A Contribution to Early Diagnosis of Primary Hepatic
Cell Carcinoma Occurring in Patients with Liver
Cirrhosis

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In cases where liver cirrhosis can be diagnosed, we must give the occurrence of primary hepatic cell
carcinoma careful consideration because most cases of hepatoma are associated with liver cirrhosis.

Among 311 patients with liver cirrhosis, in whom the diagnosis was made laparoscopically and
histologically in the past 6 years and the clinical course was observed for at least 1 year after initial
diagnosis, primary hepatocellular carcinoma developed in 20 patients, in whom alpha-fetoprotein
in the serum, sonography, scintigraphy, computed tomography, selective angiography and echo
or laparoscopy guided needle biopsy of the liver were utilized regularly after initial diagnosis of
liver cirrhosis.

Based on our own experience, we wish to stress that the combination of sonography, scinti-
graphy, computed tomography and selective angiography can contribute to early diagnosis of
primary hepatocellular carcinoma occurring in patients with liver cirrhosis.

(Key Words: Primary Hepatic Cell Carcinoma, Sonography, Scintigraphy, Computed Tomography,
Angiography, Laparoscopy, Echo or Laparoscopy Guided Needle Biopsy of the Liver)

INTRODUCTION

For diagnosis of primary hepatic cell carcinoma, palpation of the enlarged, nodose liver, laboratory findings, laparoscopy, scintigraphy and hepatic artery angiography are still important and valuable methods, but they are insufficient for detection of primary hepatic cell carcinoma in its early stages. Alpha-fetoprotein is very interesting in the detection and study of primary hepatic cell carcinoma.

In any case, we must make efforts to achieve an early diagnosis of primary hepatic cell carcinoma by means of these diagnostic tools. For the purpose of detecting primary hepatic cell carcinoma in its early stage, we must pay close attention to the tendency of association of primary hepatic cell carcinoma with liver cirrhosis. In other words, we must give the occurrence of primary hepatic cell carcinoma careful consideration in cases where liver cirrhosis can be diagnosed because most cases of primary hepatic cell carcinoma are associated with liver cirrhosis.

This paper reports an investigation of the early diagnostic procedures of primary hepatic cell carcinoma in liver cirrhosis.
MATERIALS AND METHODS

Among 311 patients with liver cirrhosis, in whom the diagnosis was made laparoscopically and histologically in the past 6 years and the clinical course was observed for at least 1 year after initial diagnosis, primary hepatic cell carcinoma developed in 20 patients, in whom alpha-fetoprotein in the serum, sonography, scintigraphy, computed tomography, selective angiography and echo or laparoscopy guided needle biopsy of the liver by means of laparoscopy or sonography were utilized after initial diagnosis of liver cirrhosis. In particular, alpha-fetoprotein in the serum, sonography and scintigraphy were examined periodically immediately after the diagnosis of liver cirrhosis.

RESULTS

As shown in Fig. 1, the lapse of time after initial diagnosis of liver cirrhosis until initial diagnosis of primary hepatic cell carcinoma ranged from 1 year to 11 years; 3.05 years on the average. Survival time after initial diagnosis of primary hepatic cell carcinoma ranged from 1 to 19 months, i.e. 3.3 months on the average, in the 14 cases which died because of cirrhotic troubles of the liver. It was impossible to recognize a definite correlation between the lapse of time after initial diagnosis of liver cirrhosis until initial diagnosis of primary hepatic cell carcinoma and the lapse of time after initial diagnosis of primary hepatic cell carcinoma until death. The six remaining cases are alive 4 to 18 months, 9.33 months on the average, after initial diagnosis of primary hepatic cell carcinoma.

As stated above, alpha-fetoprotein in the serum was estimated once every 4 weeks and scintigraphy of the liver was performed once every 2 months in the clinical course of these 311 patients with liver cirrhosis after initial diagnosis. In 13 out of 20 patients with primary hepatic cell carcinoma, alpha-fetoprotein level in the serum increased abruptly (Table 1), while the estimated level of serum alpha-fetoprotein remained within the normal range or showed, at most, an insignificant elevation up to that time. The quantitative estimation of alpha-fetoprotein in the serum was definitely useful for diagnosis of primary hepatic cell carcinoma in 65% of the cases. The abrupt elevation of alpha-fetoprotein level in the serum presented an opportunity to diagnose primary hepatic cell carcinoma in 13 out of 311 patients with liver cirrhosis. In the seven remaining cases of primary hepatic cell carcinoma, periodic sonography and scintigraphy after initial diagnosis of liver cirrhosis permitted the detection of primary hepatic cell carcinoma.

