Table 6. Prognostic variables by multivariate analysis using Cox's proportional hazard model

Variable		Hazard ratio	95% C.I.	*P* value
m-JIS	m-JIS 1 vs m-JIS 0	1.44	1.33, 1.56	0.0001
	m-JIS 2 vs m-JIS 0	2.17	2.00, 2.35	0.0001
	m-JIS 3 vs m-JIS 0	3.45	3.16, 3.77	0.0001
	m-JIS 4 vs m-JIS 0	4.99	4.52, 5.51	0.0001
	m-JIS 5 vs m-JIS 0	8	7.09, 9.03	0.0001
Age (years)	≥60 vs <60	1.12	1.08, 1.16	0.0001
Sex	Male vs female	1.01	0.98, 1.05	0.54
HBsAg	Positive vs negative	1.16	1.10, 1.22	0.0001
HCVAb	Positive vs negative	1.04	0.99, 1.09	0.09
Tumor size (cm)	>2.0 vs ≤2.0	1.1	1.08, 1.11	0.0001
Number of tumors	Multiple vs solitary	1.06	1.02, 1.11	0.002
Portal vein invasion	Present vs absent	1.48	1.41, 1.56	0.0001
Hepatic vein invasion	Present vs absent	1.31	1.23, 1.40	0.0001
Extrahepatic metastasis	Present vs absent	1.81	1.69, 1.94	0.0001
AFP (ng/ml)	>400 vs ≤400	1.61	1.55, 1.66	0.0001

C.I., confidence interval

Table 7. The predictive model based on the m-JIS score

Parameter	Estimate	Standard error	*P* value	Hazard ratio	95% C.I.
Score 1 (m-JIS 1 vs m-JIS 0)	0.544	0.055	<0.0001	1.72	1.55, 1.92
Score 2 (m-JIS 2 vs m-JIS 0)	1.06	0.053	<0.0001	2.89	2.60, 3.20
Score 3 (m-JIS 3 vs m-JIS 0)	1.712	0.054	<0.0001	5.54	4.89, 6.16
Score 4 (m-JIS 4 vs m-JIS 0)	2.328	0.058	<0.0001	10.3	9.15, 11.5
Score 5 (m-JIS 5 vs m-JIS 0)	3.375	0.068	<0.0001	29.2	25.6, 33.4

Table 8. The predictive model based on the m-CLIP score

Parameter	Estimate	Standard error	*P* value	Hazard ratio	95% C.I.
Score 1 (m-CLIP 1 vs m-CLIP 0)	0.538	0.036	<0.0001	1.71	1.60, 1.84
Score 2 (m-CLIP 2 vs m-CLIP 0)	1.103	0.036	<0.0001	3.01	2.81, 3.24
Score 3 (m-CLIP 3 vs m-CLIP 0)	1.623	0.04	<0.0001	5.07	4.69, 5.48
Score 4 (m-CLIP 4 vs m-CLIP 0)	2.344	0.048	<0.0001	10.4	9.49, 11.4
Score 5 (m-CLIP 5 vs m-CLIP 0)	3.156	0.06	<0.0001	23.5	20.9, 26.4
Score 6 (m-CLIP 6 vs m-CLIP 0)	3.336	0.089	<0.0001	28.1	25.6, 33.4

Table 9. Generalized estimating equation analysis of the absolute value of the residuals

Parameter	Estimate	Standard error	*P* value
Intercept	0.0145	0.0002	<0.0001
Scoring method (m-JIS vs m-CLIP)	−0.0047	0.0001	<0.0001
Score value	0.0057	0.0001	<0.0001

throughout more than 50% of the liver. This criterion is used to determine not only the CLIP score but also the BCLC stage.[9,10] The assessment of tumor extension relative to total liver volume is poorly reproducible. In addition, tumor extension of more than 50% is indicative of highly advanced disease. Because the recent promotion of screening programs of high-risk populations with hepatitis B or C viral infection has led to the increasingly early detection of HCC, the majority of tumors detected are small. In this study, 77% of patients had

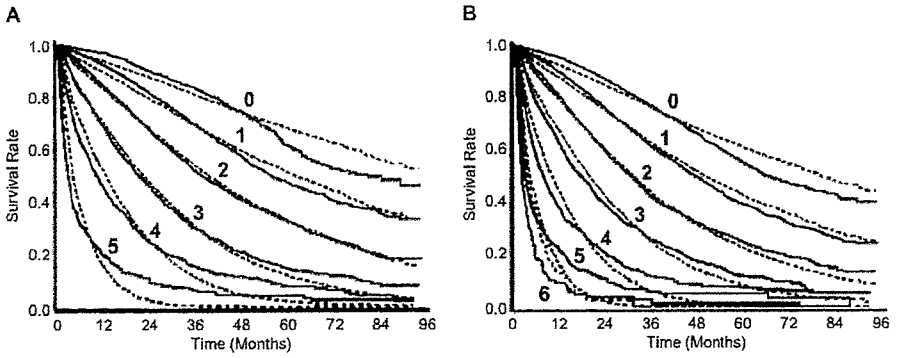

Fig. 3A,B. Comparison of the observed survival curves (*solid lines*) and the predicted survival curves (*dashed lines*) in the validation sample (n = 21 142 patients). **A** Predictions based on the modified Japan Integrated Stage score; **B** those based on the modified Cancer of the Liver Italian Program score

tumors 5 cm or less in diameter. Therefore, a precise evaluation of tumor character should be included in a staging system.

Recently, the TNM staging systems proposed by both the LCSGJ and the International Union Against Cancer/American Joint Committee on Cancer (UICC/AJCC) have been revised.[7,16] The new classification system designed by the LCSGJ is quite simple and convenient for clinical practitioners. Tumor status is determined by tumor size and number and by the presence or absence of vascular or bile duct invasion. The tumor size cutoff is 2 cm in the LCSGJ TNM classification and 5 cm in the UICC/AJCC classification. To facilitate more precise estimation of patient prognosis, the working group of the International Scientific Committee of the International Hepato-Pancreato-Biliary Association recommended the TNM staging system proposed by the LCSGJ.[17] In this study, the LCSGJ TNM stage had good ability to predict the survival of patients with HCC.

Kudo et al.[12] originally proposed the JIS score, which is defined by the LCSGJ TNM stage and the Child-Pugh classification. Using 4525 patients with HCC at five institutions, they validated the JIS score as a good prognostic staging system with good internal reproducibility.[13] Our study evaluated the m-JIS score, which extends the JIS score, using a large HCC population. The difference between these two systems is the scoring system for liver function. The Child-Pugh classification is used extensively internationally to evaluate liver function in patients with HCC. This classification was devised to predict the tolerance of patients with portal hypertension to portosystemic shunting. Encephalopathy is one of the variables in the Child-Pugh classification. In a recent report of the LCSGJ, mild to severe encephalopathy was observed in only 5.0% of all patients with HCC.[2] The indocyanine green (ICG) clearance test, one of the best laboratory tests to evaluate liver function precisely,[18] is widely used in Eastern countries. In the LCSGJ report, ICG retention rates at 15 min ($ICGR_{15}$) were less than 15% in 33% of patients, 15%–40% in 54%, and more than 40% in 13%.[2] Therefore, the LCSGJ proposed the degree of liver damage classification system, defined by ascites, serum bilirubin level, serum albumin level, $ICGR_{15}$, and prothrombin activity, but excluding encephalopathy, to evaluate liver function precisely. To assess the prognosis of patients with HCC more effectively, we have modified the JIS score to incorporate the degree of liver damage classification instead of the Child-Pugh classification. The m-JIS score is calculated from TNM staging, determined using imaging studies, and the degree of liver damage classification, determined by clinical data. The m-JIS score indicated the most important predictor with the highest hazard ratio among several variables. Patient populations with m-JIS scores of 0–5 were well discriminated using this system.

