Long-term clinical outcomes of hepatocellular carcinoma ; surveillance program for early detection in high risk patients

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Long-term clinical outcomes of hepatocellular carcinoma ; surveillance program for early detection in high risk patients

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Abstract

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Although most liver clinics conduct some forms of surveillance for the early detection of hepatocellular carcinoma (HCC) in high risk patients, it is still debated whether such surveillance may increase the patient survival. The aim of this study was to elucidate whether strict adherence to surveillance interval affected the clinical outcomes of patients diagnosed with HCC. Another aim was to compare the outcomes of patients diagnosed with HCC during different periods of surveillance.

Between May 1990 and December 2005, a total 10,307 high risk patients (32-87 years of age) were followed-up with at least two times of regular ultrasound examination and serum alpha-fetoprotein measurements for at least one year in our institution. Among those, 400 patients diagnosed with HCC were divided into two groups according to surveillance interval; Group 1 (interval ≤6months, n=219) and Group 2

(interval >6months, n=181). These patients were also divided into three groups according to surveillance period; Group I (1990-1995, n=123), Group II (1996-2000, n=157), and Group III (2001-2005, n=120).

The mean follow-up duration was 30±24 months (range; 1-141). The mean age of all patients was 57 years (range; 33-85) and there was a male predominance (72%). The etiology of HCC was hepatitis B virus in 289 (72.3%) patients, hepatitis C virus in 76 (19.0%), and non B-non C in 32 (8.0%). Single nodular HCC was more prevalent in Group 1 than in Group 2 (90.4% vs. 72.9%, $P<0.001$). On the contrary, diffuse type HCC was more common in Group 2 (4.1%, vs. 11.6%, $P<0.001$).The frequency of solitary HCC ≤3cm was significantly higher in Group 1 compared with Group 2 (62.1% vs. 51.5%, $P=0.003$). Five-year survival in Group 1 was significantly better than that of Group 2 (25% vs 16%, $P=0.006$, log-rank test). In comparison according to surveillance period, the patients in Group III were diagnosed with HCC at an earlier stage compared to Group I or II; the frequency of patients in TNM stage I/II was 65.1%, 67.6%, and 85.8%, respectively ($P<0.05$). In addition, the frequency of single nodular HCC was 82.1%, 73.2%, and 95.0%, respectively ($P<0.05$). The mean tumor size was also significantly lower in Group III compared to Group I or II (4.2cm vs. 3.2cm vs. 2.9cm, $P<0.005$). The proportion of patients in whom surveillance interval was ≤6 months was significantly higher in Group III compared with Group I or II (46.3% vs. 39.5% vs. 80.8%, $P<0.001$). The comparison of 5-year survival among three groups showed a significant difference between Group I (or II) and

Group III (17%, 19%, and 65%, P <0.0001).

Our data suggest that strict adherence to surveillance interval (≤6 months) resulted in the detection of HCC at an earlier stage and improved survival. Furthermore, the patients developing a HCC during the last 5 years survived longer than previously, probably as a consequence of more intensive surveillance program in this period.

Key words: surveillance, hepatocellular carcinoma, early detection.

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I. INTRODUCTION

Hepatocelluar carcinoma (HCC) is one of the most common malignancies in the world.[1] Most of these cases occur in the Far East where hepatitis B virus (HBV) is highly endemic, whereas chronic hepatitis C is the main cause in developed Western

countries. It is estimated that about 11,000 new cases of HCC occur each year in Korea. Moreover, the incidence of HCC has substantially increased in the United States over the 20-30 years.[2] In spite of the recent advance in diagnostic and therapeutic modalites, the prognosis for patients with HCC is very poor if they are diagnosed in a symptomatic stage (mean survival <4 months).[3-5] The application of curative treatments such as surgical resection, liver transplantation (LT), and radio-frequency ablation (RFA) is often limited because HCC is usually large in size before it gives rise to symptom. In addition, the features that multifocal tumors or bilolar involvement in HCC are common and approximately 80% of the HCC patients have associated cirrhosis make effective therapy difficult. Nevertheless, small HCC is potentially treatable by partial hepatectomy or LT.[6] In this regard, it seems to be practical to perform some forms of surveillance for the early detection of HCC in high risk patients including those with chronic viral hepatitis, although the impact of surveillance on patient survival remains controversial due to a lack of prospective results.[7,8] Actually, periodic serologic and imaging tests for the patients known to be affected by chronic liver diseases have been implemented in the current clinical practice. Until now, however, the surveillance interval or tool for early detection of HCC has not been yet standardized around the world. Most hepatology clinics surveills the patients with alpha-fetoprotein (AFP) and/or liver ultrasonography (US) at time intervals ranging from 3 to 12 months.

We have conducted a surveillance program since 1990 to follow-up high risk patients

for the occurrence of HCC with regular determinations of AFP levels and US.

In this report, we intended to assess the long-term clinical outcomes of surveillance program in our institute and to compare the survival of patients diagnosed as HCC by surveillance in different periods.

II. MATERIALS AND METHODS

1. Patients

Between 1990 and 2005, a total of 10,307 high risk patients, aged 32-87 years, were followed-up with at least two times of regular US examination of the liver and serum AFP measurements for at least one year in the liver clinic of Severance Hospital, Seoul, Korea. The high risk patients included those who were chronically infected by HBV or hepatitis C virus (HCV) as well as those who were diagnosed as alcoholic liver diseases or inherited/metabolic liver diseases. Of these patients, a total of 400 patients diagnosed as HCC by the surveillance program during the same time period were recruited in this study. The patients who had extrahepatic malignancies at enrollment were excluded from the anaylsis. The differentiation between chronic hepatitis and liver cirrhosis (LC) was made mainly by clinical, imaging, and laboratory findings. Namely, LC was demonstrated by ultrasonography (i.e., coarse liver architecture, nodular liver surface, and blunt liver edges) and evidence of hypersplenism (i.e., splenomegaly on ultrasonography and a platelet count of

<100,000/mm^3). A fine-needle biopsy of the liver was undertaken as indicated.

