Hepatitis C and Hepatocellular Carcinoma

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Ryota Masuzaki, Tatsuo Kanda, Haruhiko Yoshida, Naoya Kato, and Masao Omata

Abbreviations

HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IFN	Interferon
UTRs	Untranslated lesions
ALT	Alanine aminotransferase
NS	Nonstructural
DAA	Direct-acting antiviral
SVR	Sustained virologic rate
US	Ultrasonography
CT	Computed tomography
NASH	Nonalcohlolic steatohepatitis
AST	Aspartate aminotransferase
MDCT	Multi-detector computed tomography
AFP	Alpha fetoprotein
HGF	Hepatocyte growth factor
IGF-1	Insulin-like growth factor
SUV	Standardized uptake value
QALY	Quality-adjusted life-year
DCP	Des-gamma-carboxyprothrombin

R. Masuzaki (✉)
Department of Surgery, Vanderbilt University Medical Center, 2213 Garland Ave. MRB4, Nashville, TN 37232, USA
e-mail: ryota-m@umin.ac.jp

T. Kanda
Department of Gastroenterology and Nephrology, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba, 260-8670, Japan
e-mail: kandat-cib@umin.ac.jp

H. Yoshida
Department of Gastroenterology, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan
e-mail: yoshida-2im@h.u-tokyo.ac.jp

N. Kato
The Advanced Clinical Research Center, the Institute of Medical Science, the University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo, 108-8639, Japan
e-mail: kato-2im@h.u-tokyo.ac.jp

M. Omata (✉)
Yamanashi Prefectural Hospital Organization, 1-1-1 Fujimi, Kofu, Yamanashi 400-0027, Japan
e-mail: momata-tky@umin.ac.jp

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Contents

17.1 Introduction

Hepatocellular carcinoma (HCC), one of the most common cancers worldwide [1], usually develops in a liver already chronically damaged, often from cirrhosis. The etiology of liver disease, and consequently that of HCC, differs geographically. In most areas, chronic viral hepatitis due to either hepatitis B virus (HBV) or hepatitis C virus (HCV) is the main cause of HCC [2–5]. In this chapter, we focus on HCC among patients with hepatitis C.

17.2 Epidemiology

HCV infection has shown rapid worldwide expansion in recent years [6]. HCV is transmitted as a blood-borne infection, although it is much less infectious than HBV (Table 17.1). Mother-neonate transmission and horizontal sexual transmission are uncommon with HCV. Therefore, the recent rapid spread of HCV must be associated with some artificial change in the environment. Epidemiological studies have shown that viral spread began in the United States in the mid-1960s, mainly among intravenous drug users, and then began to decline by the 1990s, when general concern regarding human immunodeficiency virus (HIV) infection increased substantially. Indeed, in the United States, the transmission route of HCV overlapped that of HIV. This led to a serious medical problem, HCV/HIV coinfection, in which liver damage progresses more rapidly due to comorbid immunosuppression. Currently, approximately one-tenth of all patients with HCV infection in the United States are also infected with HIV. With improved treatment for HIV, HCV-related disease is currently the primary cause of mortality in patients with HIV/HCV coinfection [7]. In contrast, in Egypt, where the estimated prevalence of HCV infection is 10 % or higher, the virus is thought to be transmitted via a peculiar iatrogenic route due to parenteral antischistosomal therapy using serum from infected donors, which was widely practiced from the 1960s to the early 1980s [8]. This resulted in the predominance of HCV genotype 4a, which is unique to Egypt.

In Japan, HCC-related mortality has more than tripled since the mid-1970s. The emerging cases of HCC were typically negative for HBV and developed in patients with so-called non-A non-B hepatitis, which was later revealed to be almost entirely equal to chronic hepatitis C [9]. Presently, HCV infection is responsible for 75–80 % of the cases of HCC in Japan, while HBV is responsible for 10–15 % [10]. About 40 % of HCV-related HCC patients in Japan have a history of blood transfusion, typically within the 1950s and 1960s. At that time, the supply of blood for transfusion in Japan was dependent upon paid blood donors, many of whom were also intravenous drug users, mainly methamphetamine, among whom HCV is thought to have spread first in Japan after the end of World War II. In addition, the routine reuse of syringes and needles in medical practice at that time may have contributed to further viral spread. Commercial blood banks were abolished by 1969 in Japan and replaced by the Japanese Red Cross Society, which is fully dependent upon voluntary blood donation. Syringe and needle reuse were also strongly discouraged in the 1970s. Consequently, viral spread in Japan began to decline in the 1970s, although HCV transmission through blood transfusion continued until the advent of a sensitive HCV detection system in the early 1990s. In Japan, there was an interval of at least 30 years between peak HCV spread and peak incidence of HCV-related HCC. Considering the interval of 20 years between the peak viral spread in Japan versus the United States, and the fact that it takes 20 years or longer from HCV infection to HCC development, a further increase in the incidence of HCC in the United States appears to be inevitable [11, 12].

