for HBsAg and negative for HCV and 57 patients were negative for HBsAg and positive for HCV: However, the type of hepatitis had no significant effect on the survival and recurrence rates. The CS had no significant effect on the prognosis.

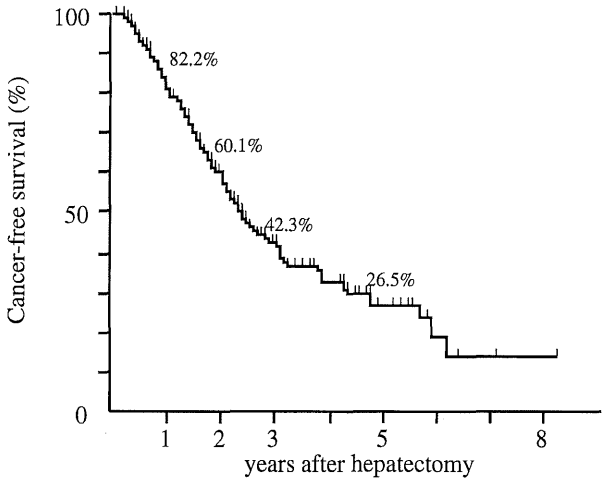

Fig. 1. Cumulative cancer-free survival rate of patients with HCC who received a hepatectomy

Table 2 shows the relationship between the clinicopathological factors and the actual survival rates. Tumor size, infiltration of cancer cells into the fibrous capsule of the tumor (fc-inf), invasion into the portal vein (vp) and microscopic intrahepatic metastasis (im) had a significant effect on the prognosis.

Tumor size was divided into 3 groups: 1) less than or equal to 2 cm in maximum diameter, 2) greater than 2 cm and less than or equal to 5 cm, and 3) greater than 5 cm. No significant difference was found between groups 1 and 2, but patients with a tumor larger than 5 cm had a significantly lower survival rate than the other groups.

Patients who were positive for fc-inf, vp and im exhibited a significantly lower survival rate than those who were negative for each factor. On the other hand, fc, Edmondson and Steiner's classification[5], the surgical margin (Tw), the extent of the hepatic resection (Hr) and perioperative blood transfusion had no significant effect on survival

Table 1. Relationship between HCC patients' background and prognosis

Category	No. of Pts	Survival Rate 3-Yr	Survival Rate 5-Yr	p-value	Non-Recurrence Rate 3-Yr	Non-Recurrence Rate 5-Yr	p-value
Gender							
Male	96	80.4	47.7	N.S.	36.6	22.5	N.S.
Female	36	76.1	46.4		45.9	33.4	
Age							
40–49	15	92.3	46.2	N.S.	74.0	49.4	
50–59	39	74.8	43.6		32.7	18.7	
60–69	62	77.2	41.7		31.9	22.8	
70≤	14	90.0	67.5		63.3	42.2*	p<0.05
HBV & HCV							
HBsAg (+) HCV (–)	17	92.3	61.5	N.S.	50.2	33.4	N.S.
HBsAg (–) HCV (+)	57	69.3	34.2		17.4	5.5	
Clinical Stage (CS)							
I	78	86.0	50.6	N.S.	47.7	37.4	N.S.
II	43	72.4	51.0		25.5	13.1	

Table 2. Relationship between clinicopathological factors and survival rate after hepatectomy

Category	No. of Pts	Survive Rate 3-Yr	Survive Rate 5-Yr	p-value
Tumor size (mm)				
0<d≤20	40	86.6	53.3	
20<d≤50	70	82.6	53.8	p<0.05
50<d	17	53.9	26.9	
Capsular formation (fc)				
–	23	86.5	48.7	N.S.
+	108	77.5	41.8	
Capsular invasion (fc-inf)				
–	46	87.4	78.2	p<0.05
+	64	74.0	35.6	
Portal invasion (vp)				
–	92	84.5	62.9	p<0.01
+	39	66.8	23.8	
Intrahepatic metastasis (im)				
–	116	81.2	53.1	p<0.01
+	16	63.4	18.2	
Edmondson's grade				
I	11	80.0	40.0	
II	75	79.6	46.7	N.S.
III	28	66.6	44.4	
Surgical margin (Tw)				
–	53	81.3	50.0	N.S.
+	79	77.6	45.1	
Extent of resection				
partial.	70	78.5	54.3	
subsegment.	40	82.5	58.8	N.S.
segment.	8	85.7	28.6	
lobectomy	14	66.7	14.6	
Blood transfusion				
–	119	80.5	50.6	N.S.
+	12	63.6	31.8	