In 14 out of 20 cases, sonography was repeated regularly once every two months and it was useful as a first step to detect minute hepatocellular carcinoma. In five out seven cases, in which alpha-fetoprotein level in the serum was diagnostically insignificant at the time of initial diagnosis of primary hepatic cell carcinoma, sonography revealed the outline of a tumor in a hepatic lobe and in the two remaining cases, sonography was not performed (Table 2). In addition, scintigraphy was performed in these 20 cases and showed significant results in 17 cases (Tables 1 and 2). In two cases,
in which the alpha-fetoprotein level in the serum was diagnostically insignificant and sonography was not performed, scintigraphy showed a space occupying lesion in a hepatic lobe (Table 2).

Scintigraphy revealed a space occupying lesion in a hepatic lobe in 17 out of 20 cases of primary hepatic cell carcinoma and showed no space occupying lesion in the liver in three cases. In one of these cases, a 79-year-old male, sonography showed an outline of a tumor in the hepatic lobe but the alpha-fetoprotein level in the serum remained within the normal range. Diagnostic efficacy of computed tomography, angiography and laparoscopy is shown in Table 1.

![Diagram](image-url)

**Fig. 1** Cases of primary hepatocellular carcinoma occurring in patients with liver cirrhosis

**Table 1** Frequency of positive diagnostic procedures in patients with primary hepatocellular carcinoma on the basis of liver cirrhosis (n = 20)

<table>
<thead>
<tr>
<th>Diagnostic procedure</th>
<th>Frequency (Percentage)</th>
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<tr>
<td>AFP</td>
<td>13/20 (65%)</td>
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<tr>
<td>Sonography</td>
<td>14/14 (100%)</td>
</tr>
<tr>
<td>Scintigraphy</td>
<td>17/20 (85%)</td>
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<tr>
<td>Computed tomography</td>
<td>11/11 (100%)</td>
</tr>
<tr>
<td>Angiogram</td>
<td>18/20 (90%)</td>
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<td>Laparoscopy</td>
<td>4/20 (20%)</td>
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<tr>
<td>Laparoscopy guided needle biopsy of the liver</td>
<td>15/20 (75%)</td>
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<tr>
<td>Echo guided needle biopsy of the liver</td>
<td>5/5 (100%)</td>
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Table 2  The results of diagnostic procedures contributing to early diagnosis of primary hepatocellular carcinoma on the basis of our own 20 cases

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
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<th>Scintigraphy</th>
<th>Computed tomography</th>
<th>Angiography</th>
<th>Laparoscopy</th>
<th>Echo guided needle biopsy</th>
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<tr>
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<tr>
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<td>+</td>
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<tr>
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CASUISTICS