Genotyping HCV has been important for at least two major reasons in clinical practice: from an epidemiological perspective and because of the predictive value in antiviral therapy. Epidemiological studies have revealed the geographical distribution of HCV genotypes worldwide [13]. From a clinical viewpoint, subtyping HCV is very useful for predicting the likelihood of a treatment response and, in many cases, determines the duration of treatment [14–16]. In addition, there are several reports that genotype 1b is associated with an increased cytopathic effect. According to Silini et al. [17], HCV genotype 1b infection is very rarely found in patients with minimal chronic liver disease, which is associated with persistently normal alanine

Table 17.1 Epidemiology of chronic HBV or HCV infection in Japan

Virus	HBV	HCV
Vertical transmission	Common until early 1980s	Rare
Horizontal transmission	Rare in adulthood	Common until 1990 Ta (Peaked in 1950s–1960s)
Prevalence	0.8 %	1.5–2.0 %
Etiology in HCC	10–15 %	75–80 %

aminotransferase (ALT) and slow disease progression. Feray et al. [18] reported that the recurrence of hepatitis with genotype 1b after liver transplantation was more severe and progressive than for other genotypes.

17.3 Pathology

HCV, a positive-stranded RNA virus, is a major causative agent of HCC worldwide. However, the molecular mechanisms of HCV-induced hepatocarcinogenesis remain unclear. HCV is distantly related to the flaviviruses and pestiviruses of family Flaviviridae. There have been no reports that flaviviruses or pestiviruses are integrated into the human genome, so it may be impossible for HCV to exert its oncogenecity through integration into the host genome. HCV has an approximately 10-kilobase genome containing a large open reading frame encoding a polyprotein precursor of around 3000 amino acids and untranslated regions (UTRs) at the 5′- and 3′-ends of the genome (Fig. 17.1). The putative organization of the HCV genome includes (from the 5′- to 3′-end), the 5′-UTR, three or four structural proteins (core, E1, E2/p7), six nonstructural (NS) proteins (NS2, NS3, NS4A, NS4B, NS5A, and NS5B), and the 3′-UTR [19–21]. It is thought that continuous inflammation, apoptosis or necrosis, and hepatocyte regeneration caused by HCV infection may increase the chance of gene alteration and cause hepatocarcinogenesis. However, accumulated data suggest that HCV proteins are directly involved in regulating hepatocyte proliferation. In fact, HCV proteins have various functions other than HCV replication in host cells, some of which may be directly or indirectly related to hepatocarcinogenesis (Table 17.2) [22].

Recently, it was shown that HCV infection enhances DNA damage and the mutation of cellular genes, including proto-oncogenes [23–25]. In addition, the expression of the core protein impairs DNA repair in human hepatoma cells [26]. The resulting accumulation of mutations in cellular genes may lead to cell transformation. Moreover, iron overload is reported to induce mitochondrial injury and increase the risk of HCC development in transgenic mice expressing HCV polyprotein [27].

HCV proteins regulate the transcription of cellular genes, including p53 and p21, activate signal transduction pathways, and suppress apoptosis. These functions of HCV proteins may lead to hepatocyte proliferation and transformation. To clarify the molecular mechanisms of HCV-induced hepatocarcinogenesis, comprehensive functional analyses of HCV proteins are needed. The recently