* d=largest diameter

Table 3. Relationship between clinicopathological factors and non-recurrence rate after hepatectomy

Category	No. of Pts	Non-recurrence Rate 3-Yr	Non-recurrence Rate 5-Yr	p-value
Tumor size (mm)				
0<d≤20	40	48.3	35.2	
20<d≤50	70	43.6	27.2	p<0.001
50<d	17	53.9	26.9	
Capsular formation (fc)				
–	23	59.3	39.5	N.S.
+	108	36.1	23.3	
Capsular invasion (fc-inf)				
–	46	45.0	36.1	p<0.01
+	64	31.5	15.1	
Portal invasion (vp)				
–	92	49.8	35.9	p<0.001
+	39	18.3	5.5	
Intrahepatic metastasis (im)				
–	116	44.3	29.1	p<0.01
+	16	8.0	8.0	
Edomondson's grade				
I	11	49.4	49.4	
II	75	40.8	24.1	p<0.01
III	28	21.3	14.2	
Surgical margin (Tw)				
–	53	48.0	38.2	
+	79	33.7	17.2	N.S.
Extent of resection (Hr)				
partial.	70	39.2	35.3	
subsegment.	40	48.1	37.1	N.S.
segment.	8	29.2	0.00	
lobectomy	14	23.4	15.6	
Blood transfusion				
–	119	42.3	27.2	p<0.01
+	12	14.1	14.1	

* d=largest diameter

rate.

The relationship between clinicopathological factors and the actual non-recurrence rates was likewise examined, as shown in Table 3. Tumor size, fc-inf, vp, im, Edmondson's classification and blood transfusion were found to be significant prognostic factors.

With Edmondson's classification, a significantly higher recurrence rate was found in the patients with grade III (poorly differentiated type), but no significant difference was found between grade I (well differentiated type) and II (moderately differentiated type).

Ten of 12 (83.3%) patients who received perioperative blood transfusion, relapsed within 3 years after the operation and a significant difference was observed in the non-recurrence rate ($p<0.01$).

On the other hand, the presence of a fibrous capsule (fc) had no significant influence. As to surgical treatment, the surgical margin (Tw) and the extent of the hepatic resection (Hr) was discussed, but this was found not to have a significant influence on recurrence after hepatic resection.

The Cox regression was used to analyze the variables (Multivariate analysis) most significantly related to survival and recurrence after hepatic resection (Table 4). The factors that had a significant effect on mortality were fc ($p<0.001$), vp ($p<0.00004$), Tw ($p<0.04$), and blood transfusion. However, vp ($p<0.01$), CS ($p<0.04$) and blood transfusion ($p<0.008$) were significant contributing factors on recurrence.

DISCUSSION

Since 1980, surgical treatment for HCC has made much progress and the operative mortality rates, recently reported to be less than 5%[12,22], have continued to decrease. The reasons can be

Table 4. Cox regression analysis of death and recurrence distributions in HCC patients

