Liver Cancer
—Prevention and Early Diagnosis—
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Michio IMAWARI
Professor of Medicine, Jichi Medical School, Omiya Medical Center

Abstract: Primary liver cancer occurs mainly as a result of chronic liver disorders due to hepatitis virus infection. The important thing in preventing liver cancer is to prevent hepatitis virus infection and eliminate hepatitis virus in chronic hepatitis patients. In order to eliminate hepatitis virus in chronic viral hepatitis, therapies with interferon or recently introduced lamivudine are indicated for hepatitis B patients, and therapies with interferon and combination of interferon and ribavirin are indicated for hepatitis C. However, there exist patients for whom antiviral therapy is ineffective or not beneficial, and drugs to control inflammation act to delay onset of liver cancer in such patients. In patients of the high-risk group for liver cancer such as those with advanced chronic hepatitis or cirrhosis, early diagnosis of liver cancer is essential. For this purpose, it is recommended to perform cancer screening regularly by diagnostic imaging using ultrasonic examinations of the abdomen and measurements of liver cancer markers such as AFP or PIVKA-II.

Key words: Liver cancer; Hepatitis virus; Ultrasonic examination of the abdomen; Tumor markers

Introduction

There are two types of liver cancers; primary carcinoma and metastatic tumor. The incidence is higher for the latter than for the former in clinical medicine. In prevention and early diagnosis of liver cancer, however, the focus is on primary carcinoma. According to the Japanese Ministry of Welfare & Health statistics, death by primary liver cancer is 34,000 in 1999, showing a gradual but steady increase. According to the report of the follow-up study for 1996–1997 by the Japanese Study Group of Liver Cancer, 95% of primary liver cancer is hepatocellular carcinoma, followed by 3.4% of cholangiocarcinoma, and less than 1% of carcinomas of mixed origin, cystic liver carcinoma, hepatoblastoma, and sarcoma, respectively. Autopsy findings reveal that cirrhosis is concurrently found in 77% of hepatocellular carcinoma, and chronic liver disease in 93% including chronic hepatitis and hepatic fibrosis. Sixteen percent of hepatocellular carcinoma is HBs antigen positive, 75% is HCV antibody

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HBs-antigen positive, there are hardly any new cases with persistent hepatitis B in recent years. About 10% of persistent hepatitis B patients progress to chronic hepatitis, 20–30% of whom progress to cirrhosis, who then develop hepatocellular carcinoma. Therefore, elimination of virus or controlling hepatitis in chronic hepatitis B patients means prevention of hepatocellular carcinoma.

However, genes of hepatitis B virus are characteristically integrated into host genes, and if the site where genes are integrated is involved in carcinogenesis, hepatocellular carcinoma occurs without persistent hepatitis. It is reported that interferon therapy, steroid withdrawal therapy, or their combination, and administration of propagermanium targeting at elimination of hepatitis B viruses can be expected to succeed in 10–40% of the cases, particularly in cases with a smaller amount of virus and a high transaminase level.

In those with past history of jaundice or cirrhosis, these therapies cause severe liver damage by augmented immune responses, leading to hepatic insufficiency in some cases. Lamivudine, a recently introduced drug, is an anti-viral drug without function of immunomodulation and its administration for a year achieves virus exclusion in about 10%, normal-

![Fig. 1 Pathogenesis of hepatocellular carcinoma by hepatitis virus infection](image-url)
ization of transaminase in about 60%, HBV DNA lowering, and transaminase improvement in about 80%, indicating that this will be the drug of first choice in treatment of chronic hepatitis B in the near future. This drug sometimes develops emerging of resistant viruses, and careless suspension may lead to rapid increase of viruses and severe hepatitis. To chronic hepatitis patients with a high transaminase level for whom anti-viral drug is ineffective or cirrhotic patients for whom anti-viral drug is not indicated, drugs acting on the liver such as ‘Strong Neo Minophagen C’ or ursodesoxycholic acid are administered.