In particular, to investigate whether the difference in periods of surveillance affected the patient survival, we retrospectively stratified the 400 HCC patients accrording to 3 quinquennia of surveillance: 1990-1995; 1996-2000; 2001-2005.

2. Laboratory testing

Serum samples were tested for hepatitis B surface antigen (HBsAg) and its antibody (anti-HBs), antibody to hepatitis B core antigen (anti-HBc) by commercially available enzyme immunoassay kit (EIA, Abbott Laboratories, North Chicago, IL). Antibody to hepatitis C virus (anti-HCV) was tested by microparticle enzyme immunoassay (Abbott Laboratories, North Chicage, IL). Serum AFP levels were determined by electrochemiluminescence assay (Bayer, Leverkusen, Germany; normal <20 ng/mL). Since 2001, we began to determine both levels of AFP and prothrombin induced by vitamin K absence or antagonist-II (PIVKA-II), which were measured by sensitive enzyme immunoassay (Sanko Junyaku co., Tokyo, Japan; normal <40 mAU/mL).

3. Surveillance strategy and diagnosis of HCC

Throughout the study period, patients with high risk for the HCC occurrence were followed-up by the liver clinic and were managed according to the surveillance program, which consisted of 3-12 monthly AFP (and PIVKA-II since 2001) determination and US examinations. Any focal lesions detected on US or abnormal

AFP values (≥20 ng/mL) or abnormal PIVKA-II values (≥40 mAU/mL) were followed by further investigations such as liver spiral computerized tomography (CT), dynamic magnetic resonance imaging (MRI), hepatic angiography, or biopsy if clinically indicated. The clinical diagnosis of HCC was made if the patient fit one of the following situations: 1) a positive result in at least one of the three imaging findings (spiral CT, MRI, or hepatic angiography) if serum AFP level ≥400 ng/mL (or PIVKA-II ≥40 mAU/mL); or 2) positive results in at least two of three imaging findings if serum AFP <400 ng/mL (and PIVKA-II <40 mAU/mL). The positive finding for typical HCC in CT or MRI means arterial enhancement followed by venous washout in portal/delayed phase.

4. Staging of HCC and treatment modalities

The gross types of HCC were classified as solitary nodular, multinodular, massive, and diffuse as described previously.[9] Tumor staging was performed in accordance with tumor-node-metastasis (TNM) staging of the Union Internatinal Contre le Cancer (UICC) staging system.[10] To detect metastasis, all the patients underwent chest radiography. Bone scintigraphy and CT scans of the chest or the brain were performed when extrahepatic spread was suspected. The treatment for HCC was not standardized, and therefore it was provided primarily according to the physician's decision and treatment options available. For example, our institution developed a novel percutaneous transhepatic treatment modality using radioactive material for

single nodular HCC, namely percutaneous holmium-166 injection therapy described elsewhere.[11] It has been found that the overall outcomes were comparable between surgical resection and holmium injection in patients with small HCC. Therefore, we have actively applied the holmium injection therapy in single HCC rather than RFA which is more commonly used worldwide. Patients were also evaluated for suitability for surgical resection,[12] and in particular, LT was indicated if the patient met the Milan criteria.[13] Patients with compensated liver disease and lack of evidence of portal vein thrombosis and of extrahepatic metastases, in whom surgical treatment was not feasible or who refused operation, were treated by transarterial chemoembolization (TACE). In patients with distant metastasis or obstructive (or painful) symptoms, systemic chemotherapy with 5-fluorouracil (or cisplatin), radiotherapy for palliative aim, or conservative treatment was performed as indicated.

5. Data collection

From the start of this study, we had developed a data base system in which demographic, clinical, laboratory, and radiological findings of the followed high risk patients were input and stored. The following data were used for the analysis in the current study; patient demography including age, sex; etiology of underlying liver disease; Child-Pugh class; interval of US examinations; year of diagnosis; tumor number, type, and size; presence or absence of vascular invasion and distant metastasis; stage; biochemical and hematologic variables; AFP and PIVKA-II levels

at diagnosis of HCC; treatment details; survival measured in months.

6. Statistical anaylsis

Statistical analyses were performed using SPSS version 11.0 (SPSS Inc, Chicago, IL, USA). The results were expressed as median and range or mean ± SD, as appropriate. The patient survival was calculated from the time of HCC diagnosis to the time of death or until October 9, 2006. Categorical variables were evaluated with standard Chi-square and two-tailed *t* test was used to compare means for continuous variables. Life table estimates were calculated according to the Kaplan-Meier method, and the survival curves were compared by the log-rank test. A *P* value less than 0.05 was considered to be statistically significant.

III. RESULTS

1. Demographic, clinical, and laboratory characteristics of the 400 HCC patients

During the study period from March 1990 to November 2005, four hundred patients out of 10,307 high risk patients were diagnosed as HCC by the surveillance program. The demographic and clinical features of these 400 patients are presented in Table 1. The mean age of the patients was 57 years (range; 33-85) and there was a male predominance (72%). Two hundred eight nine (72.3%) patients were positive for HBsAg and 76 (19.0%) patients were positive for anti-HCV. Three (0.8%) patients

were positive for both HBsAg and anti-HCV, and the remaining 32 (8.0%) patients were cirrhotics of non-viral origin. The AFP level determined at the time of HCC diagnosis, which was available in 395 patients, was less than cut-off (20 ng/mL) in 146 (37%) patients. On the contrary, in 110 (27.8%) patients, the level was higher than 400 ng/mL. The distribution of tumor stage according to UICC system was 28% in stage 1, 44% in stage 2, 15% in stage 3, and 13% in stage 4.