Variable	Category	Survival			Recurrence		
		Coefficient	χ^2-Statistic	p-value	Coefficient	χ^2-Statistic	p-value
Gender	(Male, Female)	–0.35	1.37	0.24	0.10	0.21	0.64
Age	(40–49, 50–59, 60–69,70–)	0.15	0.54	0.46	0.10	0.52	0.47
HBsAg	(–, +)	0.11	0.07	0.79	0.09	0.09	0.76
Tumor size (mm)	(0–20,21–50,51–)	0.32	1.92	0.17	0.22	1.80	0.18
Capsular formation (fc)	(–, +)	–0.74	10.4	0.001**	–0.09	0.33	0.56
Vascular invasion (vp)	(–, +)	1.78	16.8	0.00004**	0.66	5.42	0.02*
Intrahepatic metastasis (im)	(–, +)	0.62	3.44	0.06	0.22	0.81	0.37
Edmomdson's grade	(I, II, III~)	–0.15	0.61	0.43	0.23	2.34	0.13
Hepatic resection (Hr)	(Hr0, S, 1, 2~)	–0.28	2.46	0.12	–0.08	0.35	0.55
Surgical margin (Tw)	(–, +)	–0.71	4.15	0.04*	0.01	0.003	0.96
Clinical stage (CS)	(I, II)	0.26	0.90	0.34	0.45	4.39	0.04*
Blood transfusion	(–, +)	0.42	5.12	0.02*	0.40	7.03	0.008**

summarized as follows: 1) an increase of cases with HCC in less advanced stages due to the improvement of non-invasive detection systems such as CT, US and MRI; 2) improved evaluation of preoperative hepatic function reserved for HCC patients with chronic hepatitis or liver cirrhosis; 3) the development of hepatic resection methods for segments as described by Couinaud[4] and for smaller parts of the liver by the US guided approach[15], and 4) the development of pre- and postoperative management for HCC patients[22]. However, the long term prognosis for HCC treated by curative resection is still poor because of the high incidence of recurrence in the remnant liver.

Generally, HCCs are nourished by the hepatic artery and it is thought that cancer cells spread through the portal tract[16]. Accordingly, various efforts, such as preoperative TAE, anatomical hepatic resection along the portal tract, wide surgical margins and postoperative preventional TAE for recurrence in the remnant liver have been carried out with little improvement in prognosis. As a result, we investigated the clinical and pathological factors that affect recurrence in surgically treated cases of HCC.

The backgrounds of the patients with HCC, such as gender, age, HBsAg, HCV and clinical stage were investigated. With regard to age, patients older than 70 years old had a lower recurrence rate than those younger than 70 years old, although only a limited hepatic resection was performed in the former. Many reports indicate that there is no relationship between patients' age and prognosis[9], although some have demonstrated a better prognosis in older patients with HCC due to the fact that many older patients have a solitary tumor of which most are well differentiated types[17].

Clinical Stage (CS) indicates the grade of severity of hepatic dysfunction such as chronic hepatitis and liver cirrhosis. CS-II are cases with a lower hepatic function reserve than CS-I, which thus permits only a limited hepatic resection. In this current study, clinical stage was a significant factor for prognosis of recurrence as analyzed by the Cox regression. This may be due to an inadequate extent of hepatic resection, insufficient postoperative TAE and a high incidence of multicentric occurrence after the operation in the CS-II cases.

Using univariate analysis, a significant correlation was found between non-recurrence rate after hepatic resection and the clinicopathological factors of tumor size, fc-inf, vp, im, Edmondson's grade and perioperative blood transfusion.

Tumor size is thought to be a good indicator for intrahepatic recurrence and long term survival from HCC[1,9,22], because the incidence of portal involvement increases with the growth of a tumor. Our results also indicate that patients with HCCs more than 5cm in diameter have significantly higher recurrence and poorer survival rates than those with HCCs less than 5cm. In general, the incidence of portal venous involvement increases with a tumor size larger than 2cm in diameter. An HCC less than 2cm is considered to be an early stage of HCC[22]. However, some cases of poorly differentiated HCC less than 2cm have portal venous involvement. In these cases, intrahepatic recurrence occurs in the early period after operation and the prognosis becomes very poor. Furthermore, in some cases, what are believed to be secondary multicentric tumors develop[18]. Unfortunately, at present there are no methods for accurately distinguishing intrahepatic metastases from secondary multicentric tumors. For these reasons, in this study no significant difference in recurrence rate was observed between patients with a tumor diameter less than 2cm and those with tumor a

diameter of 2.1~5cm.

