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Regular hospital visits improve the prognosis of hepatocellular carcinoma after initial diagnosis: A single regional community hospital study

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ABSTRACT

Background/Aims: The aims of this study were to investigate the relationship between regular hospital visits and prognosis of hepatocellular carcinoma (HCC) and to suggest methods to avoid poor prognoses in HCC.

Materials and Methods: In total, 103 patients with initial HCC were classified into 3 groups based on hospital visits occurring 1 year before diagnosis: group A was patients with regular hepatologist visits (n=41), group B was those with regular visits to other hospital divisions (n=50), and group C was those with no hospital visits (n=12). The relationships between the 3 groups and survival rates, backgrounds, hepatic reserve, and stages of HCC were analyzed.

Results: Survival rates of groups A, B, and C after diagnosis at 36 months were 77.9%, 66.3%, 31.3%, respectively. These were significantly higher in group A than in B and in group B than in C (p=0.042 and p=0.003, respectively; generalized Wilcoxon test). Child-Pugh classification, Japan integrated staging (JIS) score, and Barcelona clinic liver cancer (BCLC) staging were poor in group C compared with group A (p<0.01) and group B (p<0.01 or p<0.05). Males with viral infection (15 of 16 males in group B, p<0.01) and non-virally infected patients (34 patients in group B, p<0.01) had fewer regular hepatologist visits.

Conclusion: Hepatologist visits appeared to improve the prognosis of initial HCC. Males and non-virally infected patients should be screened to avoid delays in diagnosis. Since cases of non-viral HCC are likely to increase in Japan, surveillance methods for all clinicians should be established.

Keywords: Hepatocellular carcinoma, diagnosis, prognosis, community health

INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men worldwide and the seventh in women. The survival rate of HCC is poor in most patients who do not receive curative therapy, such as surgical resection or ablation therapy in the early stage. Eastern Asia, including Japan, is a high prevalence area for HCC (1). In Japan, the age-standardized incidence rate of liver cancer is 30.7 per 100,000 person-years, and approximately, 30,000 people died from liver cancer in 2012 (2,3). Chronic infection with hepatitis B or C virus (HBV, HCV) is well known as an important cause of cirrhosis and HCC. The annual incidence rates of HCC in patients with HBV- and HCV-related cirrhosis are estimated to be 2.5% and 7%-8%, respectively. In Japan, chronic HBV and HCV infections are present in 10%-15% and 80% of patients with HCC, respectively (2).

Therefore, testing for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb) has been promoted

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at general check-ups conducted by municipalities or employers in Japan. Patients with chronic HBV or HCV infection should be managed to receive optimal anti-viral therapy and regular surveillance for early detection of HCC following a guideline established by the Japan Society of Hepatology (4-6). The surveillance recommendations for early detection of HCC include combining testing for tumor markers, such as α-fetoprotein (AFP) and des-γ-carboxy prothrombin (DCP), with diagnostic imaging modalities, such as ultrasound, contrast-enhanced computed tomography (CT), or magnetic resonance imaging (MRI), depending on the patient's age and progression of hepatic fibrosis, both of which are recognized as high risk factors for HCC (4-7).

However, it is estimated that many patients have either never been tested for HBV and HCV infections or remain untreated despite their known HBV or HCV diagnosis (8). In addition, it appears that the occurrence rate of HCC has been increasing recently in patients who are not infected with HBV or HCV but have a history of alcohol intake, diabetes mellitus, obesity, or non-alcoholic steatohepatitis (NASH) (9,10). Therefore, it is of concern that the traditional algorithm to detect early stage HCC in high-risk patients may not be useful for these individuals; consequently, the prognosis of HCC may worsen in the future.

The aim of this study is to characterize patients with HCC in the central region of Saitama to investigate the relationship between regular hospital visits and the prognosis of HCC after initial diagnosis, identify high-risk patients, and suggest improvements to the medical care system for avoiding deterioration in the prognosis of HCC in community health.

MATERIALS AND METHODS

Statement of Ethics

This study was approved by a suitably constituted ethics committee at our facility and conformed to the provisions of the Declaration of Helsinki. All patients provided informed consent prior to inclusion in the study.

