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LIVER CANCER

Efficacy of ultrasonography and alpha-fetoprotein on early detection of hepatocellular carcinoma

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Abstract

AIM: To evaluate the effectiveness of ultrasonographic screening for early detection of hepatocellular carcinoma (HCC).

METHODS: The data of 14 968 patients who had ultrasonography (US) for chronic liver diseases were collected into a database program from June 1995 to June 2005. The risk factors for HCC were also studied. A total of 6089 patients who had repeated US were enrolled, 264 patients were diagnosed with HCC during follow-up (mean, 39 mo).

RESULTS: The detection rate of small HCC (≤ 3 cm in diameter) was 67.7%. The tumor size detected by screening at the intervals of 6 mo was significantly smaller than that at longer intervals. Only 29.3% of HCC patients had an elevated serum alpha fetoprotein (AFP) level above 400 ng/mL. The risk of HCC development during follow-up was higher in patients with liver cirrhosis (10.9%) and hepatitis C (9.0%) than in patients with chronic hepatitis (4.2%), hepatitis B (4.9%) and non-B, non-C hepatitis (NBNC, 3.9%).

CONCLUSION: US screening at a interval of 6 mo is beneficial to high-risk patients over 40 years old and the early detection of HCC prolongs survival.

Key words: Hepatitis C; Hepatocarcinogenesis; Interferon; Retreatment

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INTRODUCTION

Hepatocellular carcinoma (HCC) ranks fifth in frequency of cancers worldwide[1-3]. As the prognosis of HCC is extremely poor and effective treatment for patients with advanced HCC has not yet been established, the early detection of HCC is important for its effective treatment. Chronic hepatitis B and C as well as cirrhosis, irrespective of their etiology, are recognized as the major factors increasing the risk of HCC[4-7]. Thus, HCC screening has been extended to include patients with chronic hepatitis B or C as those with cirrhosis[8,9]. The most important tumor marker for HCC is alpha-fetoprotein (AFP). The common method for screening high risk patients using AFP marker can detect more early tumors and prolong the survival of patients[10]. Although HCC screening test has become an accepted procedure among high risk populations, there are still some arguments about its effectiveness because there is no randomized controlled study showing a decrease in disease mortality[11,12]. In addition, the usefulness, frequency and cost-effectiveness of HCC screening may differ in different areas, which may reveal a different prevalence of hepatitis B or C. The aim of this study was to evaluate the usefulness of a screening system in early diagnosis of HCC and to assess the risk factors for HCC development in patients with chronic liver diseases.

MATERIALS AND METHODS

Patients

From June 1995 to June 2005, all data of patients undergone US for HCC or chronic liver diseases in our hospital were collected into a special database program. A total of 14 968 patients had 29 926 examinations during a period of 10 years. We excluded patients with a history of liver cancer or other diseases that might affect survival. In addition, patients with focal hepatic lesion detected at admission or within 3 mo after enrollment were also excluded. All patients were periodically followed up for occurrence of any liver disease. A total of 6089 patients enrolled in this study had US periodically for at least 1 year more.

To assess the risk factors for HCC development, the clinical parameters were collected from 1982 patients. We entered all detailed data into the database program. The age distribution was mostly between the fifth and seventh decades (data not shown). Seventy-seven percent of subjects were positive for hepatitis B surface antigen (HBsAg), 15.5% were positive for anti-hepatitis C virus

Table 1 Comparison of liver status at initial screening and detection of HCC

Liver status	Patients, *n* (%)	
	At initial screening	At detection of HCC
CH	63 (23.9)	9 (3.4)
LC	201 (76.1)	255 (96.6)
Child A	85 (42.2)	122 (47.8)
Child B	38 (19.0)	58 (22.7)
Child C	78 (14.9)	75 (26.1)

Table 2 Underlying liver diseases at initial US of patients with HCC, *n* (%)

Liver status	HBV (+)	HCV (+)	BC	NBNC	Total
CH	45 (17.3)	13 (4.9)	3 (1.1)	3 (0.6)	42 (23.5)
LC	145 (54.8)	37 (14.0)	2 (0.9)	17 (6.4)	201 (76.1)
Total	190 (72.1)	50 (18.9)	5 (2.0)	19 (7.0)	264 (100.0)