The BCLC staging classification considers several critical prognostic factors, including performance status, tumor stage, Okuda stage, Child-Pugh classification, portal hypertension, and bilirubin levels.[10] The CUPI system is another common prognostic staging system that utilizes similar prognostic indicators.[11] Unfortunately, we could not compare the BCLC and CUPI staging systems with m-JIS staging, because portal hypertension, performance status, and alkaline phosphatase levels were not included in the original survey items within the database. The CLIP score proposed in 1998 is determined by Child-Pugh classification, tumor morphology, AFP levels, and portal vein thrombosis.[9] This score has been validated not only in multiple series using the same group[19] but also in Canadian and Japanese patients with HCC.[20,21]

In an evaluation of several HCC staging systems, Wildi et al.[8] reported that the CLIP score is the most well documented and analyzed staging system for prognostic purposes. In this study, we examined the m-CLIP score, based on a maximum tumor diameter greater than 10 cm and the grade of liver damage by LCSGJ, because the original CLIP score could not be calculated with the information from the database, which did not include >50% tumor extension or the Child-Pugh classification. Also, we used 400 ng/ml as the cutoff level for AFP in the m-CLIP score. The m-CLIP score may

be much better than the original CLIP score in its stratification ability and the survival prediction of each score, because the grade of liver damage by LCSGJ evaluates liver function more precisely than the Child-Pugh classification, and 400 ng/ml for AFP is a more useful cutoff level than 400 ng/dl in our patient population. The m-CLIP score also had a good discriminating ability for patients with HCC in the training sample.

In our comparison of the m-JIS score and the m-CLIP score using cross-validation and GEE analyses, the m-JIS score had a greater predicative accuracy than the m-CLIP score for the survival of patients with HCC. In both the m-JIS and m-CLIP analyses, only patients on whom ICG tests had been performed were included. In this study, 40.6% of total patients had an m-JIS score of 0 or 1 and 10.0% had an m-JIS score of 4 or 5, while 60.9% had an m-CLIP score of 0 or 1 and 7.6% had an m-CLIP score of 4, 5, or 6. This patient distribution is similar to that in the study of Kudo et al.[13] The difference in patient distribution might be an important factor leading to the better predicative accuracy of the m-JIS score.

One of the differences between these scoring models is the cutoff level of tumor morphology. In the m-CLIP scoring system, tumor morphology is evaluated by whether it is uninodular and has a maximum diameter greater than 10 cm. In our patient sample, only 7.6% of patients possessed tumor(s) larger than 10 cm. As tumor size is one of the most important factors used to select treatment modalities, more precise evaluation of tumor character is useful for more accurately predicting outcome in patients with HCC. Another difference is the tumor marker included in the m-CLIP score. We previously observed that AFP is an independent prognostic factor for patients with HCC who undergo liver resection.[6] Protein induced by vitamin K absence or antagonist-II (PIVKA-II) has also been shown to be a useful prognostic factor in a univariate analysis.[6] Recently, Marrero et al.[22] reported that PIVKA-II is more sensitive and specific than AFP for differentiating HCC from other nonmalignant chronic liver diseases. *Lens culinaris* agglutinin-reactive AFP is reported to be another useful predictor in patients with HCC.[23] These tumor markers should be evaluated further to determine their suitability for use in a prognostic staging system for patients with HCC.

In conclusion, the m-JIS score can be effectively used to predict the prognosis of HCC patients in Japan, where HCC screening programs for high-risk populations have been established. Next, we plan to validate the usefulness of this scoring system in non-Japanese patient populations.

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INTERNAL MEDICINE

REVIEW ARTICLE

Clinical Aspects of Hepatocellular Carcinoma in Japan

Kiwamu Okita

Abstract

HCC in Japan has very different characteristics from that in other Asian countries. Because, among the Japanese HCC patients approximately 80% of the patients are HCV positive and they are aged over 60 years old. On the other hand, in many Asian countries HBV-positive HCC patients are dominant and their age is younger than the Japanese patients.

Early diagnosis of HCC is mainly performed by means of imaging diagnostic technique such as abdominal ultrasonography, dynamic CT, dynamic MRI and CT angiography. If small HCC less than 3 cm in diameter is found and liver function is well preserved, local ablation therapy or surgical treatment promises better than 5 years survival (over 60%). While, TAE or TACE is performed in cases of HCC larger than 3 cm in size, if liver failure is not complicated. In advanced HCC cases with multiple tumors, arterial infusion of anti-cancer drug has been applied. However, its efficacy is not estimated.

Chemoprevention is another modality for HCC. Eradication of HCV with an anti-viral agent has proven to prevent hepato-carcinogenesis. As for chemoprevention of HCC, some trials are on going in Japan.

Key words: hepatocellular carcinoma, clinical aspects

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Introduction

Hepatocellular carcinoma (HCC) is currently a very common malignancy and its incidence is increasing, both in the far eastern Asian countries and in the US. Particularly, in Japan, persistent hepatitis C virus (HCV) infection is a major risk factor for the development of HCC, which is quite different from other Asian countries. Therefore, we have to recognize that HCV-associated chronic liver diseases are an extremely risky condition considering the complication of HCC.

However, the molecular mechanism of hepatocarcinogenesis in HCV infection remains unclear. Because, HCV belongs to RNA virus, and is not integrated into host hepatocyte DNA which causes the mutation. Whereas, concerning HBV, it is well known that integrated HBV genome into hepatic DNA may play an important role in hepatocarcinogenesis (1-3).

As for the mortality rate among the patients of HCC, it reached to over 30 per 100,000 population by 1995. Each year thereafter, in every year, over 30,000 patients dye of HCC. On the other hand, according to the "White Paper on the Trend of National Public Health in 2004" published by the Japanese Ministry of Health, Labor and Welfare, the mortality tends to decline gradually from 1996 in accordance with the recent progress of early detection and treatment of HCC.

In spite of the improvement in the mortality rate, there is a large number of patients with HCV-associated chronic liver diseases of over approximately 2 million that predisposes for HCC. Therefore, in order to improve the high mortality rate of HCC, we must determine epidemiological and clinical aspects of HCC in our country.

Characteristics of HCC in Japan

1. Epidemiology

Chronic infection with HCV or HBV is the major cause of HCC in Japan. Approximately 80% of Japanese HCC cases are derived from HCV-associated liver cirrhosis and chronic hepatitis, whereas the remaining less than 20% of patients are HBV positive. The frequency of HCC patients has increased rapidly since after 1980. Although it is not clear why the number of patients has increased, we must re-

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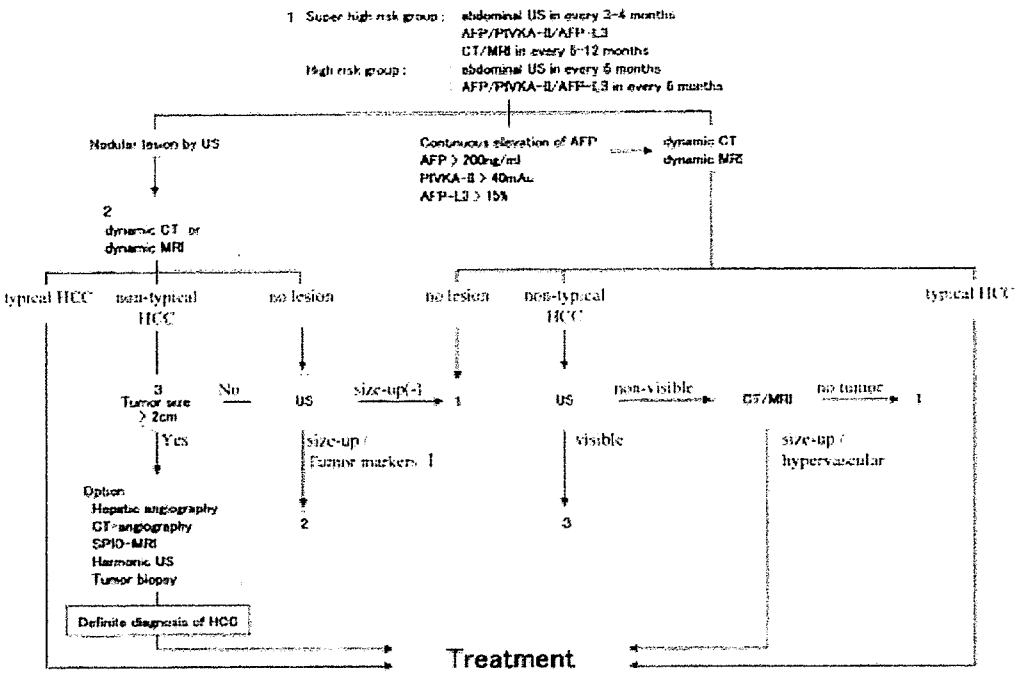

Figure 1. Algorism of HCC surveillance. (cited from Guidlne for Management of HCC based upon EBM and translated into English by author)

member the huge number of stimulant abusers during the social disorder soon after the 2nd world war and their HCV infected blood was sold to the blood bank for transfusion in many medical institutions. Because, until 1965, surgical treatment with a large volume of blood transfusion was performed among the huge number of patients with pulmonary tuberculosis. Such social background may be a trigger of the an explosive outbreak of HCC after 1980.