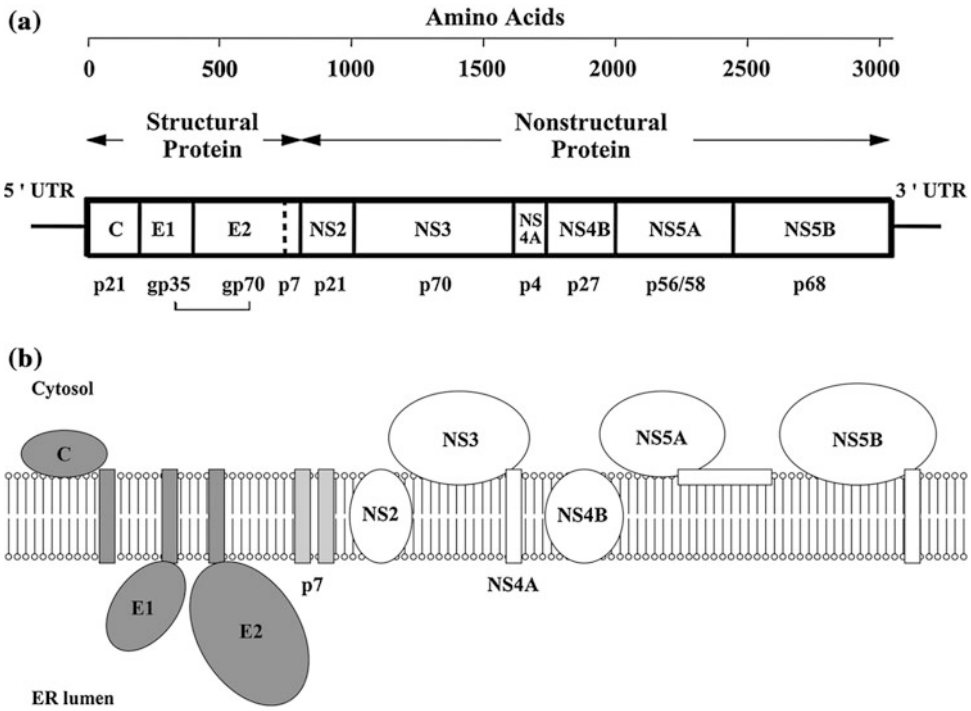

Fig. 17.1 **a**, **b** Structure of hepatitis C virus

Table 17.2 Function and oncogenic potentials of proteins

Protein	Function	Oncogenic potentials
Core	Nucleocapsid	Cell transformation Carcinogenesis in transgenic mice Transcriptional regulator Anti-apoptosis Activation of proto-oncogenes Repression of tumor suppressor genes Impairment of DNA repair
E1	Envelope	Unknown
E2	Envelope	Unknown
P7	Ion channel	Unknown
NS2	Metalloprotease	Unknown
NS3	Serine protease Helicase	Cell transformation Anti-apoptosis Repression of tumor suppressor genes
NS4A	Serine protease cofactor	Unknown
NS4B	Unknown	Cell transformation
NS5A	Unknown	Cell transformation Anti-apoptosis Repression of tumor suppressor genes Induction of chromosome instability
NS5B	RNA-dependent RNA polymerase	Repression of tumor suppressor genes

developed HCV subgenomic replicon [28] and robust HCV infection systems [29–31] will facilitate analyses of the effect of not only HCV proteins, but also HCV replication.

17.4 Primary Prevention of HCC

HCC is a unique malignancy in that known acquired factors (i.e., chronic viral hepatitis B and C) are the predominant causes of carcinogenesis, which is of enormous clinical importance [32, 33]. By screening for HBV/HCV infection, we can identify patients at high risk of HCC and perform cost-effective surveillance. Screening policies should be based on the prevalence of each viral infection in specific geographic areas. This will result in the secondary prevention of HCC through early detection and treatment. Furthermore, the primary prevention of HCC (i.e., reducing its risk factors) is possible by controlling virus infection. In fact, HBV vaccination has been shown to be effective in decreasing HBV-related HCC and the awareness of the control of blood-borne infection in both medical practice and the general population has apparently curbed further propagation of HCV infection. Antiviral therapy for patients already infected is another aspect of primary prevention.

The primary prevention of HCV-related HCC includes strategies for the prevention of HCV infection and for viral eradication. Regarding the former, novel HCV transmission in the general population has been declining in many countries, as evidenced by the lower prevalence of HCV infection among younger generations. Viral transmission through blood transfusion can be prevented by screening donor blood using sensitive assays. Although campaigns against blood-borne viral transmission, including both HCV and HIV, should be sustained vigorously, effort can now be focused on viral eradication in patients who have already been infected with HCV.

The effect of interferon (IFN) therapy on the prevention of HCC is controversial. Studies performed in the United States have failed to show a reduction in the incidence of HCC after IFN therapy. In contrast, many clinical studies performed in Japan have clearly demonstrated that the incidence of HCC was reduced among IFN-treated patients showing a sustained virologic response (SVR) [34, 35]. The resolution of cirrhosis was also noted following a SVR [36]. These beneficial effects are expected to be enhanced by the advent of combined PEG-IFN and ribavirin therapy [14, 15]. The discrepancy in the preventive effect of IFN therapy on HCC between Japanese and American studies may result from different patient characteristics, such as the ages of HCV-infected patients; further investigation is required.

In the recent progress of direct-acting antiviral agents (DAAs) against HCV, IFN-free treatments are now available for compensated or decompensated cirrhosis [37–39]. DAAs combination therapies now offer SVR rates greater than 90 % for treatment-naive and experienced patients with genotypes 1 through 4. In patients with compensated cirrhosis, sofosbuvir-including regimens for 12 weeks could lead to more than 90 % SVR rates [40]. Recent studies showed the usefulness of sofosbuvir plus ledipasvir for 12 weeks against HCV genotype-1 patients with decompensated cirrhosis. In patients with cirrhosis and moderate or severe hepatic impairment, 86–89 % SVR12 rates were achieved [38]. These treatments have less adverse events during therapies or shorter duration of treatment than IFN-including treatment. Limitations still exist in the current agents, with suboptimal outcomes for genotype 3 and limited data in genotypes 5 and 6.