Settings

This was a single-center, retrospective, case-control study conducted at our hospital, which is accredited as a key hospital in the east-central region in Saitama, 40 km from Tokyo, Japan. Our hospital is equipped with ultrasound, multi-detector row CT, 1.5 tesla MRI, and offers liver resection, radio-frequency ablation (RFA), transcatheter arterial chemoembolization (TACE), molecular targeted therapy, and radiation therapy for patients with HCC.

Patients

In total, 103 patients who were initially diagnosed with HCC between January 2012 and June 2016 were classified into 3 groups based on hospital visits occurring 1 year before their diagnosis. Group A composed of patients who had regular hepatologist visits, group B of patients with regular visits to other hospital divisions, and group C of patients with no regular hospital visits.

Methods and Definitions

Regular hospital visits were defined as visitations to a hospital (general such as our hospital, specialized, or clinics) to receive examinations or treatments for liver or other diseases once or more in the year before diagnosis of initial HCC. Hepatologist visits were defined as visits to an attending physician who was a board-certified gastroenterologistof the Japanese Society of Gastroenterology, board-certified surgeon in gastroenterology of the Japanese Society of Gastroenterological Surgery, or board-certified surgeon of the Japan Surgical Society who has engaged in the treatment of liver diseases, and was a board-certified member of the Japan Society of Hepatology.

Surveillance for HCC by imaging modalities was defined as a systematic examination at least once a year by ultrasound, CT, or MRI for early detection. Fortuitous detection of HCC by examinations for other purposes was excluded, for example, ultrasound for initial or temporal abnormalities related to liver function, chest CT for surveillance of lung cancer, and cardiac ultrasonography for heart diseases.

Statistical Analysis

The relationship between regular hospital visits and survival rates was analyzed using the generalized Wilcoxon test. For analyzing the relationships between the type of hospital visits and backgrounds of patients before diagnosis, condition of patients at diagnosis, and treatments after diagnosis of initial HCC, categorical variables and quantitative variables were analyzed using the χ^2 test and Kruskal-Wallis test, respectively. Additionally, Bonferroni correction and the Steel-Dwass test were applied for adjustment of categorical variables and quantitative variables, respectively. All statistical tests were performed using Ekuseru-Toukei 2015 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

RESULTS

Of the 103 patients diagnosed with HCC in this study, 41 (39.8%), 50 (48.5%), and 12 (11.7%) patients were classified into group A (regular hepatologist visits), group B (regular visits to other hospital divisions), and group C (no regular hospital visits), respectively (Figure 1) (Table 1). Chronic HCV infection was the leading cause of HCC (42 patients). Conversely, 54 (52.4%) patients had non-viral HCC. In this study, 27 (26.2%) patients obtained pathologic diagnosis for liver injury and HCC by liver biopsy, hepatic resection, or necropsy. Of these, the disease in 3 patients was compatible with NASH. The HCC cause in 25 (24.3%) patients was classified into cryptogenic or possibility of non-alcoholic fatty liver disease (NAFLD).

Table 1. Patient characteristics

Regular hospital visits	
Hepatologist (group A)	41 (39.8%)
Other hospital divisions (group B)	50 (48.5%)
None (group C)	12 (11.7%)
Age	72 (38-99)
75≤	46 (44.7%)
Sex	
Male/female	68 (66.0%)/35 (34.0%)
Cause of HCC	
Viral/Non-viral	49 (47.6%)/54 (52.4%)
HCV	42 (40.8%, including 6 SVR)
HBV	6 (5.8%)
HBV+HCV	1 (1.0%)
Alcoholism	23 (22.3%)
Autoimmune liver diseases	3 (2.9%)
NASH	3 (2.9%)
Cryptogenic or possibility of NAFLD	25 (24.3%)
BMI (kg/m^2)	23.2 (14.7-37.0)
History	
Alcohol intake	49 (47.6%)
Diabetes mellitus	33 (32.0%)
Performance status	
0	84 (81.6%)
1	8 (7.8%)
2	3 (2.9%)
3	4 (3.9%)
4	4 (3.9%)
Platelets (×104)	11.3 (3.9-222)
Prothrombin time (%)	79 (40-100)
Total bilirubin (mg/dL)	1.1 (0.4-11.5)
Albmin (g/dL)	3.7 (1.7-4.8)
Alpha-fetoprotein (ng/mL)	11.6 (2.4-200000)
Des-γ-carboxy prothrombin (mAU/mL)	42 (0-75000)
Maximum tumor size (cm)	2.3 (0.5-14.0)
Number of tumors	
1	67 (65.0%)
2	9 (8.7%)
3	7 (6.8%)
4≤	20 (19.4%)
Child-Pugh score	6 (5-14)
A or non-cirrhosis	66 (64.1%)
B	28 (27.2%)
C	9 (8.7%)
TNM stage	
I	37 (35.9%)
II	31 (30.1%)
III	13 (12.6%)
IV	22 (21.4%)
JIS score	
0	28 (27.2%)
1	29 (28.2%)
2	15 (14.6%)
3	17 (16.5%)
4	11 (10.7%)
5	3 (2.9%)
BCLC staging	
0	24 (23.3%)
A	39 (37.9%)
B	8 (7.8%)
C	18 (17.5%)
D	14 (13.6%)
Initial treatment for HCC	
Hepatic resection	14 (13.6%)
RFA	19 (18.4%)
TACE, TAE	48 (46.6%)
Molecular targeted agents	5 (4.9%)
Radiation	1 (1.0%)
Palliative therapy or others	16 (15.5%)