As for an association with genotype of HCV and HCC, the incidence of genotype 1b is markedly high among the patients. In Japan, genotype 1b is undoubtedly the dominant type. Consequently, it is not clear whether genotype 1b plays an important role in hepatocarcinogenesis in comparison with genotypes 1a, 2a, 2b, 3 and 4.

The annual incidence of HCC from HCV positive liver cirrhosis and chronic hepatitis is 6~7% and 1~2% (4), respectively. As for hepatocarcinogenesis among the patients with HCV positive liver diseases, HCC develops frequently in cirrhotic liver, whereas among the patients with HBV positive liver diseases HCC occurs not only in the cirrhotic liver , but also in chronic hepatitis. This difference may depend on the different properties of two viruses. That is, HBV is DNA virus and its X genome inhibits activity of *p53* known to be a suppressor oncogene (3). On the other hand, HCV known to be a RNA virus does not directly affect the host hepatic DNA. There is a report that HCV core protein enhances cell proliferation via activation of mitogen-activated protein kinase (MAPK) /extracellular signal-regulated kinase (ERK) (5-7).

The mitogen-activated protein kinase (MEK) /ERK signaling pathway is fundamental (8) in controlling cell development, proliferation and cell cycle. While, there is increasing evidence that reactive oxygen species are produced by the interaction of HCV core to host liver mitochondria and results in DNA damage (9, 10). This DNA damage may cause mutation of hepatocytes as a result of genetic change. Taken together, HCV core may be involved in hepatocarcinogenesis in some role.

The incidence of HCC is higher in male patients, as compared with females. This difference is also not clear. However, it may be depend on different expression of the aldosterone receptor between male and female patients (11). This biological characteristic has been applied to hormone therapy in HCC with Tamoxifen (12). However, its therapeutic effect has not been confirmed.

The incubation period from initial infection of HCV to outbreak of HCC is about 30 years on average. Since 1989 when the check system for serum HCV was introduced into Japan, HCV positive blood has been excluded from medical use, and thereafter nowadays the number of new patients of HCV-related liver diseases has remarkably decreased. Therefore, the incidence of HCV positive liver diseases of a young age, below 20 years old, is extremely low, as compared with those over 40 years old. The peak age among the patients with HCC has been older than 60 years old. Therefore, HCC in Japan is recognized to be a malignancy particularly in the aged (13). This is quite in contrast to the countries where are the high incidence of HBV positive HCC patients are younger age.

2. Establishment of high risk group for HCC

According to Tsukuma (14), the following factors are im-

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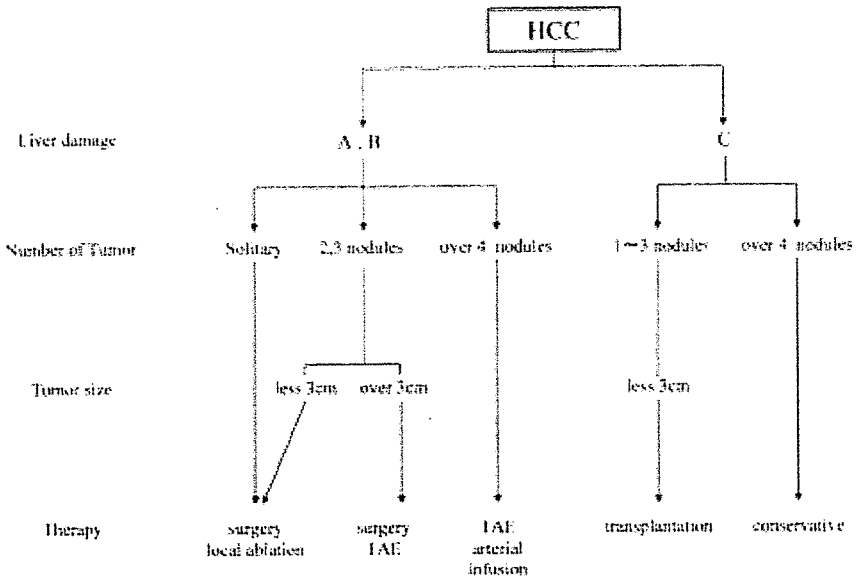

Figure 2. Algorism of HCC therapy. (cited from Guideline for Management of HCC based upon EBM and translated into English by author)

portant in the prediction of HCC among the Japanese: male, the aged, smoker, liver cirrhosis or thrombocytopenia less $10^4/mm^3$ and over 20 ng/ml of AFP. However, for the purpose of early detection of HCC, an imaging diagnostic technique, such as abdominal ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI) is superior. Accordingly, we must recognize the patients who are positive for the prediction factors mentioned above to be high risk group for HCC, and for early detection of HCC those patients should be followed by ultrasonography every 3-4 months and CT or MRI every 6-12 months..

Clinical Aspects of HCC in Japan

1. Diagnosis

Progress of the screening system of HCC has made if possible to detect it in an early stage and the advancement of treatment has improved the 5-year survival rate. At present, the 5 year survival rate of HCC in Japan is over 60% among the patients indicating the stage of liver damage A according to the Liver Cancer Study Group of Japan (15) or the stage 0 due to the Japan Integrated Staging Score (JIS) (16).

Tumor markers such as α-fetoprotein (AFP), AFP-L3, and PIVKA-IIare often used for screening of HCC. However, detection of early or small HCC (less than 3.0 cm in diameter) is difficult by means of these tumor markers. While, these tumor markers are useful for the prediction of recurrence of HCC. Different from tumor markers, the imaging diagnosis using ultrasound (US), computed tomography (CT), magnetic resonance (MR) and hepatic angiography with or without CT is extremely useful for the detection of small HCC. Imaging diagnosis clearly indicates localization of HCC inside the liver. Whenever a suspected lesion is found by routine imaging diagnostic technique, angiography (with or without CT), dynamic CT or dynamic MR should be applied for confirmation of the diagnosis of HCC. A rigid check system in Japan for the early detection of HCC has made clear of the presence of borderline lesions known to be adenomatous hyperplasia or dysplasia. In general, HCC is fed by arterial blood, but borderline lesions are fed by portal blood. Consequently, in the case of hepatic angiography HCC is stained in the arterial phase with contrast medium injected via catheter placed into the hepatic artery, and also in the case of dynamic CT or MRI HCC is stained in the early phase within 30 seconds with the contrast medium injected intravenously. Combination with hepatic angiography and CT, so-called CT-angiography, is the strongest weapon for the early detection of HCC. On the contrary, in general borderline lesions are not stained those methods. Another characteristic of borderline lesions is that the size is usually less than 15 mm. However, confirmed diagnosis of a borderline lesion is only available by histological study of biopsied specimen (17).

The study group for "Guidelines for the Management of HCC Based upon EBM" (group chief: Professor M. Makuuchi, Tokyo University School of Medicine) proposed by the Minisry of Health, Labor and Welfare made an algorism for the surveillance of HCC (Fig. 1). Application of this algorism will be useful for early detection of HCC.

2. Therapy

Surgical resection should be the first choice in the therapy of HCC as well as in other solid cancers. However, HCC develops usually in the cirrhotic liver accompanied with se-

vere liver damage and therefore surgical treatment is so limited. The study group mentioned above also proposed an algorism on the treatment of HCC (Fig. 2). The concept that surgical resection should be the first line must be correct, because the operated group has indicated a better than 5 year survival rate and good cost benefit in comparison with the patients group treated by local ablation therapy.

However, in general, patients do not want to have open surgery, even if we strongly recommend a surgical therapy in the case of small HCC developed in Child A cirrhotic liver such as liver damage A or JIS 0~1in HCC staging system. In such cases, we have applied a local ablation therapy using radio-frequency ablation (RFA). RFA is easy to operate if the operators have sufficient experience with ultrasonography and therefore the number of cases treated by RFA is markedly increasing. But, we must pay attention to severe complications such as perforation of the gastrointestinal tract, intraperitoneal bleeding, hemobilia and liver abscess. In addition, we must note the spread of cancer cells through the inserted RFA needle into HCC due to increased pressure inside of the tumor caused by ablation. There are two types of ablation needles; one is the cool-tip type, and the other is Christmas tree like. We do not know which one is more convenient or stronger in ablation. Usually, RFA is applied to therapy of HCC in which the main tumor is less 3 cm and there are less than 3 satellite nodules.

