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Current Status of Liver Diseases in Korea:
Report from the Epidemiology Study Group of the KASL

Current status of liver diseases in Korea: Hepatocellular carcinoma

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= Abstract =

Primary liver cancer, most of which is hepatocellular carcinoma (HCC), is the third common leading cancer in Korea. During the last two decades, the incidence rate of primary liver cancer has shown a modest decrease, but its mortality rate has slightly increased. The incidence of HCC, according to age, peaks in the late sixth decade in men and in the early seventh decade in women. Hepatitis B virus (HBV) is the most important risk factor, which represents approximately 70% of all HCC, and hepatitis C virus (HCV) and alcohol are the next in order of major risk factors for the development of HCC in Korea. HBV-associated HCC occurs 10 years earlier than HCV-associated HCC due to a more prolonged exposure to HBV, which is vertically transmitted almost from HBsAg-positive mother in HBV-endemic area. National Cancer Control Institute, which was reorganized in 2005, is now working for several national projects such as National Cancer Registration Program, National R&D Program for Cancer Control and National Cancer Screening Program. International collaboration for the clinico-epidemiologic research would be needed to provide the specific measures for managing HCC in diverse etiologic situations. Finally, the mechanisms of hepatitis virus-associated hepatocellular carcinogenesis might be clarified to provide insights into the advanced therapeutic and preventive approaches for HCC in Korea, where the majority of HCC originate from chronic HBV and HCV infections.

Key words: Hepatocellular carcinoma; Incidence; Risk factor; Mortality; Survival

Abbreviations: CDLT, cadaveric donor liver transplantation; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICD, International Classification of Disease; LDLT, living donor liver transplantation; LT, liver transplantation; PEIT, percutaneous ethanol injection therapy; RFA, radiofrequency ablation; TACE, transcatheter arterial chemoembolization

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Introduction

Hepatocellular carcinoma (HCC) is the most serious malignant neoplasm which affects approximately over half a million persons worldwide. Korea is known to be a high endemic area of chronic hepatitis B virus (HBV) infection, and 5~6% of general populations are infected by HBV. In general, the geographic prevalence of HCC occurrence is based on the epidemiologic distribution and the natural history of HBV infection.[1,2]

In early 1980s, Hann et al[3] presented that there were clustering of chronic carriers of HBV in families of Korean patients with HCC and emphasized the importance of preventive strategy for HBV infection in endemic areas. Since then, several articles[4-6] have been reported in Korea, which suggest that chronic HBV infection is a major risk factor for HCC when considering the results of the evaluation for HBsAg and HBeAg status in patients with chronic hepatitis, liver cirrhosis or HCC, as well as control subjects. In 1990s, hepatitis C virus (HCV) was revealed to be another key risk factor for HCCs developing in patients with HBsAg-negative chronic liver disease, especially in those older than 60 years.[7,8] Thereafter, anti-HCV-seropositive patients were also strongly recommended to be included in the surveillance program for the early detection of HCC.

This review will introduce the state of art in HCC in Korea including its comprehensive epidemiology, clinical characteristics, treatment and prognosis.

Incidence

Primary liver cancer, which includes HCC, cholangiocarcinoma, Klatskin tumor, mixed HCC and cholangiocarcinoma, and hepatoblastoma in the order of their incidence, is the 3rd common leading malignancy in Korea following stomach and lung cancers.[9,10] According to the statistics in 2005, the age-adjusted incidence rate of primary liver cancer is 44.9 per 100,000 persons in men, ranked 3rd following 66 for stomach and 48.5 for lung cancer; 14.7 per 100,000 persons in women, ranked 7th following 37.3 for breast, 36.2 for thyroid, 34.1 for stomach, 28.0 for colon, 17.9 for lung and 16.7 for cervix cancer during 2003~2005 (Fig. 1).[11] The incidence of primary liver cancer tends to show a modest decrease from 1999 to 2005, indicating a different pattern from other cancers. These statistical informations were provided on the annual reports of National Cancer Registration Program, which were based on the International Classification of Disease (ICD) codes revised in 1995.[12] Because primary liver cancer, according to Code ICD-10 (C22), include intrahepatic cholangiocarcinoma as well as HCC, a more informative analysis using strict definition (C22.0 and C22.9) would be needed for more accurate statistics for HCC in Korea.