HCC: hepatocellular carcinoma; HBV: hepatitis B virus; HCV: hepatitis C virus; SVR: sustained virologic response; NASH: nonalcoholic steatohepatitis; NAFLD: non-alcoholic fatty liver disease; BMI: Body Mass Index; TNM stage: tumor node metastasis staging system; JIS score: the Japan Integrated Staging score; BCLC staging: Barcelona clinic liver cancer staging; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization; TAE: transcatheter arterial embolization; TNM: tumor size, nearby lymph nodes, metastasis

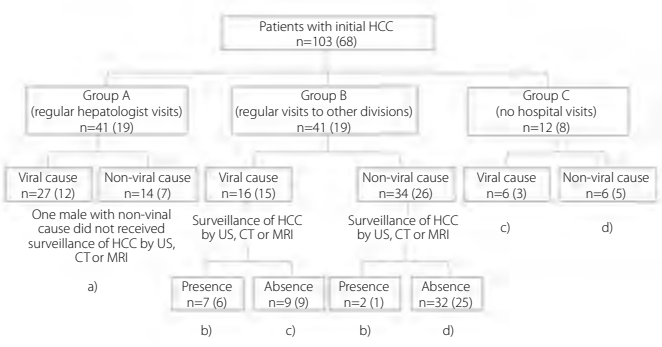

Figure 1. Distribution of 103 patients and classification by detection of HCC. Parentheses indicate numbers of male patients. Annotations (a), (b), (c), and (d) are subgroups, which summarize the difficulty of detection of HCC in the discussion part of this study

HCC: hepatocellular carcinoma; US: ultrasound; CT: computed tomography; MRI: magnetic resonance imaging

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Table 2. The relationship between the types of hospital visits and backgrounds, hepatic reserve, status of HCC, and initial treatment for HCC