Trans-hepatic arterial embolization (TAE) or trans-hepatic chemo-embolization (TACE) is usually performed in cases of bigger HCC over 3 cm in size. Of course, in cases that the tumor is less 3 cm in size and hypervascular, TAE or TACE is performed in combination with percutaneous ethanol injection (PEI) or RFA. TAE or TACE should be avoided in the patients whose residual hepatic function is poor, such as Child C. Otherwise, TAE or TACE in Child C makes hepatic function worse.

Arterial infusion of anti-cancer drug has been applied in the therapy of advanced cases of HCC which are not indicated for surgical treatment, local ablation and TAE or TACE. Before introduction of continuous infusion of anticancer drug, one shot arterial injection of the drug has been performed, but the effectiveness of this method was not clarified. Since the introduction of continuous arterial infusion, several regimes have been used as follows: 1) low dose of cisplatin and 5-fluorouracil (18), 2) low dose of cisplatin and 5-fluorouracil with leucovolin (19), 3) methotorexate, 5-fluorouracil, cisplatin and interferon-α2b (20), 4) 5-fluorouracil and subcutaneous interferon-α (21). The effectiveness of arterial infusion of chemotherapeutic agents has not been estimated in a scientific manner. Because, the subjects are all Child C stage, and the data reported are not evidence based. However, although the number of enrolled patients was not sufficient, our study showed significant prolongation of the survival period among the patients treated as compared with the control (19).

On the other hand, from the view point of the patient's quality of life we have to carefully select the chemotherapy for each individual patient, especially in advanced case, sbecause of longer admission and severe adverse effects due to toxicity of chemotherapeutic agents.

Chemoprevention is another ,method of the therapy. Almost all HCC occurs in the liver of chronic hepatitis and liver cirrhosis caused by HBV and HCV. Consequently, eradication of these hepatitis viruses with anti-viral agents may decrease a risk of HCC (22-24). In the therapy of chronic liver diseases caused by HBV and HCV, the therapy using antiviral agents, interferon and lamivudine against HBV and interferon with or without rivabirin, against HCV, should be the first choice. Of course, HCV genotype 1b which is dominant among the HCV positive patients in Japan is remarkably resistant to interferon therapy, fortunately however combination therapy with PEG-interferon and rivabirin has improved the success rate for the eradication of HCV up to 60%.

Phlebotomy improves the liver function accompanied by a decrease in the serum iron level and significantly inhibits the development of HCC, as compared with the control in whom phlebotomy was not applied (25). Although it is known whether iron radical is very toxic, there is also increasing evidence that ROS produced by infection of HCV may play an important role in hepatocarcinogenesis (9, 10). Our studies showed clearly that attachment of HCV core to hepatic mitochondria disrupts electron transport and accelerates ROS production (9). Consequently, anti-oxidant may lead to the decrease of risk of HCC (26, 27). On a different line of agents than anti-viral and anti-oxidative agents, the following two agents developed in Japan have been noted from the view points of chemoprevention of HCC: one is acyclic retinoid (28, 29), and the other is vitamin K2 (30). Although the pharmaceutical action of these drugs is not fully understood, acyclic retinoid may induce the clonal deletion due to the induction of apoptosis in premalignant lesions and vitamin K2 may act as an anti-proliferative agent (31). A clinical trial for the evaluation of these drugs is now ongoing in Japan.

We must bear in mind that HCC can be a preventable disease if we exclude HCV by anti-viral agents and directly ROS by antioxidants. Concerning acyclic retinoid and vitamin K2, we must wait for the results of the clinical trial currently underway.

Liver transplantation is another modality to relieve the patients of HCC. However, in Japan it is quite difficult to pursue liver transplantation for HCC patients even if they want it due to the shortage of donors. To date, the number of HCC patients transplanted is so limited. However, over 70% of the transplanted patients are surviving free of HCC. Liver transplantation for HCC patients should be become more available.

Conclusion

In this article, epidemiology of HCC in Japan and its medical practice at present are described. The mortality rate

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of the patients with HCC is ranked the 3rd in males and 4th in females among malignancies. Therefore, we, physicians, must pay attention to the characteristics of Japanese patients and possible to apply to make an effort to detect HCC in the early stages when it is possible to apply curative therapy.

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Journal of Gastroenterology

Review

Management of hepatocellular carcinoma in Japan

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Key words: hepatocellular carcinoma, epidemiology, surveillance, high-risk population, management

Introduction

Hepatocellular carcinoma (HCC) ranks as the fourth most common cancer in Japan and is responsible for more than 40000 death annually.[1] As for the etiology of HCC, approximately 80% of patients have chronic infection with hepatitis C virus (HCV) and less than 20% have chronic infection of hepatitis B virus (HBV).[2] However, the increase of HCC among patients with cryptogenic liver cirrhosis has presumably resulted from the advance of nonalcoholic steatohepatitis, although its frequency is still quite low.[3,4] The high incidence of HCC among HCV-positive Japanese patients is unique in Southeast Asia countries, where HBV-positive HCC patients are dominant. Recently, Bruix and Sherman published a review article on the management of HCC based on documents collected from practices in Europe and North America.[5] They mentioned that the management of HCC in Japan is somewhat different from that in Western countries. Therefore, in the present article, focus is on management of HCC based on Japanese practice.

Epidemiology of HCC in Japan

The report of the Japanese Ministry of Health and Welfare on the incidence of mortality from HCC in 1996 revealed an increase in western Japan. According to the data, in eastern Japan, including the east side from a line connecting Shizuoka Prefecture, Nagano Prefecture, and Niigata Prefecture, more than 30 deaths/100000 population a year were observed only in Yamanashi Prefecture, whereas in western Japan, including the west side from a line connecting Aichi Prefecture, Toyama Prefecture, and Ishikawa Prefecture, the following 17 prefectures showed a high incidence of HCC in comparison with eastern Japan: 37.4 in Osaka, 34.0 in Hyogo Prefecture, 41.8 in Wakayama Prefecture, 38.5 in Shimane Prefecture, 31.1 in Okayama Prefecture, 39.8 in Hiroshima Prefecture, 36.0 in Yamaguchi Prefecture, 35.7 in Tokushima Prefecture, 31.8 in Kagawa Prefecture, 32.9 in Ehime Prefecture, 35.4 in Kochi Prefecture, 38.7 in Fukuoka Prefecture, 39.9 in Saga Prefecture, 32.6 in Nagasaki Prefecture, 32.5 in Kumamoto Prefecture, 31.7 in Oita Prefecture, and 30.3 in Kagoshima Prefecture. It has been not clear why such high a mortality rate was observed in western Japan, although of course it has been known that the prefectures showing a higher frequency of HCC are also those with a higher HCV carrier rate.

Another interesting fact is that age-specific incidence has shifted toward older people, i.e., over 60 years of age (Fig. 1).[1] This observation is quite different from observations in the United States because, according to El-Serag, patients with HCC have shifted toward a relatively younger age as compared with Japan, although HCC remains an affliction of the elderly (mean age, 65).[6] The increase in HCC patients also parallels the shift of HCV carriers toward old age.[2] The spread of HCV infection in Japan causing an increasing incidence of HCC today can be attributed to the chaos such as the appearance of so many drug abusers after World War II and the use of HCV-contaminated blood for transfusion until 1989. However, prevention of HBV infection with vaccination among infants born from HBV-carrier mothers and exclusion of HCV from medical intervention have resulted in prevention of a new outbreak of viral hepatitis, which is closely related to hepatocarcinogenesis.