Table 1. Demographic and clinical characteristics of 400 patients diagnosed as hepatocellular carcinoma by surveillance program

Characteristics	Number
Males	289 (72%)
Mean age, yr (range)	57 (33-85)
Etiology of underlying liver disease	
HBV	289 (72.3%)
HCV	76 (19.0%)
HBV + HCV	3 (0.8%)
Non-B non-C	32 (8.0%)
Child-Pugh grade	
A	223 (56%)
B	103 (26%)
C	74 (18%)
*AFP, ng/mL	
≤20	146 (37.0%)
21-400	139 (35.2%)
>400	110 (27.8%)
TNM stage	
1	112 (28%)
2	177 (44%)
3	60 (15%)
4	51 (13%)

*AFP levels at the diagnosis of HCC were available in 395 patients.

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; TNM, tumor-node-metastasis.

2. Characteristics of HCC detected by surveillance

The overall annual detection rate by surveillance US examination and AFP determination was 2.4%. The detection rate was only 0.7% in the first year of study. However, it rose with time and reached 3.3% in 2005 (Figure 1). The most commonly found type of HCC during surveillance was solitary nodule (82.5%), followed by multinodular (8.3%), diffuse (7.5%), and massive type (1.8%). In particular, among the 330 cases of solitary nodular HCC, 191 (57.9%) cases showed lesion size ≤3cm. The mean tumor size, which was measured by the sum of maximal diameter of all nodules in nodular or massive HCC and defined as 5cm in diffuse HCC, was 3.5 ± 2.2cm. Of note, portal vein (and/or hepatic vein) tumor thrombosis and distant metastasis occurred in 31 (7.8%) and 5 (1.3%) patients, respectively (Table 2).

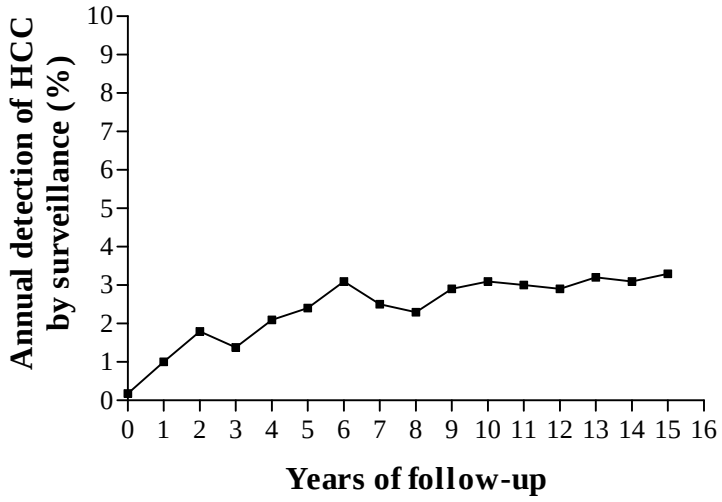

Figure 1. Annual detection rates of hepatocellular carcinoma in 10,307 high risk patients under surveillance program

Table 2. Gross types, tumor size, and invasiveness of hepatocellular carcinoma detected by surveillance

Variables	Values
Type of HCC	
Single nodular	330 (82.5%)
Multinodular	33 (8.3%)
Massive	7 (1.8%)
Diffuse	30 (7.5)
Tumor size (cm, mean ± SD)	3.5 ± 2.2
Solitary HCC	
≤3cm	191 (57.9%)
>3cm	139 (42.1%)
†Vascular thrombosis	31 (7.8%)
Distant metastasis	5 (1.3%)

†Vascular thrombosis means portal vein and hepatic vein thrombosis.

*Tumor size was measured by the sum of maximal diameter of all nodules.

3. Treatment of HCC and overall survival

The most commonly adopted treatment modality for HCC was TACE (63.3%), followed by conservative treatment (16.0%), percutaneous locoregional therapies including holmium-166 injection and RFA (8.3%), and surgical resection (7.3%). Although LT has been accepted as the only definitive therapy for curing both small HCC and LC, the number of patients who underwent LT was only two (0.5%) because of absolute donor organ shortage. Infusional therapy with cisplatin through hepatic artery was performed in 4 (1.0%) patients with diffuse type HCC, and

systemic chemotherapy with 5-fluorouracil was performed in 1 (0.5%) patient. For 64 (16%) patients with advanced cirrhosis and poor performance status, only conservative treatment was provided (Table 3). The median follow-up duration of patients with HCC were 26 months (range; 1-141 months), and the median duration of survival was 29 months (range; 1-76 months). The 1, 3, and 5 year survival rate in all patients was 75%, 43%, and 22%, respectively (Figure 2).

Table 3. Treatment modalities of all the 400 patients

Treatments	Number (%)
Surgical resection	29 (7.3)
Liver transplantation	2 (0.5)
Holmium injection/RFA	33 (8.3)
TACE	253 (63.3)
Intrahepatic cisplatin infusion	4 (1.0)
Systemic chemotherapy	1 (0.3)
Radiotherapy	14 (3.5)
Conservative treatment	64 (16.0)

RFA, radio-frequency ablation; TACE, transarterial chemoembolization.