HCC is rare among people under the age of 30, but its incidence progressively increases from the 4th up to the 7th decade.[13] A crude incidence of HCC, according to age, peaks in the late sixth decade in men and in the early seventh decade in women,[7,14,15] but age-specific incidence rate of HCC reaches a peak in the early 8th decade, which differs from the incidence pattern in Japan or Western countries. HBV-associated HCC occurs approximately 10 years earlier than HCV-associated HCC.[7,16] A more prolonged exposure to HBV, which is vertically transmitted almost from HBsAg-positive mother in HBV-endemic area, seems to be a possible explanation for relatively earlier occurrence of HCC. Though the incidence rate of HCC shows a slightly decreased pattern in the recent years, the distribution of peak crude incidence appears to be shifting toward a younger

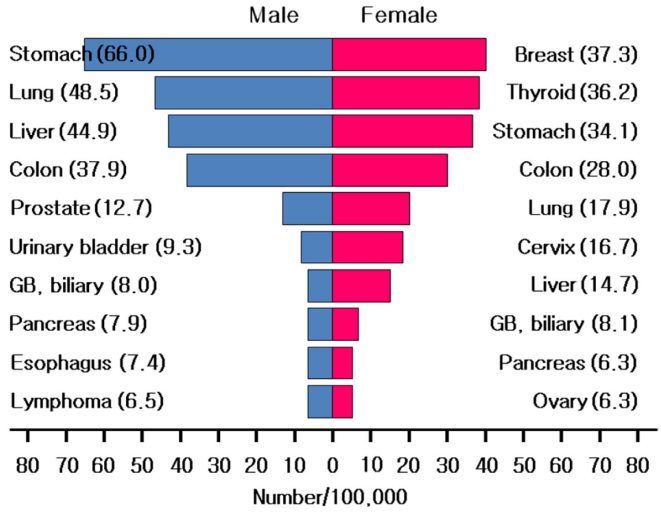

Figure 1. Incidence of major malignancy in Korea (2003~2005). The majority of primary liver cancer is hepatocellular carcinoma (HCC), and the remainder includes cholangiocarcinoma, Klatskin tumor, mixed HCC and cholangiocarcinoma, and hepatoblastoma in the order of their incidence.

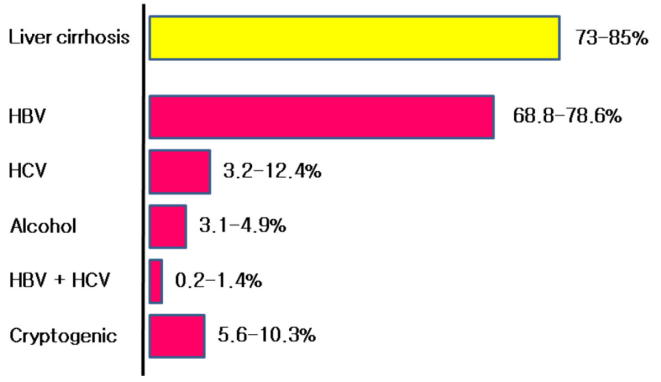

Figure 2. Risk factors for the development of HCC in Korea. Liver cirrhosis is the most important and independent risk factor.

age. At the age of peak incidence of HCC in Korea, HCC develops approximately 4.2~5.9 times more commonly in men than in women, which might be related to the fact that chronic liver disease is more prevalent in men than women.[7,13,15-17]

Risk factors

Annual detection rate of HCC in patients with chronic liver disease was reported to be 1.64~4.2%.[18,19] Liver cirrhosis, irrespective of etiology, is known to be the most important and independent risk factor for the development of HCC. Seventy-three to eighty-five percent of patients with HCC have liver cirrhosis.[16] In addition to liver cirrhosis, HBV, HCV, and alcohol are major risk factors for HCC in Korea. Several studies conducted in Korea reported that HBsAg was found in 68.8~78.6% of patients with HCC, anti-HCV in 3.2~12.4%, both in 0.2~1.4%, alcohol abuse in 3.1~4.9%, and underlying liver disease was cryptogenic in 5.6~10.3% (Fig. 2).[15,16,18,20,21] Also, HBsAg or anti-HCV seropositivity, age over 50 years old and male gender, esophagogastric varices were indicated to be the factors which increased the risk of development of HCC in patients with liver cirrhosis.[18,22,23] The cumulative incidence rates for the development of HCC were 2.6, 6.7, 12.3, 18.8, 21.5 and

26.2% at 1, 2, 3, 4, 5 and 6 year, respectively, after the first esophageal variceal bleeding in cirrhotic patients.[18] HBV- or HCV-related cirrhosis was more frequently complicated by HCC than alcoholic cirrhosis with the 5-year cumulative incidence in each group being 24, 28, and 5%, respectively.[24] A recent study reported a significantly increased incidence of cryptogenic HCC during last decade, and suggested that non-alcoholic fatty liver disease and its risk factors might be involved in the development of cryptogenic HCC.[25] Besides, hepatitis B viral load itself has been reported to be a risk factor for post-treatment recurrence of HCC.[26,27]