Fc-inf, vp and im depend on whether tumor cells, localized within the fibrous capsule of the tumor, will progress into an adjacent region of the liver and spread through the portal tract. Therefore, in cases where these factors are positive, there is the possibility of the existence of microscopic metastases. Thus our finding that the patients in which these factors were positive had a significantly higher recurrence rate and a poorer survival rate than those in which these factors were negative is reasonable.

Edmondson's classification indicates the various stages of cell differentiation of HCC. However, many investigators reported no relationship between Edmondson's grade and prognosis of HCC[1,10]. In our study, poorly differentiated HCC had a significantly higher recurrence rate and poorer prognosis, but no significant difference was found between well- and moderately differentiated types on prognosis. The development of new analytic grading methods on the malignant potential of HCC, such as via DNA flow cytometric analysis[3,6] or the mitotic index[9], will undoubtedly improve clinical prognoses.

Surgical margin (Tw) is defined as the microscopic 10mm-disease-free margin. Our result indicated that there was no significant difference between the cases with and without a 10mm-disease-free margin. It is thought that tumor cells spread through portal tracts beyond a 10mm-disease-free margin, because in clinical cases, intrahepatic metastasis occurs randomly and ubiquitously in the remnant liver. On the other hand, surgical margin has a practical implication in the resection of microscopic metastases around a primary tumor and in preventing local recurrence, especially in the cases that have an extra-capsular invasion of tumor cells.

Moreover, with regard to the extent of hepatic resection for HCC, many investigators[1,21] have discussed whether wide hepatic resection could prevent intrahepatic recurrence after operation. Our results indicate no significant difference between limited resection, such as partial hepatectomy or subsegmentectomy, and wide hepatic resection, such as segmentectomy or lobectomy. But most of the cases with wide hepatic resection are advanced cases of HCC and precise assessment of the role of wide hepatic resection was impossible in this study.

We did not perform preventional wide hepatic resection for the following reasons: 1) intrahepatic recurrences do not always occur in the adjacent segment to a primary tumor, 2) other additional therapies, such as PEI or TAE, are necessary for achieving extended survival, because of a high incidence of recurrence, and 3) wide hepatic resection reduces the hepatic function reserve and prevents additional therapy for recurrent tumors.

Blood transfusion was one of the most significant prognostic factors as assessed by the univariate and multivariate analyses in our study. A similar relationship between perioperative blood transfusion and poor survival has been reported in colorectal cancer[2] and lung cancer[11]. The exact mechanism of the effect of blood transfusion on cancer patients remains unclear, but laboratory data indicate an increased suppressor cell activity of both T-cells and adherent cell populations[7,20] or decreased natural killer cell activity after blood transfusion[8,14]. These results indicate that perioperative blood transfusion should be avoided in HCC patients if possible.

(Received February 16, 1998)
(Accepted July 22, 1998)