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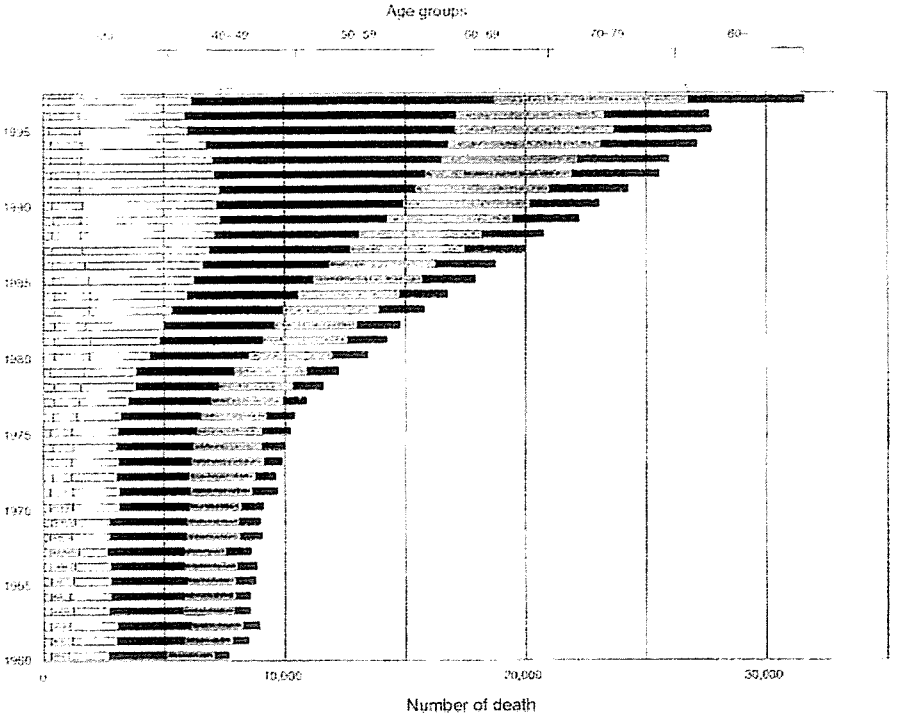

Fig. 1. Yearly deaths as a result of liver cancer in Japan[1]

Surveillance of HCC in Japan

According to the World Health Organization (WHO), there are 10 criteria for cost-effective screening programs[7]: (1) the condition is an important health problem; (2) accepted treatments are available; (3) facilities for diagnosis and treatment are available; (4) the condition is recognizable in the latent/early stage; (5) suitable tests for screening are available; (6) the screening tests are acceptable to the population; (7) the natural history of the condition is well understood; (8) an agreed-upon policy on whom to treat is available; (9) the cost of diagnosis and treatment is economically balanced with overall medical expenditure; and (10) case finding should be continued. Based on the concept proposed by WHO, a study group appointed by the Japanese Ministry of Health, Welfare and Labor drew up an algorithm for screening of HCC in Japan (Fig. 2).[8] This screening, aimed at early diagnosis of HCC, has been opened for the public. However, the present issue of this screening is not based on a randomized controlled trial (RCT).

Definition of high-risk population

There is no doubt that HBV- and HCV-positive patients with chronic hepatitis and liver cirrhosis belong to a high-risk population for HCC. Therefore, those patients should be followed not only by monthly checkups for tumor markers such as alpha-fetoprotein (AFP), AFP-L3,[9] and PIVKA-II[10] but also by imaging diagnosis by abdominal ultrasonography every 4 months and computed tomography (CT) in each half-year (see Fig. 2). According to this screening program, a patient must pay at least approximately 57000 yen per year in cash, which corresponds to 30% of the total fee under the national health insurance system. The base of calculation is shown in Table 1.

Diagnosis of HCC

Definite diagnosis of HCC is performed by means of imaging such as hepatic angiography in combination with CT scan, dynamic CT scan, and dynamic magnetic resonance imaging (MRI). A mass more than 20 mm in diameter, if it is located within a cirrhotic liver, is highly suspicious for HCC. However, a dynamic study should be performed for the definite diagnosis of HCC. If a lesion shows arterial hypervascularity or early enhancement in the arterial phase and washes out in the delayed-phase venous phase, the diagnosis of HCC is conclusive. Tumor biopsy is not recommended because lesions more than 20 mm in diameter are highly suspicious for HCC and seeding of cancer cells through the biopsy needle should be avoided. Lesions 10–20 mm in size in a cirrhotic liver revealed during surveillance may or may not be HCC. Of course, if the dynamic study

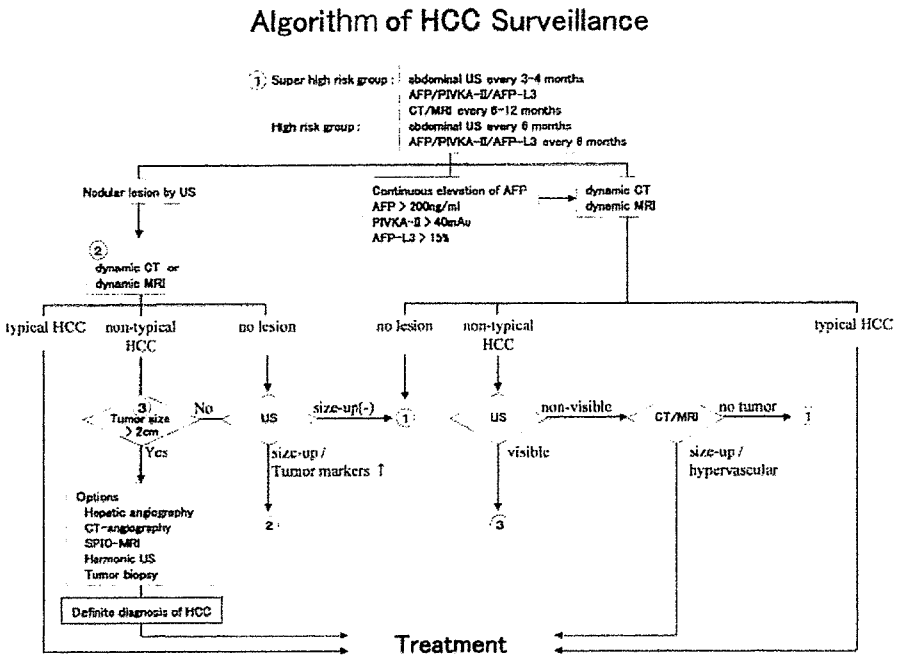

Fig. 2. Algorithm of hepatocellular carcinoma (HCC) surveillance[8] (originally published in Japanese)

Table 1. Patient fees for surveillance of hepatocellular carcinoma (HCC)

Item	One-time fee[a]	Times	Total fees[a]
Medical administration	6	12	72
Blood chemistry	50	12	600
AFP measurement	20	6	120
PIVKA-II measurement	25	6	150
Abdominal ultrasonography	50	4	200
Computed tomography (CT)	400	1	400
Upper GI endoscopy	100	1	400
Annual total			1542

As shown in the table, the fee for each patient is at least US $1542 per year. However, under the Japanese national health insurance system, as a burden of 30% of the total fee, each patient pays about US $453 per year in cash
AFP, alpha-fetoprotein
[a]In U.S. dollars

indicates the characteristic figures of HCC, HCC will be diagnosed. However, if a lesion does not show typical figures by dynamic imaging, tumor biopsy will be recommended. If the biopsied specimen indicates dysplasia or adenomatous hyperplasia, this lesion should be followed with specific intention because it is known that HCC appears frequently from a dysplastic nodule or adenomatous hyperplasia.[11] If this lesion tends to grow or the levels of tumor markers increase in the patient's blood, dynamic CT scan or dynamic MRI should be performed again. On the other hand, in the case of a small lesion less than 10 mm in diameter, there is time for observation until the lesion grows to more than 10 mm in diameter.