Eradication of HCV could bring better reserve liver function in patients with cirrhosis and HCV infection although it is unknown whether the occurrence or recurrence of HCC would be reduced in cirrhotic patients [41]. Further studies are needed.

17.5 Surveillance

Ultrasonography (US) and tumor marker tests play important roles in HCC surveillance in patients with chronic liver disease and are widely used. However, there is insufficient evidence to suggest that such surveillance improves the prognosis of patients with HCC or increases the effectiveness of local therapies, such as resection and local ablation therapy, or indeed radical treatments, such as liver transplantation. Similarly, the usefulness of computed tomography (CT) or magnetic resonance imaging (MRI) in HCC surveillance remains unclear.

The primary objective of screening and HCC surveillance should be to reduce mortality as much as possible in patients who actually develop cancer, in an acceptable, cost-effective fashion. To attain this objective, two distinct issues deserve meticulous consideration: the target population and mode of surveillance.

17.5.1 Target Population

HCC shows significant regional clustering [4]. HBV, HCV, and other environmental factors may play important roles in the development of HCC, with the relative importance of individual factors varying widely according to geographic area [3, 5, 42, 43]. In Japan, HCV infection is responsible for about 80 % of the cases of HCC, whereas HBV infection is responsible for 10 % and alcohol for about 5 % [44, 45]. These values may differ substantially in other countries. For example, in China, where the prevalence of HBV infection is much higher, HBV infection is by far the predominant etiologic factor for HCC. In the United States, nonalcoholic steatohepatitis (NASH) is reportedly a major factor in HCC.

Given the low incidence of HCC in individuals without risk factors, surveillance is not recommended for the general population. A commonly accepted rate that requires surveillance is greater than 0.2 % per year. Therefore, the first step in screening for HCC is to screen patients at risk of developing HCC. Because chronic viral hepatitis due to either HBV or HCV may be asymptomatic, mass screening for hepatitis virus infection, either HBV or HCV, is justified if the prevalence of infection is reasonably high in a region. Indeed, in Japan, the general population over 40 years of age has undergone mass screening for HBV and HCV infection since 2002, although the cost-effectiveness of this program remains to be evaluated.

Persistent HBV infection is a major risk factor for HCC. HBV carriers have a 223-fold higher risk of developing HCC than noncarriers [46]. Among HBV carriers, HBe antigen-positive patients are at a higher risk of HCC than HBe antigen-negative patients (relative risk, 6.3-fold) [47, 48]. Recently, the results of a large-scale, long-term cohort study conducted in Taiwan showed that the serum HBV DNA level is the strongest risk factor for both the progression to cirrhosis and the development of HCC among HBV-positive patients, independently of serum HBe antigen/antibody status or ALT levels [49]. Together with the advent of reliable quantitative assays, the determination of HBV DNA levels may replace the determination of HBe antigen/antibody status as a risk indicator for HCC.

While the prevalence of chronic HBV infection is high in some geographic areas, such as East and Southeast Asia and sub-Saharan Africa, the prevalence of chronic HCV infection has recently increased in some developed countries, including Japan, southern European countries, and the United States. In chronic hepatitis C patients, the risk of developing HCC increases with the progression of liver fibrosis (Table 17.3) [34, 50], and chronic hepatitis C patients with cirrhosis have a very high risk of HCC [51]. In European countries and United States, annual incidence rate of HCC is reported to be 0.5–5 % [52]. The reason of this difference is not well known, but maybe related to the difference in the age of patients. Ethnic difference maybe also involved. In Japan, HCV infection spread nationally mainly in the 1950s and 1960s and is currently, after several decades required for progression to cirrhosis, the predominant cause of HCC. Peak viral spread in the United States occurred two decades later, and the incidence of HCV-related HCC is now increasing rapidly [2, 53]. In addition to the degree of liver fibrosis, male gender, older age, and heavy alcohol consumption are the known risk factors for HCV-related HCC.