Table 3 Tumor size at diagnosis

Diameter (cm)	Patients, *n* (%)
≤ 2	106 (40.8)
> 2-3	70 (26.9)
> 3-5	57 (21.9)
> 5	27 (10.4)
Total	260 (100.0)

Table 4 Tumor size according to US interval

US interval (mo)	Patients, *n* (%)	Tumor size (cm)
≤ 6	124 (47.2)	2.7 ± 1.3[a]
≤ 3	26 (10.0)	3.4 ± 1.8
4-6	98 (37.2)	2.5 ± 1.1
> 6	140 (52.8)	3.4 ± 2.0
7-12	90 (34.0)	3.0 ± 2.1
> 12	50 (18.8)	4.4 ± 1.7
Total	264 (100.0)	3.1 ± 1.7

[a]$P < 0.01$ *vs* > 6-mo group.

Table 5 Median survival according to tumor size

Diameter	Patients, *n* (%)	Median survival (mo)
≤ 2	106 (40.8)	42
> 2-3	70 (26.9)	35
> 3-5	57 (21.9)	20
> 5	26 (10.4)	10
Total	260 (100.0)	31

Table 6 Serum AFP level at detection of HCC

AFP level (ng/mL)	Patients, *n* (%)
≤ 20	107 (41.1)
≥ 1-400	86 (29.6)
> 400	70 (29.3)

(anti-HCV), 0.5% were positive for both and 8.4% were negative for both.

All patients were prospectively monitored by measurement of serum AFP and US at the intervals of 3 mo or 12 mo according to the status of underlying liver disease. The mean follow-up time was 39 ± 28 mo. The duration of HCC development was calculated by the time interval between the date of initial US and diagnosis of HCC. When US showed a new focal lesion or the serum AFP was increased, additional investigations were performed, such as a repeated AFP test, contrast computed tomography, or magnetic resonance imaging. HCC was diagnosed by histology or typical imaging features and elevated serum AFP level (≥ 400 ng/mL).

Serum AFP level was measured by a commercial enzyme-linked immunosorbent assay kit (Abbott, North Chicago IL, USA). US was performed by internal physicians.

Statistical analysis

The data were analyzed using the chi square test, logistic regression, or Kaplan-Meier method. All statistical analyses were done with SAS program and SPSS for windows (7.5.1) (Kaplan-Meier method and Cox regression hazard model).

RESULTS

HCC was found in 264 patients by screening during follow-up, and the annual detection rate was 2.1%. At enrollment, cirrhosis was found in 201 patients (76.1%), chronic hepatitis was diagnosed in 63 patients (23.9%). However, most patients (96.6%) progressed to liver cirrhosis when HCC was detected (Table 1). Of the 264 HCC patients, 190 (72.1%) were associated with hepatitis B, 50 (18.9%) with hepatitis C, and 19 (7.0%) not associated hepatitis B or C (Table 2).

The mean diameter of tumor at diagnosis was 3.1 ± 1.7 cm, and the detection rate of small HCC (≤ 3 cm) was 67.7%. Of the 260 patients, 27 (10.4%) had a tumor larger than 5 cm in diameter (Table 3). The mean diameter of the detected tumors at the intervals of 6 mo was significantly smaller than that at longer intervals (2.7 cm *vs* 3.4 cm, $P < 0.01$). However, there was no difference in tumor size at different time intervals (Table 4). The median survival time was 31 mo (Table 5) and the smaller the tumor size the longer the survival time. Of the 263 HCC patients, 70 (29.3%) had an elevated serum AFP level above 400 ng/mL (Table 6). However, the serum AFP levels were below 20 ng/mL in 107 patients (41.1%).

The incidence of HCC was higher in patients with liver cirrhosis (10.9%) than in those with chronic hepatitis (4.2%) and HBsAg carriers (1.5%). No patient with fatty liver developed HCC. The incidence of HCC was higher in hepatitis C-related group (9.0%) than in hepatitis B- (4.9%) and NBNC-related group (3.9%). However, there was no significant difference between hepatitis C and B patients older than 40 years.