Staging systems

Although the prognosis of solid tumors is generally related to tumor stage, survival of HCC is regulated by two factors, such as tumor stage and severity of underlying liver disease. Several attempts to produce a staging system for prediction of prognosis and helping in the selection of therapy have been performed in Japan, such as the Okuda staging system[12] and the Japan Integrated Staging (JIS) score.[13] Of these, the JIS score based on a combination of the Child–Turcotte–Pugh stage for assessment of reserved hepatic function and the TMN staging system[14] by the Liver Cancer Study Group of Japan (LCSGJ) demonstrated better stratifi-

Table 2. Degree of liver damage categorized by the Liver Cancer Study Group of Japan

Clinical and laboratory findings	Grade		
	A	B	C
Ascites	None	Controllable	Uncontrollable
Serum bilirubin (mg/dl)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dl)	>3.5	3.0–3.5	<3.5
ICG R15 (%)	<15	15–40	>40
Prothrombin activity (%)	>80	50–80	<50

In a national survey of primary liver cancer, the survival rate is estimated based on the degree of liver damage as stated by the Liver Cancer Study Group of Japan (LCSGJ) at the time of initial treatment

cation ability and prognostic predictive power than the staging systems in Europe known as the Cancer of the Liver Italian Program (CLIP) score[15] and the Barcelona Clinic Liver Cancer (BCLC) scoring system.[16]

Treatment of HCC

The treatment of HCC is mainly divided into nonsurgical and surgical treatment, including liver transplantation. Recently, an algorithm of HCC treatment was drawn up based on the Japanese experience (see Fig. 2).[8] Survival will depend on the effect of initial treatment, which is chosen based on the degree of liver damage (Table 2) determined by the Liver Cancer Study Group of Japan (LCSGJ)[15] and the character of the tumor itself. JIS is considered to be a good staging system for predicting prognosis but may not be suitable for selection of treatment.

Nonsurgical treatment

Transarterial embolization (TAE),[16] chemoembolization (TACE),[17] percutaneous ethanol injection (PEI),[18] and percutaneous microwave coagulation (PMC)[19] have been developed and distributed to other parts of the world. TAE and TACE aim to stop the arterial blood supply because HCC exhibits intense neoangiogenetic activity during its progression. However, in small HCC less than 30 mm in diameter, neovascularization is not so intense. Therefore, instead of TAE and TACE, percutaneous local therapy such as PEI, PMC, and radiofrequency ablation (RFA)[20] have been adopted. At present, RFA is superior to PEI because of strong necrotic effect in all tumor sizes.[21] Estimation of PMC is equivocal. Interest in PMC has declined following the introduction of RFA because of the difficulty in controlling ablation power by users. Table 3 shows the survival of patients treated by PEI, RFA, TAE, or TACE, derived from the 16th report published in 2004 by LCSGJ.[22]

Systemic chemotherapy or continuous hepatic artery infusion chemotherapy via ports has been applied to patients in the advanced stage who were not subjects for curative treatment. However, there is no RCT evidence that those therapies could contribute to prolongation of survival, although marginal effects such as shrinkage of tumor size or decrease of tumor number have been observed in selected cases.

Surgical resection

Advances in surgical technique and postsurgical management have magnified the significance of surgical resection.[23,24] According to the recent report by LCSGJ (see Table 3), there is no significant difference in 5-year survival between surgical resection and local therapy, even in subjects with liver damage. Therefore, at the time of informed consent by patients, both treatments should be proposed equally and the selection of therapy placed in the patient's hands.

Liver transplantation

In Western countries, liver transplantation has been accepted widely in the initial treatment of HCC because of life prolongation in a good manner made possible by the change to a liver from a donor.[25] On the other hand, in contrast to Western countries, in Japan liver transplantation using a living donor is mainly performed. The outcome after live donor transplantation is the same as with cadaveric donation. The development of living donation will be of promise in Japan because of the extremely small number of cadaveric donations.

Recurrence

The recurrence rate of HCC after treatment exceeds 70% at 5 years, including recurrence due to incomplete treatment and dissemination or de novo tumors.[26] Therefore, even if curative treatment has been per-

Table 3. Survival of HCC in each therapeutic modality

Therapy	*n*	Survival rate (%) 1 year	2 years	3 years	4 years	5 years	8 years	10 years
Surgical treatment (liver damage)								
A	15718	90.4	82.3	74.6	66.6	59.1	42.3	33.7
B	6884	86.1	75.5	65.1	56.2	47.7	29.6	20.6
C	713	73.7	59.8	50.1	42.9	36.4	21.4	14.1
Local therapy (total)								
A	10306	94.4	87.3	76.5	64.4	52.8	28.8	21.1
B	7444	92.4	77.4	61.5	47.6	37.1	18.4	12.1
C	1665	80.2	60.2	42.3	29.5	22.5	7.2	2.9
PEI								
A	7585	95.7	86.5	75.3	62.9	51.5	28.1	20.5
B	5488	91.7	76.1	60.1	46.4	36.1	17.6	11.3
C	1346	79.7	58.3	40.2	28.4	22.1	7.1	2.8
RFA								
A	1169	97.3	92.3	86.1	—	—	—	—
B	862	95.6	88.6	78.6	—	—	—	—
C	127	82.1	79.4	—	—	—	—	—
PMC								
A	1401	96.1	90.1	82.7	73.4	61.5	—	—
B	989	94.8	82.5	67.7	53.9	42.5	26.8	26.8
C	179	83.6	71.1	56.1	36.5	25.1	—	—
TAE & TACE								
A	10429	84.1	67.5	52.4	40.1	31.1	14.1	8.5
B	8041	75.3	54.8	37.9	26.9	19.9	7.4	5.2
C	2500	55.5	32	19.7	13.1	7.6	3.3	—

Survival of HCC is compared with two factors such as the degree of liver damage and treatment
PEI, percutaneous ethanol injection; RFA, radiofrequancy ablation; FMC, precutaneous microwave coagulation; TAE, transarterial embolization; TACE, transarterial chemoembolization

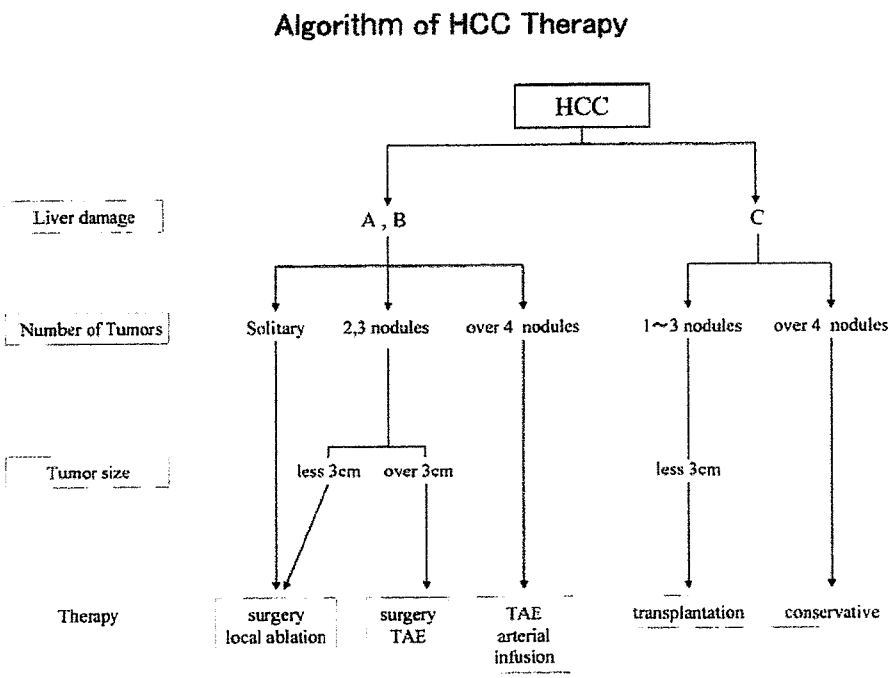

Fig. 3. Algorithm of HCC treatment[8] (originally published in Japanese)

formed, patients should be enrolled in the surveillance program and followed with close attention. If recurrence of HCC can be observed, therapy should be followed by the algorithm of HCC treatment shown in Fig. 2.

Prevention of HCC

There is no doubt that the disappearance of inflammation due to exclusion of HBV and HCV is a key issue in the prevention of HCC. There are many reports that interferon (IFN) therapy prevents development of HCC.[27-29] However, the results were not obtained by an RCT.

Several trials have been performed using IFN,[30] acyclic retinoid,[31,32] and vitamin K[33] to prevent the recurrence of HCC after curative treatment. However, estimation of the preventive effect with those agents was not made by an RCT. Prevention of its recurrence after curative treatment will be an important issue because of the very high recurrence rate of HCC.

Conclusion

In conclusion, the management of HCC in Japan is somewhat different from the practice guidelines in Europe and the United States. This difference is caused by the large number of patients with HCC and the national health insurance system in Japan.

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Surveillance Program for Early Detection of Hepatocellular Carcinoma in Japan

Results of Specialized Department of Liver Disease

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Objective: Surveillance of cirrhotic patients enables early detection of hepatocellular carcinoma (HCC) and possibly prolongs survival. The aim of this study was to explore whether early-stage HCC can be detected earlier at a specialized department of liver disease than in other institutions.