	Group A n=41	Group B n=50	Group C n=12	p	Significant difference using Bonferroni correction or Steel-Dwass test
Age	74 (48-88)	72 (38-91)	67 (51-99)	0.391	
Sex (Male/Female)	19/22	41/9	8/4	0.002	A vs B **
BMI (kg/m^2)	22.4 (14.7-32.8)	24.0 (18.5-37.0)	23.0 (18.4-31.3)	0.475	
History of alcohol intake (yes/no)	15/26	27/23	7/5	0.185	
Diabetes (yes/no)	8/33	21/29	4/8	0.073	
Causes					
Viral/Non-viral	27/14	16/34	6/6	0.006	A vs B **
HCV	25	12	5		
HBV	1	4	1		
HBV+HCV	1	0	0		
Alcoholism	6	14	3		
autoimmune	3	0	0		
Cryptogenic or possibility of NAFLD	5	20	3		
Symptoms, hepatic reserve					
Performance status (0/1/2/3/4/)	37/3/0/0/1	41/4/1/3/1	6/1/2/1/2	0.012	A vs C*
Hepatic coma (yes/no)	10/31	16/34	5/7	0.476	ns
Ascites (yes/no)	15/26	15/35	8/4	0.061	ns
Platelets (×104)	9.8 (4.8-25.9)	12.9 (5.2-222)	8.8 (3.9-24.8)	0.004	A vs B**
Prothrombin time (%)	78 (40-100)	83 (42-100)	66 (41-89)	0.023	B vs C*
Total bilirubin (mg/dL)	1.2 (0.5-3.8)	1.0 (0.4-2.9)	1.4 (0.6-11.5)	0.261	
Albumin (g/dL)	3.7 (2.7-4.7)	3.8 (2.1-4.8)	3.1 (1.7-4.7)	0.052	A vs C*
Child-Pugh classification (A/B/C)	27/13/1	36/10/4	3/5/4	0.003	A vs C**, B vs C*
Status of HCC					
AFP (ng/mL)	11.1 (2.4-1845.4)	11.3 (2.4-198796.3)	165.6 (7.8-200000)	0.049	A vs C*
Sensitivity of AFP (≤10/>10 ng/mL)	17/19	22/26	1/9	0.088	
DCP (mAU/mL)	27(0-4640)	70(10-75000)	212(13-7500)	0.011	A vs B*, A vs C*
Sensitivity of DCP (≤40/>40 mAU/mL)	24/12	18/28	3/7	0.021	A vs B*
Maximum tumor size (cm)	1.5 (0.5-6.1)	3.3 (0.9-14)	6.2 (1.3-12.9)	<0.001	A vs B**, A vs C**
Number of tumors (≤3/≥4)	39/2	39/11	5/7	<0.001	A vs C**
Vp (yes/no)	1/40	12/38	3/9	0.012	A vs B**
Vv (yes/no)	1/40	4/46	1/11	0.490	
B (yes/no)	0/41	2/48	2/10	0.032	ns
Spread to the regional lymph node (yes/no)	0/41	2/48	1/11	0.261	
Extrahepatic spread (yes/no)	0/41	4/46	3/9	0.009	A vs C*
HCC rupture (yes/no)	0/41	2/48	2/10	0.032	ns
TNM stage (I/II/III/IV)	22/14/3/2	13/16/6/15	2/1/4/5	<0.001	A vs B*, A vs C**
JIS score (0/1/2/3/4/5/)	18/11/8/2/2/0	9/17/6/12/4/2	1/1/1/3/5/1	<0.001	A vs C**
JIS score (≤2/≥3)	37/4	32/18	3/9	<0.001	A vs B**, A vs C**
BCLC staging (0/A/B/C/D)	17/16/3/3/2	7/19/4/14/6	0/4/1/1/6	<0.001	A vs B*, A vs C**
BCLC staging (0,A,B/C,D)	36/5	30/20	5/7	0.002	A vs B**, A vs C**

Table 2. The relationship between the types of hospital visits and backgrounds, hepatic reserve, status of HCC, and initial treatment for HCC (continued)

Treatment for HCC					
Aggressive/ Subordinate†	40/1	36/14	5/7	<0.001	A vs B**, A vs C**
Hepatic resection	4	9	1		
RFA	11	7	1		
TACE, TAE	25	20	3		
Molecular targeted agents	0	4	1		
Radiation	0	1	0		
Palliative therapy or others	1	9	6		
Management before occurrence of HCC					
Antiviral therapy for patients with viral infection (yes/no)	15/12	2/14	NA	0.006	
Testing for the combination of AFP and DCP (yes/no)	32/9	5/45	NA	<0.001	
Surveillance for HCC by imaging modalities (yes/no)	40/1	9/41	NA	<0.001	

**p<0.01
*p<0.05
ns: There were no significant differences between A and B, A and C, and B and C.
HCC: hepatocellular carcinoma; BMI: Body Mass index; HBV: hepatitis B virus; HCV: hepatitis C virus; NAFLD: non-alcoholic fatty liver disease; AFP: alpha-fetoprotein; DCP: des-γ-carboxy prothrombin; Vp: portal vein invasion; Vv: hepatic vein invasion; B: bile duct invasion; TNM stage: Tumor node metastasis staging system; JIS score: the Japan Integrated Staging score; BCLC staging: Barcelona clinic liver cancer staging; RFA: radiofrequency ablation; TACE: transcatheter arterial chemoembolization; TAE: transcatheter arterial embolization
†Aggressive/Subordinate, In treatment for HCC, "aggressive" included hepatic resection, RFA, TACE, or TAE, and "subordinate" included molecular targeted agents, radiation, or palliative therapy