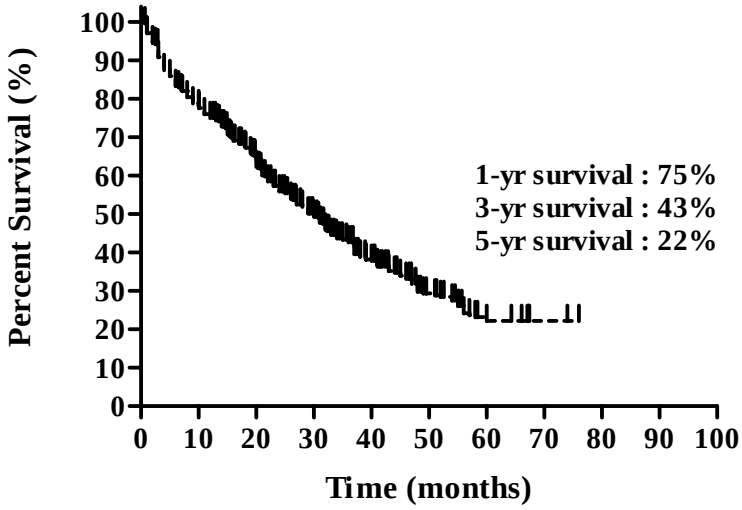

Figure 2. Overall survival rates of the 400 patients diagnosed with hepatocellular carcinoma detected by surveillance program

4. Comparison of clinical outcomes and survival according to surveillance interval

Patients were divided into two groups according to the interval of surveillance. In group 1 (203 patients), diagnosis was made during regular surveillance, based on AFP determination and US performed every 6 months or less. In group 2 (197 patients), the surveillance interval was more than 6 months. In the comparison of demographic and clinical characteristics, the distribution of underlying liver disease was not different between the two groups (P=0.32). However, while most patients in group 1 were in Child-Pugh class A (class A, 61.6%; class B, 22.4%; class C, 16.0%), the class distribution was less favorable in group 2 (P=0.03). Furthermore, AFP levels at diagnosis were significantly higher in group 2 compared to group 1 (850±3739 ng/mL

vs. 2478±6890 ng/mL, *P*=0.003). The distribution of TNM stage showed significant difference between the two groups. The prevalence of advanced cancers was lower in group 1 compared with group 2 (*P*=0.001, Table 4).

In comparison of tumor characteristics, single nodular HCC was more commonly found in group 1 than in group 2 (90.4% vs. 72.9%). On the contrary, diffuse type HCC was more prevalent in group 2 (4.1%, vs. 11.6%; *P*<0.001). The mean tumor size was significantly lower in group 1 compared to group 2 (3.0 ± 1.7cm vs. 4.0 ± 2.6cm, *P*<0.001). In particular, the prevalence of solitary HCC ≤3cm was significantly higher in group 1 compared with group 2 (62.1% vs. 51.5%, *P*=0.003). Although the frequency of distance metastasis was similar in two groups (1.4% vs. 1.1%), portal or hepatic vein tumor thrombosis was more commonly identified in group 2 (4.6% vs. 11.6%, *P*=0.03). The distribution of treatment modalities showed significant difference between the two groups. Forty-one (18.7%) patients in group 1 underwent curative treatments including LT, surgical resection, percutaneous holmium-166 injection, and RFA. On the contrary, only 22 (12.2%) patients in group 2 received such curative treatment. The frequency of conservative treatment was also significantly different between the two groups (12.3% vs. 21.0%, *P*=0.03, Table 5). The 5-year actuarial survival in group 1 was significantly better than that of group 2 (25% vs 16%, *P*=0.006, log-rank test; Figure 3).

Table 4. Comparison of demographic and clinical characteristics of patients diagnosed with hepatocellular carcinoma according to surveillance interval

Chracteristics	**Group 1 (n=219) (interval ≤6 mo)**	**Group 2 (n=181) (interval >6mo)**	***P* value**
Males (%)	157 (71.7)	132 (72.9)	0.82
Mean age (yrs, mean ± SD)	56.6 ± 9.0	58.6 ± 9.0	0.02
Etiology of liver disease (%)			0.32
HBV	166 (75.8)	123 (68.0)	
HCV	38 (17.4)	40 (22.1)	
HBV + HCV	2 (1.0)	1 (0.6)	
Non B-non C	15 (6.8)	17 (9.4)	
Child-Pugh grade (%)			0.03
A	135 (61.6)	88 (48.7)	
B	49 (22.4)	54 (29.8)	
C	35 (16.0)	39 (21.5)	
AFP level (ng/mL, mean ±SD)	850±3739	2478±6890	0.003
TNM stage (%)			<0.001
1	75 (34.2)	37 (20.4)	
2	99 (45.2)	78 (43.1)	
3	28 (12.8)	32 (17.7)	
4	17 (7.8)	34 (18.8)	

HBV, hepatitis B virus; HCV, hepatitis C virus; AFP, alpha-fetoprotein; TNM, tumor-node-metastasis.

Table 5. Comparison of tumor characteristics and treatment modalities of patients diagnosed with hepatocellular carcinoma according to surveillance interval

Characteristics	**Group 1 (n=219) interval ≤6mo**	**Group 2 (n=181) interval >6mo**	***P* value**
Type of HCC (%)			<0.001
Single nodular	198 (90.4)	132 (72.9)	
Multinodular	9 (4.1)	24 (13.3)	
Massive	3 (1.4)	4 (2.2)	
Diffuse	9 (4.1)	21 (11.6)	
Tumor size (cm, mean±SD)	3.0 ± 1.7	4.0 ± 2.6	<0.001
Solitary HCC (n=330)			0.003
≤3cm (%)	123 (62.1)	68 (51.5)	
>3cm (%)	75 (37.9)	64 (48.5)	
Vascular thrombosis (%)	10 (4.6)	21 (11.6)	0.03
Distant metastasis (%)	3 (1.4)	2 (1.1)	1.0
Treatment modality (%)			0.03
*Curative	41 (18.7)	22 (12.2)	
†Non-curative	150 (68.5)	121 (66.9)	
Conservative	27 (12.3)	38 (21.0)	

HCC, hepatocellular carcinoma. *Curative treatments include LT, surgical resection, holmium-166 injection, and RFA. †Non-curative treatments include TACE, intra-arterial cisplatin infusion, systemic chemotherapy, and radiotherapy.