Methods: The study subjects were 574 patients with HCC. Patients were subdivided into 3 groups according to the manner of HCC detection: group A, HCC was detected in 91 patients during periodic examination at Kurume University School of Medicine; group B, HCC was detected in 301 patients during periodic examination at other institutions; group C, HCC was detected incidentally or because of symptoms in 182 patients.

Results: The HCC detected in group A was significantly of smaller size (20.4 mm) compared with groups B (27.1 mm, $P < 0.0001$) and C (57.8 mm, $P < 0.0001$). The frequency of receiving treatment (surgery or local ablation therapy) was significantly higher in group A (73%) than in groups B (52%, $P = 0.002$) and C (26%, $P < 0.0001$). The 5-year survival rates were 52% for group A, 40% for group B, and 23% for group C, respectively. The survival of group A was significantly better than that of groups B ($P = 0.0157$) and C ($P < 0.0001$).

Conclusions: Surveillance for HCC at specialized Department of Liver Disease can detect early-stage HCC, resulting in a higher chance of receiving promising treatment.

Key Words: hepatocellular carcinoma, surveillance, ultrasonography, computed tomography, tumor markers

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Hepatocellular carcinoma (HCC) is the fifth most common neoplasm in the world, and the third most common cause of cancer-related death.[1] HCC has become the leading cause of death among patients with liver cirrhosis.[2] The incidence of HCC has increased in the United States over the past 2 decades.[3] HCC commonly occurs in patients with chronic liver diseases related to hepatitis C virus (HCV) or hepatitis B virus (HBV) and the incidence of HCC in patients with HCV was reported to be 1.5% to 8% per annum.[4–7] Several studies have shown that surveillance with ultrasonography (US) and α-fetoprotein (AFP) for patients with liver cirrhosis can detect early-stage HCC, resulting in higher chance of receiving early treatment.[4–11] However, some studies showed that surveillance for HCC has a limited value in prolonging survival of patients with HCC including cost effectiveness,[12,13] and there is no randomized controlled trial to establish the value of surveillance of HCC in increasing survival of patients with chronic liver disease. Nowadays, such a study is almost impossible for ethical reasons. Discrepancies in the results of surveillance of HCC are related to differences in the incidence of HCC, target population of surveillance, frequency of surveillance, effective treatment of HCC, management of liver cirrhosis, and possibly also US equipment and skill of US examiner. The improvement of US equipment and increased proficiency of US examiner for surveillance of HCC have allowed early diagnosis of HCC, and resulted in prolonging survival of patients with liver cirrhosis over 3 quinquennia.[10] US equipment and skill of US examiner vary among institutions. However, no controlled trial has compared the results of surveillance of HCC among institutions.

Three-phase computed tomography (CT) and magnetic resonance imaging (MRI) might be potentially more sensitive and specific for the diagnosis of HCC.[14] Studies from the United States indicated that the screening for HCC with CT could be a cost effective strategy in transplant-eligible patients with cirrhosis.[15] Des-γ-carboxy prothrombin (DCP), a new tumor marker of HCC is more specific or equally specific to AFP.[16,17] However, surveillance studies using 3-phase CT, MRI, and DCP have not been reported.

The aims of the present study were (1) to determine differences in detecting early-stage HCC among various departments of liver disease, (2) if such differences have an impact on survival of patients with chronic liver disease, and (3) compare the values of regular 3-phase CT or regular DCP and conventional method of surveillance program of HCC in the detection of early-stage HCC.

PATIENTS AND METHODS

Patients

The study subjects were 574 Japanese patients with HCC diagnosed at Kurume University School of Medicine between January 1995 and December 2000. The diagnosis of HCC was established by histopathology and/or imaging studies (US, CT, angiography, CT-angiography, and MRI), and/or based on high plasma levels of tumor markers such as AFP and DCP. Patients were subdivided into 3 groups according to the manner of HCC discovery: group A, 91 patients were found to have HCC during periodic follow-up examination at Kurume University School of Medicine; group B, 301 patients were found to have HCC during periodic follow-up examination in other institutions; and group C, 182 patients were found to have HCC incidentally or because of symptoms.

Surveillance Program

Surveillance of 91 patients of group A included patients with chronic liver disease irrespective of age, liver cirrhosis, or etiology (HCV, HBV, alcoholic and other chronic liver diseases). Regular surveillance program of 91 patients of group A was as follows: US+AFP, 20 patients; US+AFP+DCP, 20 patients; US+AFP+CT, 15 patients; and US+AFP+CT+DCP, 36 patients. The frequency of monitoring using US, AFP, CT, DCP were 3, 6 to 12, and 3 to 6 months, respectively. During the subsequent surveillance period, imaging studies and tumor markers, together with physical examination and routine biochemical test, were repeated every 3 months. If 1 diagnostic modality indicated possible HCC, the other modalities were then performed on an out-patient basis. When nodular liver lesion was depicted by US or CT in such patients, they were admitted to Kurume University School of Medicine, and the diagnosis of HCC was confirmed by histopathology and/or imaging studies conducted based on high plasma levels of tumor markers.

The 301 patients of group B were found to have nodular liver lesions during periodic follow-up examination at other institutions at least 6-month interval by means of direct interview of the patients. The surveillance program of the 301 patients of group B was unknown. Classification of 182 patients as group C was based on finding a nodular liver lesion incidentally or at examination for symptoms and interview of patients but not at periodic follow-up examination.

Treatment Strategy

When a diagnosis of HCC was established at Kurume University School of Medicine, the following treatment options were assessed. Liver transplantation (LT)[18,19] was not considered because of very small number of donor resources and insurance system in Japan from January 1995 to December 2000. (1) Hepatic resection (HR)[20] was assessed especially for patients with localized HCC and preserved hepatic reserve capacity. (2) Nonsurgical treatments, such as percutaneous ethanol injection (PEI),[21] microwave coagulation therapy (MCT),[22] radiofrequency ablation (RFA),[23,24] transarterial chemoembolization (TACE),[25] hepatic arterial infusion chemotherapy (HAIC),[26] and systemic chemotherapy[27] were assessed when HR was contraindicated or the patient refused surgical treatment. The most appropriate therapeutic procedure was selected according to the tumor status and the underlying liver cirrhosis. Local ablation therapies (LAT) such as, PEI, MCT, and RFA were considered in patients with 1-3 tumor nodules, each measuring ≤ 30 mm in diameter that were devoid of vascular invasion and not associated with extrahepatic metastasis. (3) TACE, HAIC, or systemic chemotherapy was considered in patients with maximum tumor size of > 30 mm, number of tumors > 3, presence of vascular invasion and/or presence of extrahepatic metastasis. (4) Best supportive care was assessed when patient had little hepatic reserve capacity or patient refused any treatment of HCC.

Outcome Measures

Outcome measures were analyzed retrospectively in groups A to C as follows: (1) tumor characteristics including size and number of HCC nodules, presence of vascular invasion, and presence of extrahepatic metastasis; (2) UNOS (The United Network for Organ Sharing) criteria for HCC[28]; (3) treatment of HCC; and (4) cumulative survival of patients with HCC.

Differences of Surveillance Program at Kurume University School of Medicine

In 91 patients of group A, 51 patients underwent regular CT (15 US+AFP+CT and 36 US+AFP+CT+DCP) and 56 patients underwent regular DCP (20 US+AFP+DCP and 36 US+AFP+CT+DCP) in addition to US and AFP for surveillance program of HCC, respectively. (1) Tumor characteristics; (2) UNOS criteria for HCC; (3) treatment of HCC; and (4) cumulative survival of patients with HCC was also compared in 51 patients with regular CT [regular CT (+) group] and 40 patients without regular CT [regular CT (−) group], and in 56 patients with regular DCP [regular DCP (+) group] and 36 patients without regular DCP [regular DCP (−) group].