Cirrhosis due to etiologies other than chronic viral hepatitis also confers a risk of developing HCC. Major etiologies include alcoholic liver disease and NASH [54–56] whose relative importance may differ geographically. Schoniger-Hekele et al. [57] reported that alcoholic liver disease accounted for 32 % of all HCC cases in an Austrian cohort. In the United States, the approximate annual hospitalization rate for HCC related to alcoholic cirrhosis is 8–9/100,000 compared to approximately 7/100,000 for hepatitis C [58]. NASH is a chronic liver disease that is

Table 17.3 Incidence of HCC according to histological fibrosis stage reported from Japan

Fibrosis stage	Annual Incidence of HCC	Risk Ratio (95 % CI)
F0/1	0.5 % (3/160)	1
F2	2.0 % (11/164)	4.431 (1.704–11.522)
F3	5.3 % (13/59)	13.097 (5.194–33.021)
F4	7.9 % (32/107)	24.011 (9.638–59.815)

gaining increasing significance due to its high prevalence worldwide and its potential progression to cirrhosis, HCC, and liver failure. Although NASH has been described in cohorts of HCC patients [59, 60], the incidence of HCC in cirrhosis due to NASH is unclear. Aflatoxin may play a role in certain areas.

In brief, the evaluation of the degree of liver fibrosis is of paramount importance in assessing the risk of HCC in patients with chronic liver disease of any etiology. Histologic evaluation of liver biopsy samples has been considered the gold standard for assessing liver fibrosis. However, the invasiveness of a liver biopsy limits its clinical feasibility. In clinical practice, repeated assessment of liver fibrosis is often required because a non-cirrhotic liver may become cirrhotic over time, sometimes rather rapidly. Consequently, the noninvasive evaluation of liver fibrosis is one of the main areas of interest in hepatology.

One such noninvasive method, transient elastography, correlates well with the histological stage of liver fibrosis [61–65]. The reported cut-off value for the diagnosis of histological cirrhosis was 12.5–14.9 kPa. Higher values of liver stiffness may require proper attention regarding decompensation and HCC development [66]. The FibroTest is based on the age and gender of patients combined with five biochemical markers (total bilirubin, haptoglobin, γ-glutamyl transpeptidase, alpha-2 macroglobulin, and apolipoprotein A1) [67]. An index of 0–0.10 had a 100 % negative predictive value, while an index of 0.60–1.00 had a greater than 90 % positive predictive value for a Metavir score of F2 to F4. APRI is the aspartate aminotransferase (AST) level/upper limit of normal divided by the platelet count (10^9/L) multiplied by 100 [68]. For a hypothetical patient with an AST of 90 IU/L (upper limit of normal 45) and a platelet count of 100 ($\times 10^9$/L), the APRI is 2.0, which means the patient has a 41 % likelihood of advanced fibrosis and 5 % chance of having minimal or no fibrosis. The applicability of these methods in surveillance requires evaluation in future prospective studies.

Patients who are considered to be at a nonnegligible risk of HCC development should be subjected to a surveillance program, as discussed below. Possible exceptions may include those with severe liver dysfunction who would not receive any treatment if diagnosed with HCC, or those with other life-threatening illnesses.

17.5.2 Surveillance Methodology

Traditionally, two methodologies have been used for HCC surveillance in high-risk patients: tumor marker determination and diagnostic imaging. Serum alpha-fetoprotein (AFP) concentration is representative of the former and liver ultrasonography (US) of the latter. The usefulness of a surveillance program should be evaluated based on the beneficial effects on the outcome of HCC patients diagnosed via these modalities relative to cost. However, few prospective randomized trials have compared the outcome of HCC patients in or outside a surveillance program. Therefore, the currently available evidence regarding the effects of surveillance on decreasing overall or disease-specific mortality has come mostly from retrospective or case-control studies.

17.5.2.1 AFP

AFP is a glycoprotein with a molecular weight of 72 kDa. The main physiological function of AFP appears to be the regulation of fatty acids in fetal and proliferating adult liver cells [69]. Since 1968, AFP has been used as a serum marker for human HCC [70]. As a marker, AFP reportedly has a sensitivity of 39–65 %, a specificity of 76–94 %, and a positive predictive value of 9–50 % [71–76]. Studies assessing the usefulness of AFP in HCC screening have varied widely in their design and in the characteristics of targeted patients in terms of etiology, severity of background liver disease, and so forth. Moreover, specificity and sensitivity inevitably depend upon the cut-off level selected for diagnosis.

An intrinsic disadvantage of AFP as a tumor marker is the fact that the serum AFP levels can increase in patients without HCC when hepatitis is active, partly due to accelerated cellular proliferation in regeneration. Because serum AFP rarely exceeds 20 ng/mL in healthy subjects, this value is often adopted as the upper limit of normal for serum AFP. However, values slightly above this level may not be indicative of HCC among patients with chronic hepatitis, whereas adopting a low cut-off value results in low specificity. AFP levels exceeding 400 ng/mL can be considered almost definitively diagnostic of HCC, but sensitivity inevitably decreases with higher cut-off levels. An additional disadvantage of AFP as a tumor marker is that small HCC tumors, the detection of which is the primary objective of surveillance, are less likely to be AFP-producing, and serum AFP level may not reach the diagnostic limit even if they are AFP-producing.