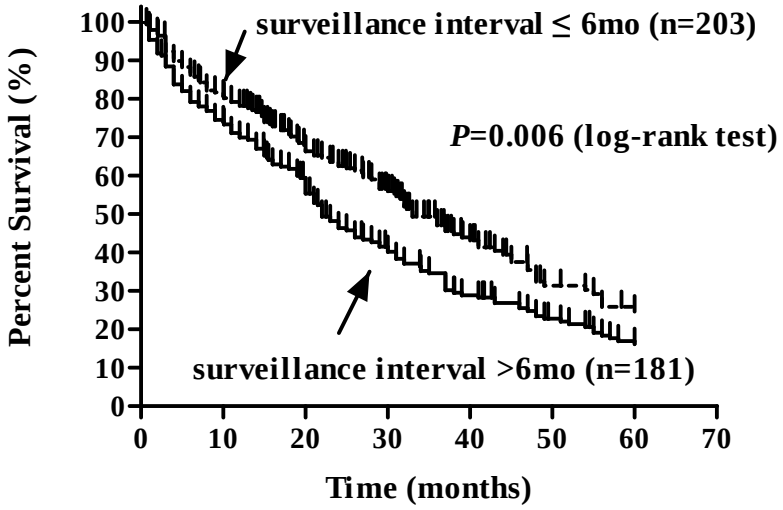

Figure 3. Survival of patients diagnosed with hepatocellular carcinoma according to the surveillance interval. The 5-year survival was significantly higher in patients with surveillance interval ≤6 months compared to those patients with interval >6 months.

5. Survival of the 400 HCC patients along the three quinquennia of surveillance

All the 400 patients diagnosed with HCC were stratified according to 3 quinquennia of surveillance: 1990-1995; 1996-2000; 2001-2005. The comparison of 5-year survival among these three group showed a significant difference between the first (or second) and the third quinquennium (first vs. third, P <0.0001; second vs. third, P <0.0001), although there was no difference between the first and the second quinquennium (P=0.33,Figure 4). The relevant clinical and tumor characteristics, and treatment modalities of the 3 groups are presented in Table 6.

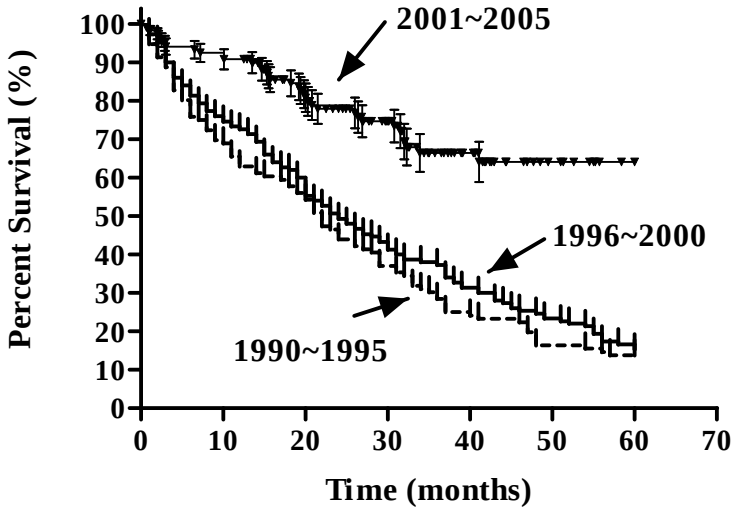

Figure 4. Comparison of survival of the 400 patients with hepatocellular carcinoma identified in different quinquennium of surveillance. The 5-year survival of patients in the last quinquennium was significantly better compared to the first or second (first vs. third, P <0.0001; second vs. third, P <0.0001).

Table 6. Clinical and treatment characteristics of the 400 HCC patients identified during 3 quinquennia of surveillance

Characteristics	**1990-1995**	**1996-2000**	**2001-2005**	***P* value**
	N=123	**N=157**	**N=120**	
Age (yrs, mean±SD)	58±9.3	57±8.6	58±9.3	NS
Etiology of liver disease				NS
HBV (%)	89 (67.5)	120 (76.4)	86 (71.7)	
HCV (%)	29 (23.6)	20 (12.7)	27 (22.5)	
HBV + HCV (%)	1 (0.8)	2 (1.3)	0	
Non B-non C (%)	10 (8.1)	15 (9.6)	7 (5.8)	
Child-Pugh grade (%)				
A	58 (47.2)[a]	73 (46.5)[b]	92 (76.7)[c]	<0.001[*]
B	32 (26.0)	46 (29.3)	25 (20.8)	
C	33 (26.8)	38 (24.2)	3 (2.5)	
AFP (ng/mL, mean±SD)	2056±5394[a]	2168±7126[b]	357±1166[c]	<0.01[†]
TNM stage (%)				
1	27 (22.0)[a]	45 (28.7)[b]	40 (33.3)[c]	<0.005[‡]
2	53 (43.1)	61 (38.9)	63 (52.5)	
3	21 (17.1)	25 (15.9)	14 (11.7)	
4	22 (17.9)	26 (16.6)	3 (2.5)	
Type of HCC (%)				
Single nodular	101 (82.1)[a]	115 (73.2)[b]	114 (95.0)[c]	<0.05[ǂ]
Multinodular	9 (7.3)	22 (14.0)	2 (1.7)	
Massive	1 (0.8)	5 (3.2)	1 (0.8)	
Diffuse	12 (9.8)	15 (9.6)	3 (2.5)	
Tumor size (cm)	4.2±2.7	3.2±2.0	2.9±1.5	<0.005[**]
Treatment modalities (%)				
Curative	18 (14.6)[a]	11 (7.0)[b]	34 (28.3)[c]	<0.001[††]
Non-curative	69 (56.1)[a]	117 (74.5)[b]	86 (71.7)[c]	0.005[‡‡]
Conservative	36 (29.3)	29 (18.5)	0	
Follow-up duration, month	21 (1-141)	23 (1-101)	30 (1-67)	

[*†‡ǂ] a(or b) vs. c; [**]a vs. b(or c); [††]a(or b) vs. c; [‡‡]a vs. b.