DISCUSSION

The prognosis of HCC is poor especially in Africa and China[13]. By contrast, the disease runs a more benign course in patients in low risk regions, although they have a mean survival time of only about 6 mo[14]. The role of chronic infection with HBV and HCV in the etiology of liver cancer is well established[15]. Some 360 million people are chronically infected and at risk of death due to cirrhosis and HCC. Five hundred thousand to 700 000 people die of HBV-related liver diseases each year[16]. More than 170 million people worldwide are chronically infected with HCV, which is responsible for more than 100 000 cases of liver cancer per year[17].

The usefulness, frequency, and cost-effectiveness of HCC screening may differ in different geographic areas or in different underlying liver disease populations because there may be differences in the incidence and growth characteristics[9,11]. Although US screening for HCC is still controversial, it is a generally accepted strategy in East Asian countries. As patients with chronic hepatitis or cirrhosis may develop HCC, emphasis has been placed on the early detection of HCC when it is small, asymptomatic and potentially curable, by screening patients at high risk[18]. Several trials in areas of high and low HCC incidence have demonstrated that screening can detect patients at early stage of the disease, increase the resection rate and prolong survival time. Randomized prospective studies in China on high risk patients showed that the survival rate of patients after HCC resection is 52.7% after three years[19,20].

Cirrhosis is recognized as the major risk factor for HCC, and the annual risk of developing HCC is between 1% and 6%[21-25]. In our study, the annual risk of HCC development in cirrhosis patients was 3.5%. Reported screening studies showed that 20%-56% of HCC patients have undiagnosed cirrhosis[26,27]. Screening has been extended to include patients with chronic viral hepatitis as well as those with cirrhosis. The overall annual detection rate of HCC in surveillance studies including chronic hepatitis varies from 0.8% to 4.1%[11,28-31]. In our study, the annual detection rate of chronic hepatitis was 1.19%.

If the sample size of the target population or the number of HCC cases is not large enough, it is difficult to evaluate the effectiveness of screening in a high-risk population with different status and etiology of liver diseases. Therefore, a large target population and a sufficient number of HCC cases can avoid sampling bias. In our study, the study subjects were enrolled from 29 926 patients who had US for HCC screening or for various chronic liver diseases. We enrolled 6089 patients who had US periodically for a period of at least 1 year by using a database program. Our study included a variety of liver diseases such as hepatitis B or C, fatty liver and liver cirrhosis-related hepatitis B and C, or non-B and C. Two hundred and sixty-four patients were found to have HCC during a mean 39-mo follow-up, and the annual detection rate was 2.0%.

As the sample size was large enough to allow estimation, we tried to evaluate the efficacy of HCC screening. Because our study was a clinic-based screening, the incidence of HCC was higher than that of Sherman *et al*[9]. In our study, 76.9% of patients with HCC had liver cirrhosis and 23.1% had chronic hepatitis. Furthermore, most of these cases progressed to liver cirrhosis before development of HCC. Although the incidence of HCC was higher in liver cirrhosis patients (10.7%) than in chronic hepatitis patients (4.0%), chronic hepatitis B or C might progress to cirrhosis and HCC, suggesting that surveillance is needed to include patients with chronic viral hepatitis over the age of 40 years in China.

Reported screening intervals vary from 3 to 12 mo. A 6-mo interval is generally accepted as a rational choice. However, some others prefer shorter intervals in high-risk patients[32,33]. In our study, the mean diameter of tumor size at diagnosis was 3.1 ± 1.7 cm and the detection rate of small HCC (< 3 cm) was 67.7%. However, there was no difference in tumor size between different time intervals (Table 4). Although a shorter screening interval can detect earlier HCC, it decreases cost-effectiveness.

Whether early detection of tumors can prolong survival time remains unclear[11]. In our study, the overall median survival of the screened group was 31 mo, suggesting that survival time correlates well with tumor size. Furthermore, survival time was remarkably improved when the detected tumor size was equal or smaller than 2 cm (Table 5). Although the resection rate was relatively low in our study, most tumors, especially those less than 3 cm in diameter, were amenable to non-surgical curative or effective therapy.

Only 70 of the 264 HCC patients (29.3%) had an elevated serum AFP level above 400 ng/mL. In addition, the serum AFP level was below 20 ng/mL in 41.1% of patients. Trials in China have shown that combination of US and AFP can achieve better results in screening HBsAg positive subjects[21,34].