It has been proposed that AFP determination should be used as a screening test only when US is either unavailable or of such poor quality that lesions smaller than 2 cm in diameter will not be detected. One such case is HCC screening in Alaskan hepatitis B carriers, among which AFP testing allowed the detection of tumors at an earlier, treatable stage [77]. Although the screened subjects had an increased survival compared to historic controls, this must have been affected by the lead-time and length-time bias inherent to retrospective studies on screening.

17.5.2.2 US

US became available for identifying intrahepatic lesions in the early 1980s [78]. This imaging modality is appealing because it is almost completely noninvasive. The ribs and air in the lungs and gastrointestinal tract surrounding the liver may hinder ultrasound imaging, but imaging of the liver has been facilitated by improvements in devices and techniques. The reported sensitivity of US for detecting HCC nodules is highly variable, ranging from 35 to 84 % [79], depending upon the expertise of the operator and the ultrasound equipment used. Indeed, more sophisticated ultrasound instruments can produce images with much better resolution, improving the detectability of small intrahepatic lesions. Note, however, that ultrasound diagnosis is heavily operator dependent. A high level of skill and experience is required to record high-quality images and make an accurate diagnosis. In addition, an ultrasound diagnosis may not be possible due to the patient's physical condition, such as severe obesity.

The reported sensitivity of US for HCC detection is as low as 20.5 % [80], based on the pathology of explanted livers that were removed from patients who underwent liver transplantation. Small HCC nodules less than or equal to 2 cm in diameter constituted 85 % of the lesions that were not detected ultrasonographically [81]. The ultrasound detectability of HCC nodules depends on tumor size: nodules >5.0, 3.1–5.0, 2.1–3.0, and 1.0–2.0 cm in diameter had detection rates of 92, 75, 20, and 13.6 %, respectively [80].

Although these data are rather disappointing, other reports indicate that the detectability of intrahepatic nodules with US is almost comparable to that of CT [82–85]. In a study of nodules that were ≤ 2 cm in diameter in patients with chronic hepatitis, the detection capability of US exceeded that of CT or MRI for nodular lesions, and US was superior for the detection of adenomatous hyperplasia and well-differentiated HCC [86]. Overall, US is indispensable in the screening of HCC, as it is noninvasive and less expensive. However, the definitive diagnosis of HCC depends upon the evaluation of its vascularity, which is not possible via conventional US. Instead, CT or MRI with contrast enhancement is required when a suspected lesion is identified via US.

US, when conducted by less-experienced operators, has several shortcomings. Moreover, the resolution may not be satisfactory in cirrhosis patients with rough echo patterns in the background liver. Therefore, effective HCC detection requires combined US with CT or MRI. However, there are few reports on HCC surveillance that actually used CT or MRI, and its cost-benefit ratio remains unclear.

Recently, several contrast enhancement materials have been developed for US. These materials are very useful in the differential diagnosis of intrahepatic nodules or the demarcation of intrahepatic lesions before percutaneous ablation. However, their role in HCC screening is yet to be defined.

17.5.2.3 Combined AFP and US in HCC Surveillance

Although serum AFP measurement is generally less sensitive than US, their specificities may be comparable when using appropriate cut-off values. HCC screening via combined US and AFP may lead to improved detection, although previous reports have been generally negative [72, 87–89]. However, in a nonrandomized study of patients with cirrhosis, the sensitivity of detection was reported to be increased using both US and AFP measurements, as compared to either alone [87].

Recently, a randomized trial evaluated HCC screening using AFP and US every 6 months compared to no screening in over 18,000 Chinese patients with HBV infection [90]. More cases of HCC were diagnosed in the screened group than in the non-screened group (86 vs. 67) and overall survival was higher in the former group (65.9, 52.6, and 46.4 % at 1, 3, and 5 years, respectively) than in the latter (31.2, 7.2, and 0 % at 1, 3, and 5 years, respectively).

A retrospective study assessed HCC screening in 367 patients of 70 years of age or older, with AFP measurements and US every 6 or 12 months. The screening allowed more frequent diagnosis of HCC at an early stage, increased the proportion of patients who could receive a curative treatment, and improved their prognoses compared to unscreened patients. The apparent survival benefit was restricted to the first 3 years after the detection of HCC, probably because of the shorter life expectancy of elderly people [91].

