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

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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 interferon; Retreatment

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.

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Key words: Hepatitis C; Hepatocarcinogenesis; Interferon; Retreatment

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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
(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.

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

| Liver status | At initial screening | At detection of HCC | Patients, n (%) |
|--------------|---------------------|---------------------|-----------------|
| CH           | 63 (23.9)           | 9 (3.4)             | 72 (26.9)       |
| LC           | 201 (76.1)          | 255 (96.6)          | 276 (97.1)      |
| Child A      | 85 (42.2)           | 122 (47.8)          | 207 (77.6)      |
| Child B      | 38 (19.0)           | 58 (22.7)           | 96 (36.1)       |
| Child C      | 78 (14.9)           | 75 (26.1)           | 153 (57.8)      |

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

| Liver status | HBV (+) | HCV (+) | BC | NBNC | Total | Patients, n (%) |
|--------------|---------|---------|----|------|-------|-----------------|
| CH           | 45 (17.3)| 13 (4.9)| 3  | 1    | 42 (23.5)| 190 (72.1) |
| LC           | 145 (54.8)| 37 (14.0)| 2  | 1    | 201 (76.1)| |
| Total        | 190 (72.1)| 50 (18.9)| 5  | 1    | 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*      |
| ≤ 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       |

P < 0.01 vs > 6-mo group.

Table 5  Median survival according to tumor size

| Diameter (cm) | 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)       |

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.

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Hepatocellular carcinoma-cause, treatment and estimation, we tried to evaluate the efficacy of HCC during a mean 39-mo follow-up, and the annual detection rate was 2.0%.

Two 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[15].

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[11,28-31]. 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%[14-20]. 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%[10,12-31]. 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[11,21-25]. 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[10]. 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[21,24].

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.

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