The incidence of HCC was higher in liver cirrhosis patients (10.9%) than in chronic hepatitis patients (4.2%). None of the patients with fatty liver developed HCC. The incidence of HCC was higher in hepatitis C-related group (9.0%) than in hepatitis B- (4.9%) and NBNC-related groups (3.9%). However, the incidence was not significantly different between hepatitis C and B in the group over 40 years of age. As the risk of HCC is negligible in hepatitis B patients under the age of 30 years and in hepatitis C patients under the age of 40 years, the screening would be better restricted to patients over the age of 40 years.

In conclusion, US screening at the intervals of 6 mo is beneficial to high-risk patients over the age of 40 years and prolongs survival. According to risk factors, the necessity for a screening test and a proper interval should be reconsidered.

REFERENCES

1 **Tang ZY**. Hepatocellular carcinoma-cause, treatment and metastasis. *World J Gastroenterol* 2001; **7**: 445-454
2 **Bruix J**, Llovet JM. Prognostic prediction and treatment strategy in hepatocellular carcinoma. *Hepatology* 2002; **35**: 519-524
3 **Okuda K.** Hepatocellular carcinoma. *J Hepatol* 2000; **32**: 225-237

4 **Yu MC**, Yuan JM. Environmental factors and risk for hepatocellular carcinoma. *Gastroenterology* 2004; **127**: S72-S78
5 **Velázquez RF,** Rodríguez M, Navascués CA, Linares A, Pérez R, Sotorríos NG, Martínez I, Rodrigo L. Prospective analysis of risk factors for hepatocellular carcinoma in patients with liver cirrhosis. *Hepatology* 2003; **37**: 520-527
6 **Ohata K**, Hamasaki K, Toriyama K, Matsumoto K, Saeki A, Yanagi K, Abiru S, Nakagawa Y, Shigeno M, Miyazoe S, Ichikawa T, Ishikawa H, Nakao K, Eguchi K. Hepatic steatosis is a risk factor for hepatocellular carcinoma in patients with chronic hepatitis C virus infection. *Cancer* 2003; **97**: 3036-3043
7 **Yano Y**, Yamashita F, Sumie S, Ando E, Fukumori K, Kiyama M, Oyama T, Kuroki S, Kato O, Yamamoto H, Tanaka M, Sata M. Clinical features of hepatocellular carcinoma seronegative for both HBsAg and anti-HCV antibody but positive for anti-HBc antibody in Japan. *Am J Gastroenterol* 2002; **97**: 156-161
8 **Villeneuve JP**, Desrochers M, Infante-Rivard C, Willems B, Raymond G, Bourcier M, Côté J, Richer G. A long-term follow-up study of asymptomatic hepatitis B surface antigen-positive carriers in Montreal. *Gastroenterology* 1994; **106**: 1000-1005
9 **Sherman M**, Peltekian KM, Lee C. Screening for hepatocellular carcinoma in chronic carriers of hepatitis B virus: incidence and prevalence of hepatocellular carcinoma in a North American urban population. *Hepatology* 1995; **22**: 432-438
10 **Lopez JB**. Recent developments in the first detection of hepatocellular carcinoma. *Clin Biochem Rev* 2005; **26**: 65-79
11 **Collier J**, Sherman M. Screening for hepatocellular carcinoma. *Hepatology* 1998; **27**: 273-278
12 **Di Bisceglie AM**, Carithers RL Jr, Gores GJ. Hepatocellular carcinoma. *Hepatology* 1998; **28**: 1161-1165
13 **Kew MC**, Geddes EW. Hepatocellular carcinoma in rural southern African blacks. *Medicine* (Baltimore) 1982; **61**: 98-108
14 **Kew MC**, Dos Santos HA, Sherlock S. Diagnosis of primary cancer of the liver. *Br Med J* 1971; **4**: 408-411
15 **Bosch FX**, Ribes J, Borràs J. Epidemiology of primary liver cancer. *Semin Liver Dis* 1999; **19**: 271-285
16 Website of the world health organization. Accessed 2 Febtuary 2005. Available from: URL: http://www.who.int/mediacentre/factsbeets/fs204/en/