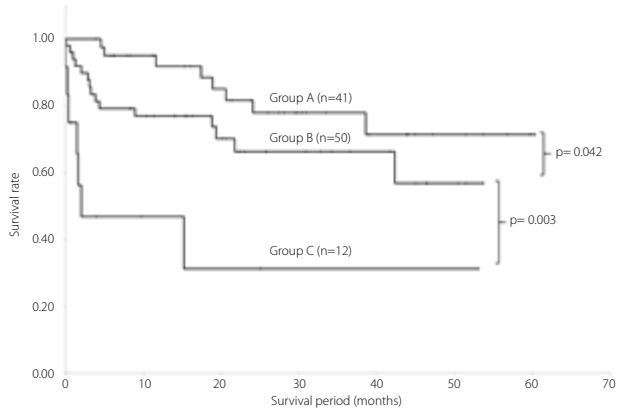

Figure 2. Survival rates among 3 types of hospital visits. Group A, patients who had regular hepatologist visits, Group B, patients with regular visits to other hospital divisions Group C, patients with no regular hospital visits

Thirty-one patients died during this study period. Survival rates of the patients after initial diagnosis of HCC in groups A, B, and C were 95.0%, 79.2%, 46.9% at 6 months; 91.8%, 76.9%, 46.9% at 12 months; and 77.9%, 66.3%, 31.3% at 36 months, respectively. Rates of survival were significantly higher in group A than in B (p=0.042) and in group B than C (p=0.003; Figure 2).

The relationship between the types of hospital visits and backgrounds, hepatic reserve, HCC status, and initial treatment for HCC is shown in Table 2. Males had fewer opportunities of regular hepatologist visits (p<0.01). Comparing the cause of HCC, non-virally infected patients tended to have regular visits to other hospital divisions. Sixteen (32.0%) patients in group B had viral infections; 15 (93.8%) of 16 males in group B did not have regular hepatologist visits until HCC occurred (Figure 1).

In this study, 6 patients had achieved sustained virologic response (SVR) by previous interferon (IFN) monotherapy or ribavirin combination therapy for chronic HCV infection; 5 of them were classified into group A and 1 was classified into group B. Age, body mass index, history of alcohol intake, and history of diabetes mellitus were not related with hospital visits.

Regarding the condition of patients at diagnosis, the performance status was poor in group C compared with group A. Hepatic encephalopathy (hepatic coma) and ascites did not show statistical significance; however, serum levels of prothrombin time and albumin in group C were unfavorable, and Child-Pugh classification was poorest in group C.

The status of HCC, such as maximum tumor size, number of tumors, invasion to intra-hepatic portal vein, and extra-hepatic spread was more favorable in group A, and ruptured HCC was not found in group A. Consequently, the TNM Classification of Tumors (TNM) stage was earliest in group A compared group B or group C. Additionally, the Japan integrated staging (JIS) score and Barcelona clinic liver cancer (BCLC) staging were most advantageous to survival after initial diagnosis of HCC in group A.

Serum levels of AFP and DCP were examined at the diagnosis of HCC in 94 and 92 patients, respectively, and they differed significantly among groups (p=0.049 in AFP and p=0.011 in DCP), with patients in group C more likely to have high serum levels and high sensitivity (90.0% and 70.0%, respectively).

The analysis of treatment for HCC indicated that patients in group A received more aggressive initial treatments for HCC, such as hepatic resection, RFA, or TACE. Conversely, patients in group C tended to receive only subordinate treatments, such as molecular targeted agents, radiation, or palliative therapy.

In comparing management before initial diagnosis of HCC between groups A and B, anti-viral therapy, such as IFN-based therapy and nucleoside analog therapy was performed at low rates for patients with viral infection in group B (12.5%). Regarding surveillance for early detection of HCC, testing for the combination of AFP and DCP and examination by imaging modalities were more common in group A (78.0 and 97.6%, respectively) than in group B (10.0% and18.0%, respectively).

One (2.4%) of the patients in group A, 41 (82.0%) in group B, and all patients in group C who did not receive surveillance for HCC by imaging modalities had fortuitous detections of HCC by ultrasound in 23 cases, CT in 23 cases, and MRI in 5 cases for other purposes. Two HCC diagnoses from breast CT and 1 cardiac ultrasonography were included in these results.