Clinical characteristics

The proportion of patients who presented with the symptoms related to HCC at the time of diagnosis was 41.3~67.4% overall, while it was 26.7~46.7% for the cases detected during periodic surveillance, and 5~12% for those noticed by chance.[16] The size of the tumors, when HCCs were detected, was 2~5 cm in 38.1% of the cases, 5~10 cm in 30.2%, huge HCC larger than 10 cm in 21.1%, while small HCC less than 2 cm only accounted for 10.6%.[15] The cases with multiple masses (62.7%) were more common than those with a single mass (37.3%). Portal vein invasions were found in 31.4~39% of patients with HCC. Because the majority of HCC are diagnosed in the state of Child-Pugh grade A (52.1~71.2%) rather than Child class B (23.3~36.1%) or C (5.5~11.8%) in Korea,[15,16] an efficient and organized application of nationwide surveillance program would enhance the chance to cure and improve the survival rate of HCC patients. There are also distinct trends; younger patients show a more frequent relationship with HBV rather than HCV, higher levels of α-fetoprotein, poorer prognosis due to more advanced tumor stages despite more preserved liver functions.[14,28,29]

Treatments

Surgical treatments

At present, liver resection is the most preferred treatment modality for resectable HCCs in patients with well preserved liver function.[30] The 5-year survival rate after curative resection is 40~50%, but 5-year recurrence rate reaches 75~100%.[31,32] Especially, after resection of HCC which meets Milan criteria in patients with Child-Pugh grade A cirrhosis, overall survival rates at 1, 3, 5, and 10 years were 92%, 78%, 69%, and 52%, respectively, and 1-, 3-, 5-, and 10-year disease-free survival rates were 79%, 57%, 44%, and 19%, respectively.[33] Thus, high recurrence rate is a challenge in patients with HCC who undergo liver resection. Various factors have been revealed to affect the recurrence of HCC after resection.[34-36] Even for a huge (≥10 cm) HCC, a curative resection appears to achieve a favorable outcome in well selected cases; a previous study reported 5-year disease free and overall survival rates after resection being 35.8% and 41.0%, respectively.[37] In metastatic HCC, metastasectomy with concurrent resection or local treatment for the primary HCC was reported to be superior to medical treatment alone or conservative management.[38-40]

Neoadjuvant or adjuvant chemotherapy for HCC, which seemed inefficient previously, are now reappraised as potential treatment modalities with methodological advances in these fields. Neoadjuvant chemoradiation therapy following surgery for unresectable HCC met with satisfactory results.[41] Minimal invasive surgery has also been introduced to the field of liver resection for HCC, and is now developing into Robot surgery.[42,43]

Liver transplantation (LT) is a feasible way, but it is usually restricted to the cases of unresectable HCC within the Milan's criteria, which are cases with single tumor less than 5 cm or multiple tumors of no more than three in number and less than 3 cm in size.[44,45] In a study including about 312 HCC patients from 4 Korean institutions, the 3-year survival rate of patients (70.4% of whole series) within the Milan criteria was 89.9% after cadaveric donor LT (CDLT) and 91.4% after living donor LT (LDLT) excluding perioperative mortality, while that in patients (77.7% of whole series) who met the criteria of University of California San Francisco was 88.1% after CDLT and 90.6% after LDLT.[46]

Non-surgical treatments

In patients who received no specific treatments for HCC, the cumulative survival rate of 6 month and 1 year were 17.0~37.5% and 7.0~16.6%, respectively, and the median survival period was 3~4 months, although there were considerable differences in Child-Pugh grades and tumor staging.[17,47]

Transcatheter arterial chemoembolization (TACE) is a treatment modality applied most frequently to the patients with HCC in Korea.[48] In patients with the liver function of Child-Pugh grade A or B, the cumulative survival rates were 66.3~64.5% and 16.5~13.9% at 1 and 3 years after TACE, respectively, which were much better than those in grade C patients.[17] TACE was also reported to have a survival benefit even in a portion of HCC patients with portal vein thrombosis.[49,50] Multinodular type and portal vein thrombosis were analyzed to be the factors affecting the recurrence after TACE.[51]

Percutaneous ethanol injection therapy (PEIT) and radiofrequency ablation (RFA) are generally accepted to be effective locoregional ablation therapies in HCC less than 3 cm in size and less than 4 in number. After a complete ablation of tumors by PEIT, the cumulative 1-, 2-, and 3-year overall survival rates were 73%, 50%, and 37%, respectively.[52] Tumor multiplicity, size, and remaining hepatic reserve were reported to be the factors associated with local recurrence and tumor-free survival after PEIT.[52,53] RFA has recently been shown to have the therapeutic results comparable to those of surgical resection for HCC.[54] Overall survival rates were reported to be 89~95.8%, 67.4~86.8%, and 46.4~80.0% at 1, 2, and 3 years, respectively, and the mean survival duration was 45 months. Child-Pugh grade, platelet count, serum albumin and bilirubin levels, and tumor size were the independent prognostic factors for local recurrence and survival after RFA.[54-56]