REFERENCES

1. **Arii, S., Tanaka, J., Yamazoe, Y., Minematsu, S., Morino, T., Fujita, K., Maetani, S. and Takayoshi, T.** 1992. Predictive factors for intrahepatic recurrence of hepatocellular carcinoma after partial hepatectomy. Cancer **69:** 913–919.
2. **Blumberg, N., Agarwal, M. M. and Chuang, C.** 1985. Relation between recurrence of cancer of the colon and blood transfusion. Br. Med. J. **290:** 1037–1039.
3. **Chen, M.F., Hwang, T.L., Tsao, K.C., Sun, C.F. and Chen, T.J.** 1991. Flow cytometric DNA analysis of hepatocellular carcinoma; preliminary report. Surgery **109:** 455–458.
4. **Couinaud, C.** 1954. Bases anatomiques des hepatectomies gauche et droite reglees; Techniques gui en decoulent. J. Chir. (Paris) **70:** 933–966.
5. **Edmondson, H.A. and Steiner, P.E.** 1954. Primary carcinoma of the liver; A study of 100 cases among 48, 900 necropsies. Cancer **7:** 462–503.
6. **Ezaki, T., Kanematsu, T., Okamura, T., Sonoda, T. and Sugimachi, K.** 1988. DNA analysis of hepatocellular carcinoma and clinicopathologic implications. Cancer **61:** 106–109.
7. **Fischer, E., Lenhard, V., Seifert, P., Kluge, A. and Johannsen, R.** 1980. Blood transfusion-induced suppression of cellular immunity in man. Hum. Immunol. **3:** 187–194.
8. **Gascon, P., Zoumbos, N.C. and Young, N.S.** 1984. Immunologic abnormalities in patients receiving multiple blood transfusions. Ann. Intern. Med. **100:** 173–177.
9. **Haratake, J., Takeda, S., Kasai, T., Nakao, S. and Tokui, N.** 1993. Predictable factors for estimating prognosis of patients after resection of hepatocellular carcinoma. Cancer **72:** 1178–1183.
10. **Hsu, H.C., Sheu, J.C., Lin, Y.H., Chen, D.S., Lee, C.S., Hwang, L.Y. and Beasley, R.P.** 1985. Prognostic histologic features of resected small hepatocellular carcinoma (HCC) in Taiwan. Cancer **56:** 672–680.
11. **Hyman, N.H., Foster, R.S., DeMeules, J.E. and Costaza, M.C.** 1985. Blood transfusions and survival after lung cancer resection. Am. J. Surg. **149:** 502–507.

12. **Iwatsuki, S. and Starzl, T.E.** 1988. Personal experience with 411 hepatic resections. Ann. Surg. **208:** 421–434.
13. **Kaplan, E. and Meier, P.** 1959. Nonparametric estimation from incomplete observations. J. Am. Stat. Assoc. **53:** 457–481.
14. **Kaplan, J., Sarnaik, S., Gitlin, H. and Lusher, J.** 1984. Diminished helper/suppressor lymphocyte ratios and natural killer activity in recipients of repeated blood transfusions. Blood **64:** 308–310.
15. **Makuuchi, M., Hasegawa, H. and Yamazaki, S.** 1985. Ultrasonically guided subsegmentectomy. Surg. Gynecol. Obstet. **161:** 346–350.
16. **Nakashima, T. and Kojiro, M.** 1986. Pathologic characteristics of hepatocellular carcinoma. Semin. Liver Dis. **6:** 259–266.
17. **Okamoto, Y., Asahara, T., Hino, H., Ochi, M., Nakahara, H., Katayama, K., Itamoto, T., Ono, E., Fukuda, Y. and Dohi, K.** 1995. Study of hepatocellular carcinoma undergoing hepatectomy in the extreme elderly patients. J.J.C.D.O. **5:** 63–69.
18. **Okuda, K., Tanaka, M., Nakayama, T., Saitsu, H., Tanikawa, K., Nakashima, O. and Kojiro, M.** 1993. Clinicopathologic comparison between resected hepatocellular carcinomas (HCC) and recurrent tumors; A special reference to multicentric carcinogenesis of HCC. Int. Hepatol. Commun. **1:** 65–71.
19. **SAS Institute, Inc.** 1985. SAS user's guide; statistics. version 5. Cary (NC). SAS Institute Inc. Cary, NC, USA.
20. **Smith, M.D., Williams, J.D., Coles, G.A. and Salaman, J.R.** 1981. The effect of blood transfusion on T-suppressor cells in renal dialysis patients. Transplant. Proc. **13:** 181–183.
21. **Sugioka, A., Tsuzuki, T. and Kanai, T.** 1993. Postresection prognosis of patients with hepatocellular carcinoma. Surgery **113:** 612–618.
22. **The Liver Cancer Study Group of Japan.** 1990. Primary liver cancer in Japan; Clinicopathological features and results of surgical treatment. Ann. Surg. **211:** 277–287.