17.5.2.4 New Serum Markers and New Methods

Recent developments in gene expression microarrays, proteomics, and tumor immunology permit thousands of genes and proteins to be screened simultaneously. In the next decade, new biomarkers should be established for cancer screening, including HCC. To establish a formal framework to guide biomarker evaluation and development, a five-phase program was adopted by the Early Detection Research Network (EDRN) of the National Cancer Institute [92]. Currently, several new markers appear promising, including des-gamma-carboxyprothrombin (DCP), AFP-L3, glypican-3, insulin-like growth factor (IGF)-1, and hepatocyte growth factor (HGF). These markers are to be further evaluated in phase 2 studies to determine their ability to detect early-stage HCC, followed by phase 3 studies that will retrospectively determine whether they can detect preclinical disease. Pending these results, phase 4 studies will be performed to assess prospectively their ability to detect early HCC and phase 5 studies will be performed to confirm that

surveillance using these markers reduces morbidity and mortality from HCC.

Although recent developments identifying serum markers for HCC hold great promise, advances in genomic analysis propelled by new techniques for high-throughout sequencing are likely to further advance the field [93]. Totoki et al. demonstrated the feasibility of sequencing the entire genome of a primary hepatitis C virus-induced HCC [94]. This analysis identified novel mutation patterns and chromosomal abnormalities. Studies such as this will identify specific targets likely to prove useful in both the detection and treatment of HCC.

The detection sensitivities of dynamic CT and dynamic MRI are both high for hypervascular HCC. Because patients with HCC undergo repeated imaging examinations and the diagnostic capabilities of dynamic CT and MRI are similar, dynamic MRI, which does not involve exposure to X-rays, may be superior to CT. However, MRI systems that allow high-quality dynamic studies are not yet as widely used as high-speed CT systems. Institutions without access to dynamic MRI may instead rely upon high-speed dynamic CT, such as helical CT, or even more advanced systems, such as multi-detector CT (MDCT). The development of MDCT has dramatically accelerated scan acquisition in liver CT [95]. With MDCT, high-speed volume coverage of the entire liver is possible in 4–10 s, which allows the acquisition of two separate series of scans in the arterial phase, termed early arterial and late arterial phase scans [96, 97]. With fluorodeoxyglucose positron emission tomography (FDG-PET), tumor cells with active glucose metabolism take up and specifically accumulate ^{18}F-FDG, blocking the metabolic pathway. In a study evaluating the diagnosis of HCC using a quantitative standardized uptake value (SUV), the SUV for HCC was lower than that of metastatic liver cancer [98]. In general, FEG-PET is not recommended for the diagnosis of HCC because it is expensive and not superior to conventional diagnostic imaging techniques, such as CT and MRI.

17.6 Standardized Recall Procedures

Once patients are identified via an abnormal surveillance test, they need to be recalled for subsequent evaluation. However, despite various recall algorithms described in the literature, none has been tested in a prospective fashion. Furthermore, recall procedures should differ based on abnormal AFP versus US findings. Increases in serum AFP need to be interpreted against background liver disease. Reactivated chronic hepatitis B is often accompanied by increased AFP levels. Pregnancy may cause temporary elevation of AFP levels, sometimes together with an increase in the proportion of the L3 fraction. Therefore, patients with increased serum AFP levels require a detailed clinical evaluation to determine the cause of the increase.

When a low-echoic lesion is newly detected with US in the liver of a patient at risk of HCC, a complete evaluation is required. Typically, this involves CT or MRI with contrast enhancement and the presence of hyperattenuation in the arterial phase with washout in the late phase can be considered as a definitive sign of HCC [99]. In ambiguous cases, a needle tumor biopsy under ultrasound guidance is recommended. However, it is controversial whether all suspicious nodules should be subjected to liver tumor biopsy because of concerns regarding potential tumor seeding.

17.7 Screening Interval

Because the risk of HCC development does not usually decrease spontaneously in patients who are targets for HCC screening, an HCC surveillance program should consist of repeated screenings at a determined interval. US is superior to CT in this regard because it is noninvasive and cost-effective. The guidelines of the American Association for the Study of Liver Diseases (AASLD) propose ultrasound surveillance for patients at high risk of HCC at an interval of 6 months. The guidelines explicitly indicate that the surveillance interval should depend not on the risk of HCC, but exclusively on tumor doubling times, to detect cancer nodules while they are small enough for curative treatments.

In contrast, in Japan, ultrasound surveillance at a shorter interval of 3–4 months is encouraged for extremely high-risk patients, whereas an interval of 6 months is recommended for high-risk patients [100]. Chronic hepatitis C patients with cirrhosis in Japan have HCC incidence rates of 6–8 % per year, constituting an extremely high-risk group. Theoretically, shorter surveillance intervals lead to tumor detection at smaller sizes. However, it is unknown whether the difference in detected tumor size, if any, is large enough to affect the prognosis in a cost-effective fashion. Although there is no prospective comparison of different schedules, one retrospective study of cirrhosis patients and a mathematical model applied to hepatitis B virus careers suggested that a longer screening interval is as effective as a 6-month interval in terms of survival.