IV. DISCUSSION

Several studies have reported that HCC surveillance improves clinical outcomes including survival.[14-17] All of those previous investigations demonstrated that regular examinations using US and AFP determination could detect HCC at earlier stage and therefore effective treatments could be applied, although the survival benefit might be offered only to the patients with Child-Pugh class A. In the absence of prospective randomized study, it may be difficult to conclude that regular examinations for early detection of HCC really prolong the survival of the surveilled patients compared with non-surveilled patients, because retrospective studies naturally accompany two biases, so called, length bias and lead-time bias. Nevertherless, prospective investigations are almost hard to conduct, especially in the areas where the easy access to diagnostic procedures raises ethical concerns and makes patient compliance very unlikely.[14] Furthermore, such studies are impossible to perform in Korea where national health insurance system have already begun to surveil almost all the domestic adult individuals. Therefore, the current issue concerning surveillance of HCC are not whether to surveil or no to surveil, but rather which are the optimal surveillance interval or tools.[8]

In this study, two interesting results regarding surveillance for detection of early HCC could be obtained. First, the 5-year survival in patients with surveillance interval less than 6 months was significantly better than that of patients with interval more than 6

months (25% vs 16%, *P*=0.006). Second, there was a definite increase in the survival of patients in whom a HCC was detected during the last quinqueninium (2001-2005) of surveillance program compared to the first (1990-1995) or the second (1996-2000) quinquennium. Because the optimal interval for HCC surveillance is not known, prospective studies should be conducted to compare the clinical outcomes among different surveillance intervals in the near future. Until now, there are a few Western studies which retrospectively investigated the survival outcomes of cirrhotic patients with different surveillance intervals. Trevisani et al. reported there was no survival benefit in semiannual surveillance using AFP determination and US compared to annual surveillance even though 6-month surveillance greatly increased the amenability rate to LT.[14] Another Western study, in which 559 hemophiliacs infected with HCV were enrolled, demonstrated that stricter surveillance for 6 years at 6-month intervals did not increase the rate of detection of small tumors, with multinodular tumors detected in 5 (2.4%) of 210 patients in the 6-month group and in 2 (0.6%) of 349 in the 12-month group.[18] Our results are in contrast with those of the previous studies. HCC was detected in earlier stage in the patients with surveillance interval less than 6 months compared to more than 6 months. This was reflected by the AFP levels (850±3739 vs. 2478±6890 ng/mL) at HCC diagnosis as well as the frequency of earlier TNM stage (I/II) (79.4 vs. 63.5%). Of note, the distribution of tumor morphology in imagings showed significant difference between the two groups; the frequency of single nodular type was 90.4% and 72.9%, respectively.

Moreover, the rate of single HCC ≤3cm was significantly higher in the more strictly surveilled group (62.1 vs. 51.5%). Such a high rate of single HCC in our study compared with the previous ones might originate from the difference of etiology of liver diseases. Two hundred eighty nine (72.3%) out of 400 HCC patients in the current study were due to chronic HBV infection, whereas most of HCC cases in previous studies were related to chronic HCV infection. It has been postulated that HCV is more involved in multicentric liver carcinogenesis than HBV.[19] In addition, HCC rarely occurs in anti-HCV-positive patients without cirrhosis.[20,21]

The demonstration that stricter surveillance (less than 6 months) was associated not only with better survival but also favorable tumor characteristics (tumor size, morphology, TNM stage, and vascular invasion) and AFP levels is in contrast to the results by Trevisani et al. in which the advantage in tumor size obtained with the seminannual program was not led to the survival benefit.[14] The finding that there was a significantly different distribution among adopted treatments modalities between the two groups in our study might contribute the survival difference. The proportion of curative treatments in two groups was 18.7% and 12.2%, respectively. In addition, the frequency of conservative treatment was 12.3% and 21.0%, respectively (P=0.03). On the contrary, there was no significant difference in distribution of treatment modalities between semiannual and annual group in the study by Trevisani et al.[14] It should be kept in mind that liver function indicated by Child-Pugh class might have contributed in generating the different prognosis between two groups in our study. The

frequencies of Child-Pugh class A in the two groups were 61.6% and 48.7%, respectively (P=0.03). The recognition that patients in strictly surveilled group more commonly had compensated liver function at the diagnosis of HCC might justify the expansion of target population of surveillance program in HBV-endemic area. By many experts, those with high risk for HCC have been usually recommended for surveillance (mean age >45 years, with cirrhosis, those with a family history of HCC), whereas inactive carriers of HBV generally are thought to be at low risk and are not surveilled.[22] However, chronic hepatitis and cirrhosis are not two distinct diseases but the same disease at different evolutionary stages and a differential diagnosis between the two conditions is difficult at an early stage with current diagnostic methods, including biopsy. A significant proportion of patients with Child-Pugh A in the current study would have been not cirrhotic, but chronic hepatitis patients. Actually, the surveillance program is now operated in the patients with chronic hepatitis B and well-preserved liver function in Korea where HBV is endemic, and future studies related to the efficacy of surveillance for these patients are needed.