DISCUSSION

Several limitations and biases of our study need to be considered. The sample size of this study is small because this study was conducted in a single hospital, the only institution that can offer treatments for HCC in a limited geographic region. However, because few patients visit our hospital from other areas to receive treatment for HCC, the results of this study are indicative of conditions in the region. The modality and period of surveillance for early detection of HCC have not been standardized worldwide. Therefore, 2 types of surveillance methods for HCC were set in this study: presence or absence of testing for the combination of AFP and DCP at least once a year and presence or absence of systematic examination at least once a year by imaging examinations such as ultrasound, CT, or MRI.

The effectiveness of surveillance for HCC has been established in (very) high-risk patients that have HBV or HCV infection and cirrhosis in Japan (4-6) and in other countries (11,12). In Japan, surveillance for "early" detection of HCC using tumor markers, ultrasound, CT, or MRI is well established with the support of the national health insurance system. This study showed that regular hospital visits were associated with a favorable prognosis for initial HCC, which may be related to the detection of HCC at an early stage because of substantial surveillance for early detection of HCC using the combination of AFP and DCP testing as well as examinations using imaging modalities. Furthermore, stable hepatic reserve is likely related to suitable management for liver damage by regional clinicians before the occurrence of HCC. It is notable that groups B and C might include patients without chronic liver diseases before the occurrence of HCC. Nevertheless, when focusing only on effects in viral-related cases, group A comprised of more patients with a history of anti-viral therapy and had a more advantageous hepatic reserve (13,14). Moreover, an earlier stage of HCC and stable hepatic reserve, which were related with regular hospital visits before occurrence of HCC, might be more amenable to curative initial treatments for HCC and contribute to an improved prognosis after the diagnosis. Of note, because patients in group B tended to have larger sized tumors compared with group A, the number of hepatic resections exceeded that of RFA in this study.

The accuracy of regular hospital visits, which this study suggested as a single prognostic factor, is not superior to those of the major staging systems, such as BCLC, cancer of the liver Italian program, and JIS score, which are composed of performance status, various tumor characteristics (eg, size, number, vessel invasion, and level of AFP), and hepatic reserve (15-17). However, it is notable that regular hospital visits are unique as a pre-diagnostic variable in that they are under patient control, unlike other irrevocable conditions of patients at diagnosis, such as tumor stage and hepatic reserve.

Conversely, patients' low awareness of their risk of HCC might render early detection more difficult. It was suggested that patients without the opportunity to visit a hospital often received sub-optimal treatments after their initial diagnosis of HCC because of poor hepatic reserve and delay in detection of HCC. From the start, specific reasons, such as an abnormality in liver function tests or HBV or HCV infection, appear to be needed for patients to decide upon a visit to a clinician, particularly a hepatologist. However, practically, the patients are often asymptomatic and are overlooked until they receive liver tests for a possibly unrelated reason. Unfortunately, once the patient has symptoms related to liver damage, such as ascites, jaundice, or hepatic coma, their underlying liver diseases have a high risk of progression.

Regarding this issue, it has been recognized that the major causes of HCC in Japan (80% or more) were associated with HCV or HBV infection; however, recent epidemiological reports indicate that cases of HCC not associated with these viral infections or "cryptogenic" HCC are increasing (2,18). A review composed of a large sample size of studies showed that non-viral HCC accounted for 15% of HCC in Japan (18). In fact, 52.4% of patients had non-viral HCC, and patients without HCV or HBV infection were less likely to receive regular hepatologist visits in this study.

For the gender difference in HCC, it has been reported that survival in HCC of women is better compared to men; however, the reason had not been clearly elucidated (19,20). According to previous research that implied the cause of the sex difference in survival with HCC, women were more closely followed-up compared to men in the detection of early-stage HCC among high-risk patients (19). Our study also revealed that males were less likely to receive regular hepatologist visits. It is a particularly concerning fact in this region that 15 (93.8%) of 16 males in group B did not visit a hepatologist until HCC occurred although they had HCV or HBV infection (Figure 1).

Recently, it has also been recognized that surveillance for HCC is required even in patients with HCV infection who achieved SVR by treatment containing IFN because of their residual susceptibility for the development of HCC (21). In this study, 1 of

6 patients with SVR for HCV had neither hepatologist visits nor surveillance for HCC, and only this patient died of HCC during this study period.