17 **Poynard T**, Yuen MF, Ratziu V, Lai CL. Viral hepatitis C. *Lancet* 2003; **362**: 2095-2100
18 **Di Bisceglie AM**, Rustgi VK, Hoofnagle JH, Dusheiko GM, Lotze MT. NIH conference. Hepatocellular carcinoma. *Ann Intern Med* 1988; **108**: 390-401
19 **Yang B**, Zhang B, Xu Y, Wang W, Shen Y, Zhang A, Xu Z. Prospective study of early detection for primary liver cancer. *J Cancer Res Clin Oncol* 1997; **123**: 357-360
20 **Zhang B**, Yang B. Combined alpha fetoprotein testing and ultrasonography as a screening test for primary liver cancer. *J Med Screen* 1999; **6**: 108-110
21 **Kato Y**, Nakata K, Omagari K, Furukawa R, Kusumoto Y, Mori I, Tajima H, Tanioka H, Yano M, Nagataki S. Risk of hepatocellular carcinoma in patients with cirrhosis in Japan. Analysis of infectious hepatitis viruses. *Cancer* 1994; **74**: 2234-2238
22 **Ikeda K**, Saitoh S, Koida I, Arase Y, Tsubota A, Chayama K, Kumada H, Kawanishi M. A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis. *Hepatology* 1993; **18**: 47-53
23 **Colombo M**, de Franchis R, Del Ninno E, Sangiovanni A, De Fazio C, Tommasini M, Donato MF, Piva A, Di Carlo V, Dioguardi N. Hepatocellular carcinoma in Italian patients with cirrhosis. *N Engl J Med* 1991; **325**: 675-680
24 **Oka H**, Tamori A, Kuroki T, Kobayashi K, Yamamoto S. Prospective study of alpha-fetoprotein in cirrhotic patients monitored for development of hepatocellular carcinoma. *Hepatology* 1994; **19**: 61-66
25 **Pateron D**, Ganne N, Trinchet JC, Aurousseau MH, Mal F, Meicler C, Coderc E, Reboullet P, Beaugrand M. Prospective study of screening for hepatocellular carcinoma in Caucasian patients with cirrhosis. *J Hepatol* 1994; **20**: 65-71
26 **Liver Cancer Study Group of Japan.** Primary liver cancer in Japan. Clinicopathologic features and results of surgical treatment. *Ann Surg* 1990; **211**: 277-287
27 **Zaman SN**, Johnson PJ, Williams R. Silent cirrhosis in patients with hepatocellular carcinoma. Implications for screening in high-incidence and low-incidence areas. *Cancer* 1990; **65**: 1607-1610
28 **Takano S**, Yokosuka O, Imazeki F, Tagawa M, Omata M. Incidence of hepatocellular carcinoma in chronic hepatitis B and C: a prospective study of 251 patients. *Hepatology* 1995; **21**: 650-655
29 **Chiba T**, Matsuzaki Y, Abei M, Shoda J, Tanaka N, Osuga T, Aikawa T. The role of previous hepatitis B virus infection and heavy smoking in hepatitis C virus-related hepatocellular carcinoma. *Am J Gastroenterol* 1996; **91**: 1195-1203
30 **Curley SA**, Izzo F, Gallipoli A, de Bellis M, Cremona F, Parisi V. Identification and screening of 416 patients with chronic hepatitis at high risk to develop hepatocellular cancer. *Ann Surg* 1995; **222**: 375-80; discussion 380-3
31 **Tsukuma H**, Hiyama T, Tanaka S, Nakao M, Yabuuchi T, Kitamura T, Nakanishi K, Fujimoto I, Inoue A, Yamazaki H. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. *N Engl J Med* 1993; **328**: 1797-1801
32 **Chen DS**, Sung JL, Sheu JC, Lai MY, How SW, Hsu HC, Lee CS, Wei TC. Serum alpha-fetoprotein in the early stage of human hepatocellular carcinoma. *Gastroenterology* 1984; **86**: 1404-1409
33 **Sheu JC**, Sung JL, Chen DS, Yang PM, Lai MY, Lee CS, Hsu HC, Chuang CN, Yang PC, Wang TH. Growth rate of asymptomatic hepatocellular carcinoma and its clinical implications. *Gastroenterology* 1985; **89**: 259-266
34 **Tong MJ**, Blatt LM, Kao VW. Surveillance for hepatocellular carcinoma in patients with chronic viral hepatitis in the United States of America. *J Gastroenterol Hepatol* 2001; **16**: 553-559

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