A series of these diagnostic procedures in the clinical course of one patient out of 20 will be given as an example. M.H., a 47 year-old male, was admitted to our clinic on May 6, 1980 because of laparoscopically and biopsy clarified chronic aggressive hepatitis at the beginning of April, 1977 in an University Hospital. He had been under constant medical treatment there. In his early history, he underwent a surgical operation with blood transfusion because of a perforated duodenal ulcer in 1958, followed by serum hepatitis. On admission, blood biochemical examination reflected a severe inflammatory change of the liver. Laparoscopy on May 9, 1980 showed a nodulated liver (Fig. 2) and the simultaneously performed liver biopsy revealed histologic findings corresponding to chronic aggressive hepatitis with pseudolobule formation (Fig. 3 a, b). At that time, scintigraphy (Fig.4), angiography (Fig. 5a, b) and computed tomography (Fig. 6) showed no focal change of the liver. These diagnostic procedures were performed repeatedly from July to October, 1980 and the results showed no focal change of the liver. At the beginning of January, 1981, alpha-fetoprotein level in the serum rose abruptly to 1,730ng/ml. Scintigraphy suggested a space occupying lesion in the right hepatic lobe.
Fig. 2 Laparoscopy on May 9, 1980: Nodulated liver
Fig. 3 Histologic findings of a laparoscopy guided needle biopsy of the liver on May 9, 1980. (a) H-E stain, 40× (b) H-E stain, 100× Chronic aggressive hepatitis in liver cirrhosis
(Fig. 7). Sonography (Fig. 8) and computed tomography (Fig. 9) outlined a focal change of the right hepatic lobe, but selective angiography showed less outstanding changes due to the tumor. The second laparoscopy in our clinic showed a nodulated liver again and histologic findings of the liver by means of laparoscopy guided needle biopsy revealed severe active inflammatory changes of the liver with pseudolobule formation (Fig. 10 a, b). Immediately, echo guided needle biopsy was attempted and fortunately, liver specimens could be obtained. Histologic examination of the biopsied specimens showed findings corresponding to primary hepatocellular carcinoma (Fig. 11 a, b). Several months later, the tumor increased in size (Figs. 12 and 13) and some daughter nodules were detected (Fig. 14). The patient had been under medical treatment with anti-cancer drugs administered through the celiac artery but died of intra-abdominal bleeding from the ruptured tumor on September 23, 1981. At the time of autopsy, the liver findings could be confirmed.

Fig. 4 Scintigram on May 7, 1980
Fig. 5  Angiogram on May 16, 1980: (a) arterial phase (b) venous phase
Fig. 6 Computed tomogram on May 26, 1980

Fig. 7 Scintigram on February 13, 1981.
A Contribution to Early Diagnosis of Hepatic Cell Carcinoma

Fig. 8  Sonogram on February 7, 1981

Fig. 9  Computed tomogram on February 25, 1981
Fig. 10  Histologic findings of the second laparoscopy guided needle biopsy of the liver on March 13, 1981: Chronic aggressive hepatitis with pseudolobule formation,
(a) H-E stain, 40 × (b) H-E stain, 100 ×
Fig. 11  Histologic findings of echo guided needle biopsy of the liver on April 17, 1981:
Primary hepatocellular carcinoma.
(a) H-E stain, 40 x (b) H-E stain, 100 x
Fig. 12 Scintigram on May 29, 1981

Fig. 13 Computed tomogram on June 3, 1981
DISCUSSION

In Japan, most cases of primary hepatic cell carcinoma are associated with liver cirrhosis. Therefore, we must give the occurrence of primary hepatic cell carcinoma careful consideration in cases where liver cirrhosis can be diagnosed. Among 311 patients with liver cirrhosis, in whom the clinical course was observed for at least 1 year after initial diagnosis of liver cirrhosis, primary hepatic cell carcinoma developed in 20 patients. In 16 out of these 20 patients, the tumor was localized in a hepatic lobe and did not occur on the surface of the liver.

Formerly, we reported that laparoscopic examination is of significance in diagnosing primary hepatic cell carcinoma with an exact diagnosis of 82.4% of 74 cases. Because of thin membranous adhesions, primary hepatic cell carcinoma was laparoscopically suspected in another 12 patients (16.2%). Thereafter, this suspicion of the disease from laparoscopic findings was clarified by means of needle biopsy and autopsy findings. Therefore, it can be said that laparoscopic examination was efficient in the diagnosis of primary hepatic cell carcinoma. The only inconvenience in this diagnostic tool occurs when the pathological change does not appear on the surface of the liver. In such cases, no reliable diagnosis can be obtained (4, 5).

In the present study, primary hepatic cell carcinoma in its early stage could be detected in the clinical course of liver cirrhosis, in which the diagnosis was first made on the basis of the laparoscopic and bioptic...
findings of the liver in our clinic. In four out of 20 cases, pathological changes of the liver occurred on the surface of the liver and the laparoscopic examination was significant in these cases, i.e. diagnosis was possible in 20% of patients with primary hepatic cell carcinoma in an early stage.