Except for a few sporadic cases, there are hardly any new hepatitis C virus infection thanks to the use of disposable medical tools and hepatitis virus screening for blood transfusion. As for development of hepatocellular carcinoma in hepatitis C patients, only those with chronic liver disorders develop carcinoma since this virus is not integrated into the host gene. The cancer incidence is higher in those in whom liver fibrosis is more advanced, and 8% of cirrhotic patients develop hepatocellular carcinoma in a year. Accordingly, chronic hepatitis patients with liver damage and cirrhosis patients are needed to be treated.

Interferon is administered in anti-viral treatment for chronic hepatitis C, with only 20 to 30% successfully responding by sustained elimination of viruses. Less than 10% of those with Type 1 hepatitis C virus, which is highly prevalent in Japan, can successfully and persistently eliminate viruses with the current method of administration. While patients whose viruses have been eliminated successfully hardly develop liver carcinoma, there is an opinion that those patients, for whom virus elimination cannot be expected, should be given treatment since cancer development is restrained in those whose transaminase was normalized even temporarily as in the case of sustained transaminase normalization. A report overseas mentions improvement in those with Type 1 hepatitis C viruses by combining ribavirin with interferon. Introduction of ribavirin in Japan is awaited.

Lowering of transaminase is attempted by administration of drugs acting on the liver of chronic hepatitis C patients for whom interferon is not at all effective or cirrhotic patients for whom interferon therapy is not indicated as in the case of chronic hepatitis B patients.

**Early Diagnosis of Hepatocellular Carcinoma**

Patients with chronic liver diseases belong to a high-risk group for hepatocellular carcinoma and should be followed up regularly for early diagnosis. For regular follow-up, diagnostic imaging and measurement of tumor markers are used. For diagnostic imaging, the abdominal ultrasonography plays an important part. For those whose liver cannot be fully imaged by abdominal ultrasonography or whose echograms are too crude to image lesions clearly, contrast CT or MRI is performed.

Alfa-fetoprotein (AFP) and PIVKA-II are used as tumor markers for hepatocellular carcinoma. About 30 to 40% of chronic liver diseases with hepatocellular carcinoma of less than 3 cm in diameter show more than 200 ng/ml of AFP that is hardly observed in chronic liver disorders without hepatocellular carcinoma. In advanced hepatocellular carcinoma showing a lesion greater than 6 cm in diameter, AFP is less than 200 ng/ml in about 25%. On the other hand, the positive ratio for hepatocellular carcinoma of less than 2 cm diameter measured by high sensitivity PIVKA-II is 40–50%, indicating the utility is about the same as that of AFP. However, the sensitivity of tumor markers for detecting hepatocellular carcinoma is lower than that of diagnostic imaging, and its utility in hepatocellular cancer screening is less than that of diagnostic imaging. It is thus more useful for monitoring treatment. There exists a fraction with different lectin-affinity in AFP, and L3 fraction is highly specific for hepatocellular carcinoma. In some patients with slightly elevated
AFP, L3 fraction is reported to increase before hepatocellular carcinoma is detected by diagnostic imaging.  

In the follow-up of those with sustained hepatitis virus infection, abdominal ultrasonography and measurement of AFP or PIVKA-II once in six to twelve months are recommended for those with normal liver functions and chronic hepatitis with mild liver damage, once in four to six months for those with chronic hepatitis with advanced fibrosis, and once in three to four months in cirrhosis patients (Fig. 2). Those in whom a tumor is detected in the liver by screening should be given contrast CT, MRI, angiography, CT with angiography, or biopsy of tumor if necessary in order to select the treatment policy.

**Conclusion**

The basic step for preventing hepatocellular carcinoma are 1) to prevent hepatitis B and C virus infections, 2) to eliminate hepatitis viruses from chronic hepatitis patients, and 3) to control hepatitis.

Hepatocellular carcinoma usually occurs by reflecting the degree of liver fibrosis, and the basis for early diagnosis is the regularly performed abdominal ultrasonography, complemented by AFP and PIVKA-II measurements.

**REFERENCES**