Statistical Analysis

We used the χ^2, Fisher exact, and Mann-Whitney tests, where appropriate, to evaluate differences in clinical features of patients and in tumor characteristics. Survival was analyzed by the Kaplan-Meier method[29] and survival curves were compared by the log-rank test. Survival was

TABLE 1. Clinical Profile of 572 Patients With HCC

	Group A	Group B	Group C
No. patients	91	301	182
Age (y, mean ± SD)	65.4 ± 7.4	65.2 ± 8.8	63.5 ± 9.3
Sex			
Male (%)	54 (59)	214 (71)	158 (87)
Female (%)	37 (41)	87 (29)	24 (13)
		$P = 0.035$	$P < 0.0001$
			$P < 0.0001$*
Etiology			
HCV-positive (%)	82 (90)	258 (86)	135 (74)
HBV-positive (%)	4 (4)	30 (10)	31 (17)
HCV-negative and HBV-negative (%)	5 (6)	13 (4)	16 (9)
			$P = 0.006$
			$P = 0.006$*
Total bilirubin (mg/dL: mean ± SD)	1.27 ± 0.64	1.22 ± 0.78	1.12 ± 0.86
Albumin (g/dL: mean ± SD)	3.39 ± 0.49	3.45 ± 0.47	3.50 ± 0.45
Child pugh class			
A (%)	53 (58)	186 (62)	126 (69)
B or C (%)	38 (42)	115 (38)	56 (31)
AFP (ng/mL)			
0 to 100 (%)	68 (75)	181 (60)	91 (50)
> 100 (%)	23 (25)	120 (40)	91 (50)
		$P = 0.011$	$P = 0.030$
			$P < 0.0001$*
DCP (mAU/mL)			
0 to 40 (%)	70 (77)	188 (62)	55 (30)
> 40 (%)	21 (23)	113 (38)	127 (70)

*Group B versus group C.

confirmed up to September 30, 2004. The statistical software package SPSS for Windows (version 10.0, SPSS Inc, Chicago, IL) was used for data analysis. A P value of < 0.05 was considered significant.

RESULTS

Patient Characteristics

Table 1 summarizes the clinical profile of 574 patients with HCC. The 3 groups were comparable for age, serum levels of total bilirubin and albumin, and Child Pugh class, whereas they significantly differed for sex (group A vs. B: $P = 0.035$; group A vs. C: $P < 0.0001$; group B vs. C: $P < 0.0001$) and etiology of liver disease (group A vs. C: $P = 0.006$; group B vs. C: $P = 0.006$). Serum levels of AFP (> 100 ng/mL) and DCP (> 40 mAU/mL) were significantly higher in group C than in groups A and B, and significantly higher in group B than in group A (AFP; group A vs. group B: $P = 0.011$, group A vs. group C: $P < 0.0001$, group B vs. group C: $P = 0.030$. DCP; group A vs. group B: $P = 0.011$, group A vs. group C: $P < 0.0001$, group B vs. group C: $P < 0.0001$).

HCC Features

The characteristics of HCC in the three groups are listed in Table 2. Significantly smaller size and fewer HCC nodules were detected in group A than in groups B and C, and significantly smaller in group B than in group C (tumor size: A, B, C; 20.4, 27.1, 57.8 mm, respectively, group A vs. group B: $P < 0.0001$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$. Number of tumors; group A vs. group B: $P < 0.0001$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$). A significantly higher proportion of tumors showed vascular invasion in group C than in groups A and B, and significantly higher in group B than in group A (group A vs. group B: $P = 0.020$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$). Extrahepatic metastasis was noted in 9 patients. A significantly higher proportion of extrahepatic metastasis was noted in group C than in groups A and B (group A vs. group C: $P = 0.042$; group B vs. group C: $P = 0.001$).

UNOS Criteria and Treatment

Of the 574, 334 patients (58%) presented with HCC within UNOS T2 criteria (Table 2). A significantly higher proportion of patients presented with HCC within UNOS T2 criteria in group A (91%) compared with group B (68%) and group C (26%), and in group B compared with group C (group A vs. group B: $P < 0.0001$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$). With regard to treatment, 10 (11%), 20 (7%), and 16 (9%) of groups A, B, and C were treated with HR, respectively. Furthermore, 56 (62%), 137 (45%), and 31 (17%) of group A, B, and C were treated with LAT including PEI, MCT, and RFA, respectively. In addition, 21 (23%), 132 (44%), and 122 (67%) of groups A, B, and C were treated with interventional radiology including TACE and HAIC, respectively. For other therapies, 2 of group C were treated with systemic chemotherapy, and 4 (4%), 12 (4%), and 13 (7%) of groups A, B, and C were

TABLE 2. Tumor Characteristics and Treatment of 572 Patients With HCC

	Group A	Group B	Group C
No. patients	91	301	182
Tumor size (mm; mean ± SD)	20.4 ± 9.5	27.1 ± 17.8 $P < 0.0001$	57.8 ± 34.0 $P < 0.0001$ $P < 0.0001$*
Tumor number			
1 (%)	57 (63)	133 (44)	43 (23)
2 (%)	30 (33)	100 (33)	54 (30)
> 3 (%)	4 (4)	68 (23) $P < 0.0001$	85 (47) $P < 0.0001$ $P < 0.0001$*
Vascular invasion			
Yes (%)	0 (0)	17 (6)	44 (24)
No (%)	91 (100)	284 (94) $P = 0.020$	138 (76) $P < 0.0001$ $P < 0.0001$*
Extrahepatic metastasis			
Yes (%)	0 (0)	1 (1)	8 (4)
No (%)	91 (100)	300 (99)	174 (96) $P = 0.042$ $P = 0.001$*
UNOS criteria			
T1-2 (%)	83 (91)	204 (68)	47 (26)
T3-4 (%)	8 (9)	97 (32) $P < 0.0001$	135 (74) $P < 0.0001$ $P < 0.0001$*
Treatment			
Surgery or local ablation (%)	66 (73)	157 (52)	47 (26)
TACE, HAIC, or systemic chemotherapy (%)	21 (23)	132 (44)	122 (67)
Supportive care (%)	4 (4)	12 (4)	13 (7)

*Group B versus group C.

followed-up conservatively without any specific treatment for HCC because of hepatic failure or patient refusal of any treatment for HCC. The frequency of receiving promising treatment (HR or LAT) was significantly higher in group A (73%) than groups B (52%) and C (26%), and significantly higher in group B than group C (group A vs. group B: $P = 0.002$; group A vs. group C: $P < 0.0001$; group B vs. group C: $P < 0.0001$).

Survival Rates

The cumulative survival rates according to the modality of HCC discovery are shown in Figure 1. The 3, 5, and 7-year cumulative survival rates were 67%, 52%, and 36% for group A; 60%, 40%, and 22% for group B; and 38%, 23%, and 9% for group C, respectively. The cumulative survival rates of group A were significantly better than those of groups B ($P = 0.0157$) and C ($P < 0.0001$), and those of group B were significantly better than those of group C ($P < 0.0001$).

Differences in Surveillance Program at Kurume University School of Medicine

The detected HCC in the regular CT (+) group tended to be smaller than the regular CT (−) group (mean tumor size: 18.7mm vs. 22.4mm; $P = 0.061$). However, the number of tumors, serum levels of AFP and DCP, frequency of meeting UNOS T1-2 criteria and frequency of receiving promising treatment were not significantly different between the 2 types of HCC discovery (Table 3). Furthermore, cumulative survival was comparable between regular CT (+) and CT (−)

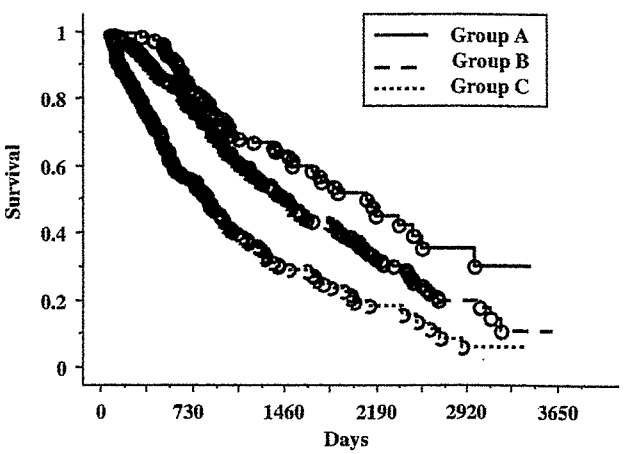

FIGURE 1. Kaplan-Meier survival curves of 574 patients with HCC according to the HCC diagnosis. The cumulative survival of group A was significantly better than that of groups B ($P=0.0157$) and C ($P<0.0001$), and group B was significantly better than that of group C ($P<0.0001$).