At present, alpha-fetoprotein in quantities of more than 20ng/ml can be estimated exactly by radioimmunoassay. This amount of alpha-fetoprotein can be seen in the clinical course of cirrhosis of the liver and chronic hepatitis. In such cases, it is very important to keep in mind that in patients with primary hepatic cell carcinoma, alpha-fetoprotein in the serum always remains at more than 200ng/ml, while in patients with cirrhosis of the liver and chronic hepatitis, alpha-fetoprotein levels in the serum show temporary fluctuations. The quantitative estimation of alpha-fetoprotein is useful for determining the therapeutic effect of radical resection of hepatic tumors. If the primary hepatic cell carcinoma is completely excised, alpha-fetoprotein disappears from the blood serum. In cases of recurrence of the disease after resection, alpha-fetoprotein increases gradually again (2). It has become clear that the cellular differentiation of primary hepatic cell carcinoma is connected with the production of alpha-fetoprotein. Alpha-fetoprotein levels increased in the 2nd and 3rd stages according to the Edmondson-Steiner classification (1, 8), while the estimation was negative in the 1st and 4th stages. In 13 out of 20 patients with primary hepatic cell carcinoma, the estimation of alpha-fetoprotein in the serum resulted in pathologic elevations and this permitted us to detect tumors of the liver. The utilization of alpha-fetoprotein in the early diagnosis of primary hepatic cell carcinoma is possible in 65% of the cases. The estimation of alpha-fetoprotein in the serum seems to be of importance in diagnosing primary hepatic cell carcinoma but is sufficiently efficient for early diagnosis of the disease.

Sonographic diagnosis can contribute to early diagnosis of primary hepatic cell carcinoma, because this diagnostic procedure seems to involve no mental tension or somatic troubles in the patients and therefore, it can be performed repeatedly at regular intervals. Moreover, it is possible to perform a sonography guided needle biopsy of the liver, although the first trial of this diagnostic procedure does not always give successful results. In 14 out of 20 cases, sonography was performed and the results were suggestive of an outline of a tumor in the hepatic lobe in 14 all cases. Even if the estimation of alpha-fetoprotein in the serum remained within the levels up to that time, sonography could outline the tumor in the hepatic lobe. Either the estimation of alpha-fetoprotein or sonography can serve as a valuable diagnostic tool.

Scintigraphy of the liver can outline space occupying lesions or cold areas of a minimal size of 2cm in diameter (6). In 17 out of 20 cases, space occupying lesions of primary hepatic cell carcinoma could be outlined in three dimensions, and their sizes ranged from 3 to 4cm in diameter. In the three remaining cases, the tumor could not be outlined in the hepatic lobe although the size of tumor ranged from 2 to 2.5cm in diameter. In addition, false positive space occupying lesions in the hepatic lobe must always be taken into consideration in the evaluation of scintigraphic findings.
Computed tomography was performed in 11 out of 20 cases and revealed an outline of a tumor in the hepatic lobe. This diagnostic procedure can serve as a diagnostic tool for detecting the existence of focal hepatic lesions and differential diagnosis of such lesions (3, 7).

Selective angiography through the truncus celcius and the arteria hepatica communis is a very reliable diagnostic tool for determining primary hepatic cell carcinoma and its metastatic localization (9). To date, we have succeeded in angiographic diagnosis in 17 out of 20 patients investigated.

The most decisive diagnosis of primary hepatic cell carcinoma in its early stage can be made on the basis of histologic findings of the liver by means of needle biopsies. Formerly, needle biopsies were performed when the tumor appeared on the surface of the liver. At present, echo guided or laparoscopy guided needle biopsies of the liver can be undertaken. If the tumor has been confirmed in three dimensions in the liver by means of sonography, scintigraphy, computed tomography and selective angiography, echo or laparoscopy guided needle biopsy of the liver can be attempted when the tumor does not appear on the surface of the liver by means of laparoscopy. In our own 20 patients with primary hepatic cell carcinoma, the combination of these diagnostic procedures brought a decisive diagnosis on the basis of histologic findings by means of echo or laparoscopy guided needle biopsy of the liver.

Based on the facts, we wish to stress that the combination of sonography, scintigraphy, computed tomography and selective angiography can contribute to early diagnosis of primary hepatic cell carcinoma occurring in patients with liver cirrhosis.

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