These trends might explain the finding that more than one-half of patients with HCC in this study had not been managed by a hepatologist and did not undergo surveillance for HCC until HCC occurred. The difficulty of detection of HCC can be summarized into 4 subgroups shown as a, b, c, and d in Figure 1.

Subgroup a is composed of cases that are managed by hepatologists following the optimal surveillance method for detection of early-stage HCC in patients with HBV or HCV infection or non-viral chronic liver diseases (patients in group A in this study) (5). This system has been already established and will be continually observed in the future.

Subgroup b includes cases with HBV or HCV infection or non-viral chronic liver diseases that are well managed by clinicians in other divisions. Advising these clinicians to avoid overlooking HCC is effective, but they may nevertheless be more likely to fail to notice the occurrence of HCC compared to hepatologists.

Subgroup c consists of patients who should be considered at (high) risk for HCC. This group includes patients infected with HBV or HCV who regularly visit other hospital divisions or do not visit the hospital and do not undergo surveillance for HCC despite the viral status. Here 80% of patients in this subgroup were males. If these cases can receive optimal management, the prognosis of HCC may be improved.

Subgroup d comprises of patients with HCC who are not associated with viral infection or may be cryptogenic. They are not under surveillance for HCC. Even if these patients visit the hospital regularly, there may be few opportunities to suspect the occurrence of HCC. When HCC is incidentally detected, the stage is often advanced. Because it is estimated that this patient type is increasing, the traditional surveillance method to detect early stage HCC, which was established for patients with (high) risk of HCC, may not have widespread utility; consequently, this may adversely affect the overall prognosis of HCC in Japan in the future (10).

It is ideal that patients with risk factors for HCC, such as infection with HBV and HCV, alcohol intake, diabetes mellitus, obesity, and NASH, are followed in community health. Nevertheless, results from this study do not suggest concrete methods to identify patients in a large population with unknown risk of HCC or cryptogenic HCC. Ultrasound and CT are definitive and indispensable assessments for early detection of HCC in high-risk patients (22). However, ultrasound of the liver can be technically difficult for clinicians in other divisions (22). Furthermore, CT would not be performed without a reason in patients at an unclear risk for HCC because of cost, radiation exposure, and potential iodine allergy (22). The optimal timing for these imaging examinations is also unclear.

Examination using only tumor markers, such as AFP and DCP, has been suggested as an inadequate modality for "early" detection of HCC in patients with high risk for HCC because of their unreliable sensitivity and/or specificity (23). The sensitivity and specificity of AFP for initial detection of HCC is 61% and 81%, respectively, and those of DCP are 74% and 86%, respectively. However, in this study, the serum level and sensitivity of AFP and DCP at the diagnosis of HCC tended to be higher in group C compared with group A (23). It is highly probable that the advanced stage of HCC restricts the more effective treatments for HCC, such as hepatic resection, RFA, and TACE as well as directly impacts the prognosis (15). Consequently, the patients without regular hospital visits had poor prognoses. Although their utility for early detection of HCC is limited, in countries with a high incidence of HCC, routine measurements of AFP, DCP, or both may be one of the few pragmatic options for a large population with an unknown risk for HCC in terms of cost, safety, and simplicity to provide the chance of any aggressive treatment, which is more effective than palliative care for patients with initial HCC.

In conclusion, in the regional community, regular hospital visits, particularly hepatologist visits, may improve the prognosis of initial HCC. In particular, regular hepatologist visits for male and non-virally infected patients should be promoted. A national prospective study to establish a method for detection of early stage HCC in various risk groups should be considered.

Ethics Committee Approval: Ethics committee approval was received for this study from Kitasato University Medical Center (Decision Date: 30.11.205/Decision No: 27-34).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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REFERENCES

1. Bosetti C, Turati F, La Vecchia C. Hepatocellular carcinoma epidemiology. Best Pract Res Clin Gastroenterol 2014; 28: 753-70. [CrossRef]
2. El-Serag HB. Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 2012; 142: 1264-73. [CrossRef]
3. Kudo M. Surveillance, diagnosis, treatment, and outcome of liver cancer in Japan. Liver Cancer 2015; 4: 39-50. [CrossRef]