Surprisingly, there was a substantial increase in the survival of patients diagnosed with HCC during the last (2001-2005) quinquennium of surveillance compared to the first (1990-1995) and the second (1996-2000) quiqueninium. Our data confirms the results of study by Sangiovanni and colleagues in which the mean yearly mortality of the cohort of 417 compensated cirrhotic patients decreased from 45% to 37% and 10% during the first (1987-1991), second (1992-1996), and third (1997-2001)

quinquennium.[17] The introduction of new imaging techniques for HCC staging and improved criteria for selection of patients for LT, hepatic resection, and locoregional ablative therapies have enabled to prolong the survival in carefully selected patients with HCC.[13,23-25] Importantly, the observed increase in survival of HCC patients identified during the last quinquennium of surveillance in our study was related with several patient and tumor characteristics. Clearly, patients in the last quinquennium were diagnosed with HCC at an earlier stage compared to the first or second quinquennium. This is reflected by the frequency of TNM stage I/II along the 3 surveillance period (65.1% vs. 67.6% vs. 85.8%, respectively) and the frequency of single nodular HCC (82.1% vs. 73.2% vs. 95.0%, respectively; $P<0.05$). In fact, there was a significant diminution in the overall tumor size detected in the 3 surveillance period, from a mean 4.2 cm in the 1990-1995 period to 2.9 cm in the 2001-2005. As mentioned previously, such a more favorable stage and tumor size of HCC identified during recent years of surveillance are likely due to the advancement of US equipment as well as triphasic computed tomography (CT) and magnetic resonance imaging (MRI) with various contrast agents.[17,26] Another factor which might contribute to the favorable outcomes in the last quinquennium of surveillance of HCC is associated with the surveillance interval. The proportion of patients in whom the interval was less than 6 months was significantly higher in the last quinquennium compared to the first or second (46.3% vs. 39.5% vs. 80.8%, respectively; $P<0.001$). Considering that it has been recommended that the patients with high risk for

developing HCC should be surveilled every 6 months in our institute, above finding may imply the compliance of patients for surveillance of HCC has been recently improved. Importantly, there was also a significant increase in the proportion of patients undergoing curative treatments including LT, surgical resection, percutaneous Holmium injection, and RFA along the 3 surveillance periods (14.6% vs. 7.0% vs. 28.3%, respectively; P <0.001). On the contrary, there was no patient who was managed only by conservative manner in the last quinquennium of surveillance, although 29.3% and 18.5% of patients in first and second quinqennium underwent conservative treatment because of advanced HCC and poor liver function. Unfortunately, the distribution of patients according to Child-Pugh class was not similar among the 3 surveillance periods. A substantial proportion of patients (97.5%) in the last quinquennium were Child-Pugh class A or B at the time of HCC diagnosis. Obviously, such a well-preserved liver function in the patients in the recently surveilled group might have contributed to the prolonged survival.

In this study, we further investigated the sensitivity of tumor markers such as AFP and PIVKA-II. Out of 120 HCC patients identified during the last quinquennium, the number of patients, in whom AFP was elevated (≥20 ng/mL) but no lesion was found in US, was 31 (25.8%). Both of AFP and PIVKA-II levels were available in 109 HCC patients in the last quinquennium. The number of patients who was positive for AFP (≥20 ng/mL), PIVKA-II (≥40 mAU/mL), and both was 66 (55%), 59 (49.2%), and 36 (74.2%), respectively.

V. CONCLUSION

We have demonstrated that stricter adherence to surveillance interval (less than 6 months) resulted in more favorable clinical outcomes including survival compared to longer interval (more than 6 months). In addition, during the recent quinquennium of surveillance, patient survival significantly increased as a consequence of higher rate of detection of early HCC and more application of curative therapies.

REFERENCES

1. Okuda K. Hepatocellular carcinoma: recent progress. Hepatology 1992;15:948-963.
2. El-Serag HB, Davila JA, Petersen NJ, McGlynn KA. The continuing increase in the incidence of hepatocellular carcinoma in the United States: an update. Ann Intern Med 2003;139:817-823.
3. Stuart KE, Anand AJ, Jenkins RL. Hepatocellular carcinoma in the United States. Prognostic features, treatment outcomes, and survival. Cancer 1996;77:2217-2222.
4. Calvet X, Bruix J, Gines P, Bru C, Sole M, Vilana R, et al. Hepatocellular carcinoma in the west: A multivariate analysis in 206 patients. Hepatology 1990;12:753-760.
5. Beasley RP, Hwang LY, Lin CC, Chien CS. Hepatocellular carcinoma and hepatitis B virus: A prospective study of 22,700 men in Taiwan. Lancet 1981;2:1129-1133.
6. Mor E, Kaspa RT, Sheiner P, Schwartz M. Treatment of hepatocellular carcinoma associated with cirrhosis in the era of liver transplantation. Ann Intern Med 1998;129:643-653.
7. Di Bisceglie AM. Issues in screening and surveillance for hepatocellular carcinoma. Gastroenterology 2004;127:S104-7.

8. Bolondi L. Screening for hepatocellular carcinoma in cirrhosis. J Hepatol 2003;39:1076-1084.
9. Trevisani F, Caraceni P, Bernadi M, D'Intino PE, Arienti V, Amorati P, et al. Gross pathologic types of hepatocellular carcinoma in Italian patients. Relationship with demographic, environmental, and clinical factors. Cancer 1993;72:1557-1563.
10. Green F, Page D, Fleming I, Fritz A, Balch C, Haller D, et al. AJCC Cancer Staging Handbook, 6th ed. New York: Springer; 2002:131-144.
11. Kim JK, Han K-H, Lee JT, Paik YH, Ahn SH, Lee JD, et al. Long-term clinical outcome of phase IIb clinical trial of percutaneous injection with holmium-166/chitosan complex (Milican) for the treatment of small hepatocellular carcinoma. Clin Cancer Res 2006;12:543-548.
12. Bismuth H, Chiche L, Adam R, Castaing D, Diamond T, Dennison A. Liver resection versus transplantation for hepatocellular carcinoma in cirrhotic patients. Ann Surg 1993;218:145-151.
13. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996;334:693-699.
14. Trevisani F, De NS, Rapaccini G, Farinati F, Benvegnu L, Zoli M, et al. Semiannual and annual surveillance of cirrhotic patients for hepatocellular carcinoma: effects on cancer stage and patient survival (Italian experience).

Am J Gastroenterol 2002;97:734-744.