It is controversial whether AFP determination should be included in HCC surveillance programs. However, if AFP is to be measured, it should be measured repeatedly and an abnormal AFP level must be interpreted not by simple comparison with a given cut-off value, but in the context of the temporal series. An abrupt elevation of serum AFP levels in the absence of exacerbation of hepatitis may indicate the development of HCC, even if US is apparently negative, and further evaluation with contrast-enhanced CT or MRI should be considered.

17.8 Cost-Effectiveness

According to a decision analysis model, the cost-effectiveness ratio for screening European patients with Child-Pugh class A liver disease ranged between $48,000 and $284,000 USD for each additional life year gained [101]. However, this study did not consider liver transplantation as a treatment option. In a group of patients who could anticipate excellent survival, the cost-effectiveness ratio ranged between $26,000 and $55,000. In another study of 313 Italian patients with cirrhosis undergoing serum AFP analysis and liver US every 6 months, the cost per case of treatable HCC was $17,934, and the cost per year of life saved was $112,993 [75]. In the United States, the cost for each quality-adjusted life-year (QALY) gained through surveillance was estimated to range from $35,000 to $45,000 [101]. HCC screening in patients waiting for liver transplantation has been associated with a cost per year of life saved ranging from $60,000 to $100,000, depending upon the screening modality used [102].

It must be emphasized that the cost-effectiveness of HCC screening has been assessed via retrospective analyses or using decision models. While retrospective studies suffer from selection bias, decision analysis models are based on a simulation of costs and health outcomes and results may vary greatly according to different assumptions, such as the incidence of HCC in the screening population, the screening interval, the modality of diagnosis, the type of treatment after diagnosis, the doubling time of tumors, and the tumor recurrence rate. In particular, there must be a feasible treatment modality that favorably affects prognosis if screening is to be cost-effective.

17.9 Prevention of Recurrence

The short-term prognosis of HCC patients has greatly improved due to recent advances in early diagnosis and treatment. However, the long-term prognosis remains far from satisfactory, as indicated by the fact that the overall survival 10 years after apparently curative treatment of HCC is as low as 22–35 % [103, 104]. In HCC patients, the slope of a typical cumulative survival curve does not level out over time after treatment. In contrast, in most other malignancies, the slope of the cumulative survival curve levels out in about 5 years after relatively curative treatment. In other words, HCC is rarely treated curatively, and the primary reason for this is the frequent recurrence of HCC, even after apparently curative treatment involving either local ablation or surgical resection [105]. Unlike liver transplantation, these locoregional therapies do not remove microscopic lesions in the remaining liver. However, this does not explain the fact specific to HCC that the risk of recurrence does not decline over time. In fact, recurrent HCC continues to develop at an annual rate of 10–20 %. This continual recurrence of HCC after initial treatment is thought to be mostly due to multicentric de novo carcinogenesis. In this respect, liver transplantation is superior to locoregional therapy.

At least theoretically, however, strategies similar to those used in primary prevention may be applicable to HCC recurrence due to multicentric carcinogenesis. Recently, the number of HCC patients undergoing resection after IFN therapy has increased. Kubo et al. evaluated the tumor-free and cumulative survival rates for patients who underwent IFN therapy before and/or after curative resection of HCC [106]. The tumor-free and cumulative survival rates of patients who showed a SVR or biochemical response (BR) were significantly higher than those of patients who were classified as nonresponders or who did not undergo IFN therapy. The proportion of patients who died of HCC was significantly lower in the SVR/BR group than in the NR/non-IFN group. In addition, neither SVR nor BR patients died of decompensation. HCV antiviral medications already cure more than 90 % of the HCV population including patients with HIV-HCV, decompensated cirrhosis, and posttransplant [38, 107, 108]. Thus, in patients who undergo liver resection for HCV-related HCC, long-term survival can be expected if antiviral therapy is further improved.

Needless to say, early diagnosis and complete removal of primary HCC lesions are requisite for antiviral therapy. In other cases, safe, effective chemotherapeutic agents would be useful as adjuvant therapy for relatively advanced HCC where undetectable intrahepatic metastases are suspected. However, conventional chemotherapeutic agents are not satisfactorily effective against HCC, nor safe enough for protective long-term use. Hasegawa et al [109] reported that the administration of uracil-tegafur (UFT) as an adjuvant chemotherapy for hepatic resection offered no evidence of potential benefit and overall survival appeared to be worse in the treatment group. The authors suggested that the adverse effects of UFT on liver function were responsible for poor survival in the treatment group. Some agents appear promising in terms of safety, but their effects remain to be confirmed [110, 111]. The prevention of the recurrence of HCC, or tertiary prevention, is currently one of the most challenging tasks in hepatology.

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