4. Makuuchi M, Kokudo N. Clinical practice guidelines for hepatocellular carcinoma - The Japan Society of Hepatology 2009 update. Hepatol Res 2010; 40: 2-144.
5. Kokudo N, Hasegawa K, Akahane M, et al. Evidence-based Clinical Practice Guidelines for Hepatocellular Carcinoma: The Japan Society of Hepatology 2013 update (3rd JSH-HCC Guidelines). Hepatol Res 2015; 45: 123-7. [CrossRef]
6. Kudo M, Matsui O, Izumi N, Iijima H, Kadoya M, Imai Y. Surveillance and Diagnostic Algorithm for Hepatocellular Carcinoma Proposed by the Liver Cancer Study Group of Japan: 2014 Update. Oncology 2014; 87: 7-21. [CrossRef]
7. Bruix J, Sherman M. Management of hepatocellular carcinoma: An Update. Hepatology 2011; 53: 1020-2. [CrossRef]
8. Izumi N. Diagnostic and treatment algorithm of the Japanese Society of Hepatology: A Consensus-based practice guideline. Oncology 2010; 78: 78-86. [CrossRef]
9. Hiwatashi K, Ueno S, Sakoda M, et al. Problems of Long Survival Following Surgery in Patients with NonBNonC-HCC: Comparison with HBV and HCV Related-HCC. J Cancer 2015; 6: 438-47. [CrossRef]
10. Tateishi R, Okanoue T, Fujiwara N, et al. Clinical characteristics, treatment, and prognosis of non-B, non-C hepatocellular carcinoma: a large retrospective multicenter cohort study. J Gastroenterol 2015; 50: 350-60. [CrossRef]
11. Davila JA, Morgan RO, Richardson PA, Du XL, McGlynn KA, El-Serag HB. Use of surveillance for hepatocellular carcinoma among patients with cirrhosis in the United States. Hepatology 2010; 52: 132-41. [CrossRef]
12. Santi V, Trevisani F, Gramenzi A, et al. Italian Liver Cancer (ITA.LI.CA) Group. Semiannual surveillance is superior to annual surveillance for the detection of early hepatocellular carcinoma and patient survival. J Hepatol 2010; 53: 291-7. [CrossRef]
13. Simmons B, Saleem J, Heath K, Cooke GS, Hill A. Long-term treatment outcomes of patients infected with hepatitis C Virus: A systematic review and meta-analysis of the survival benefit of achieving a sustained virological response. Clin Infect Dis 2015; 61: 730-40. [CrossRef]
14. Arase Y, Ikeda K, Suzuki F, et al. Interferon-induced prolonged biochemical response reduces hepatocarcinogenesis in hepatitis C virus infection. J Med Virol 2007; 79: 1485-90. [CrossRef]
15. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. The Lancet 2003; 362: 1907-17. [CrossRef]
16. The Cancer of The Liver Italian Program (Clip) Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology 1998; 28: 751-5. [CrossRef]
17. Kudo M, Chung H, Osaki Y. Prognostic staging system for hepatocellular carcinoma (CLIP score): its value and limitations, and a proposal for a new staging system, the Japan Integrated Staging Score (JIS score). J Gastroenterol 2003; 38: 207-15. [CrossRef]
18. Nishikawa H, Osaki Y. Non-B, non-C hepatocellular carcinoma (Review). Int J Oncol 2013; 43: 1333-42. [CrossRef]
19. Dohmen K, Shigematsu H, Irie K, Ishibashi H. Longer survival in female than male with hepatocellular carcinoma. J Gastroenterol Hepatol 2003; 18: 267-72. [CrossRef]
20. Yang D, Hanna DL, Usher J, et al. Impact of sex on the survival of patients with hepatocellular carcinoma: a surveillance, epidemiology, and end results analysis. Cancer 2014; 120: 3707-16. [CrossRef]
21. Asahina Y, Tsuchiya K, Nishimura T, et al. α-fetoprotein levels after interferon therapy and risk of hepatocarcinogenesis in chronic hepatitis C. Hepatology 2013; 58: 1253-62. [CrossRef]
22. Bruix J, Sherman M, Llovet JM, et al. EASL Panel of Experts on HCC. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol 2001; 35: 421-30. [CrossRef]
23. Lok AS, Sterling RK, Everhart JE, et al. HALT-C Trial Group. Des-gamma-carboxy prothrombin and alpha-fetoprotein as biomarkers for the early detection of hepatocellular carcinoma. Gastroenterology 2010; 138: 493-502.[CrossRef]