15. Yuen MF, Cheng CC, Lauder IJ, Lam SK, Ooi CG, Lai CL. Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. Hepatology 2000;31:330-335.
16. Bolondi L, Sofia S, Siringo S, Gaiani S, Casali A, Zironi G, et al. Surveillance programme of cirrhotic patients for early diagnosis and treatment of hepatocellular carcinoma: a cost effectiveness analysis. Gut 2001;48:251-259.
17. Sangiovanni A, Del Ninno E, Fasani P, De Fazio C, Ronchi G, Romeo R, et al. Increased survival of cirrhotic patients with a hepatocellular carcinoma detected during surveillance. Gastroenterology 2004;126:1005-1014.
18. Santagostino E, Colombo M, Rivi M, Rumi MG, Rocino A, Linari S, et al. A 6-months versus a 12-month surveillance for hpeatocellular carcinoma in 559 hemophiliacs infected with the hepatitis C virus. Blood 2003;102:78-82.
19. Kojiro M, Shimamatsu K. Comparison of pathology of hepatitis B- and hepatitis C-related hepatocellular carcinoma. Viral Hepatitis Rev 1995;5:89-99.
20. Trevisani F, D'Intino PE, Morselli-Labate AM, Mazzella G, Accogli E, Caraceni P, et al. Serum alpha-fetoprotein for diagnosis of hepatocellular carcinoma in patients with chronic liver disease: influence of HBsAg and anti-HCV status. J Hepatol 2001;34:570-575.

21. Shiratori Y, Shiina S, Imamura M, Kato N, Kanai F, Okudaira T, et al. Characteristic difference of hepatocellular carcinoma between hepatitis B and C viral infection in Japan. Hepatology 1995;22:1027-1033.
22. Lok ASF, McMahon BJ. Chronic hepatitis B. Hepatology 2001;34:1225-1241.
23. The Liver Cancer Study Group of Japan. Predictive factors for long-term prognosis after partial hepatectomy for patients with hepatocellular carcinoma in Japan. Cancer 1994;74:2772-2780.
24. Llovet JM, Bruix J, Gores GJ. Surgical resection versus transplantation for early hepatocellular carcinoma: clues for the best strategy. Hepatology 2000;31:1019-1021.
25. Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. Radiology 1999;210:655-661.
26. Fujita M, Kuroda C, Kumatani T, Yoshioka H, Kuriyama K, Inoue E, et al. Comparison between conventional and spiral CT in patients with hypervascular hepatocellular carcinoma. Eur J Radiol 1994;18:134-136.

국문요약

고위험군 환자에서 간세포암 조기진단을 위한 감시검사의 장기 임상결과

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간세포암은 예후가 불량하기 때문에 정기적인 초음파 검사 및 혈청 alpha-fetoprotein (AFP) 등의 종양표지자를 이용한 감시검사 (surveillance test)를 통해 조기에 진단하는 것이 중요하다. 본 연구에서는 간세포암의 조기 진단을 위해 고위험군을 대상으로 한 감시검사의 장기적 임상결과를 알아보고자 하였다. 또한, 검사 간격 (surveillance interval)에 따라 생존률 등의 결과에서 차이가 발생하는지를 조사하였고, 감시검사의 시기 (surveillance period)에 따른 임상 결과를 비교하였다.

1990년부터 2005년까지 최소 1년 이상, 2회 이상의 정기적 초음파 검사 AFP를 시행받은 환자는 모두 10,370명이었다 (연령: 32-87세). 이들 중 감시검사로 간세포암을 진단받은 환자는 400명이었고, 검사 간격에 따라 1군 (간격 ≤6개월, 219명)과 2군 (간격 >6개월, 181명)으로 나누었다. 검사 시기에 따라서는 I군 (1990-1995년, 123명), II군 (1996-2000년, 157명), III군 (2001-

2005년, 120명)의 세 군으로 나누고 각 군간의 임상결과를 비교하였다. 평균 추적관찰 기간은 30±24개월 (범위: 1-141개월)이었다. 전체 400명 환자들의 평균 연령은 57세 (범위: 33-85세)였고, 남성의 비율이 72%였다. 간세포암의 원인으로는 B형 간염 289명 (72.3%), C형 간염 76명 (19.0%), 기타 32명 (8.0%)였다. 2군과 비교하여 1군에서 단일 결절로 발견된 간세포암의 비율이 높았고 (90.4% vs. 72.9%, *P*<0.001), 침윤형 간세포암의 비율은 2군에서 유의하게 높았다 (4.1% vs. 11.6%, *P*<0.001). 3cm 이하의 단일 결절로 발견된 간세포암의 비율은 1군에서 의미있게 높았다 (62.1% vs. 51.5%, *P*=0.003). 5년 생존률은 1군과 2군에서 각각 25%, 16%로 유의한 차이를 보였다 (*P*=0.006). 검사 시기에 따른 비교에서, III군의 환자들이 I군 또는 II군에 비해 낮은 병기로 진단되어, TNM 병기 1 또는 2에 속하는 비율이 각각 65.1%, 67.6%, 85.8%였다 (*P*<0.05). 종양의 평균 크기도 I, II군에 비해 III군에서 유의하게 작았다 (4.2cm vs. 3.2cm vs. 2.9cm, *P*<0.005). 감시검사의 간격이 6개월 이하인 환자 비율 역시 I, II군에 비해 III군에서 의미있게 높았다 (46.3% vs. 39.5% vs. 80.8%, *P*<0.001). 5년 생존률은 각각 17%, 19%, 65%로 I, II군에 비해 III군에서 높았다 (*P*<0.001). 이상의 결과로, 감시검사 간격을 6개월 이하로 엄격히 지킨 고위험군 환자들에서 간세포암이 보다 조기에 발견되고 생존률이 유의하게 높은 것을 알 수 있었다. 또한, 최근 5년간 감시검사를 통해 간세포암을 진단받은 환자들의 병기가 과거보다 낮아지고 생존률도 향상되었다는 것을 알 수 있었다.

핵심되는 말: 감시검사, 간세포암, 조기진단