In addition, antiviral therapy has been found to have beneficial effects in aspects of on-treatment liver function and post-treatment recurrence in patients with HBV-related HCC.[57]

Besides the treatment modalities mentioned above, hepatic arterial infusion chemotherapy, systemic chemotherapy, radiotherapy and multi-directional combined therapy have been applied to the patients with advanced HCC, who were not candidates of effective treatments or failed to respond to previous treatments, as optional or salvage treatment modality.[58-65]

Mortality and survival

Three major causes of death in Korea have been malignancy, cerebrovascular accidents, and cardiovascular diseases during the last twenty years. Since 1980, when Korea Central Cancer Registry was introduced, the mortality rate due to cancer has been gradually increasing.[66] Annual reports of vital statistics of Korea reported that

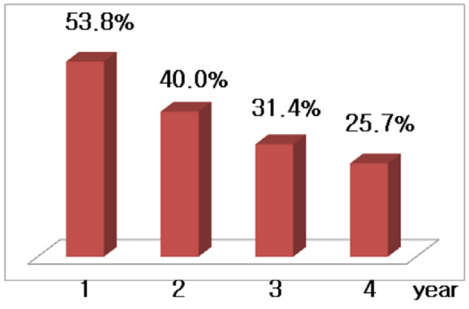

Figure 3. Survival rate of hepatocellular carcinoma in Korea. The overall median survival time was 14.3 months.

2006's death toll was 65,909, 27.0% of which was caused by cancer. Among the deaths due to malignant neoplasms, the death from primary liver cancer has ranked second (16.6%), following lung cancer (21.4%). Although the incidence rate of primary liver cancer shows a modestly decreasing pattern, the crude mortality rate increased slightly from 24 per 100,000 persons in 1983, 30.0 per 100,000 in 1989, 33.5 per 100,000 persons in 1995, 32.5 per 100,000 persons in 2001 to 34.5 per 100,000 persons in 2007.[66]

Nationwide survey for the survival rate of patients with primary liver cancer was performed with 1,151,789 subjects who were diagnosed with cancer and registered in the database of Korea Central Cancer Registry between 1993 and 2005. During this period, 5-year survival rate in these cancer patients was 47.4%, with the survival rate in female patients (58.4%) being higher than that in the males (38.6%), which reflects the relatively high survival rates of breast, cervix and thyroid cancer. In men, 5-year survival rates of primary liver cancer have increased almost 2-folds from 9.9% during the period of 1993~1995, 12.9% during 1996~2000 to 18.8% during 2001~2005. These survival data, however, are by far lower than those (43.0% during 1993~1995, 46.9% during 1996~2000, 57.0% during 2001~2005) of stomach cancer, the most frequent malignancy in Korean male. In women, 5-year survival rates of primary liver cancer have also modestly increased from 13.6% during the period of 1993~1995, 14.2% during 1996~2000 to 19.0% during 2001~2005. These survival figures are still inferior to those (78.0% during 1993~1995, 83.2% during 1996~2000, 87.3% during 2001~2005) of breast cancer, the most frequent malignancy in Korean female.[67]

Overall, the survival of HCC patients remains very poor. In a recent report from the National Cancer Center Hospital, the 1-, 2-, 3-, and 4-year survival rates of HCC were 53.8%, 40.0%, 31.4%, and 25.7%, respectively (Fig. 3.), and the overall median survival period was 14.3 months. But the survival rates were exceedingly different between subgroups according to the degree of the remaining hepatic reserve (Child-Pugh grade), tumor stage (modified 5th UICC TNM staging), and treatment modalities.[15]

There were several reasons for the prognosis of HCC being poorer than that of other malignancy. First, tumor progression and invasion are fast because of the aggressive biologic behavior of HCC itself. Second, most patients with HCC have chronic liver diseases such as cirrhosis, which could hinder the curative managements of HCC. Third, many cases of HCC are diagnosed in their advanced stages, which means a lower chance for curative treatments. Treatment modalities, Child-Pugh grade, TNM staging, portal vein thrombosis, serum α- fetoprotein level, and the number and type of tumor were analyzed as independent prognostic factors for HCC.[15,47] Causes of death in HCC patients in Korea, irrespective of treatment modality, are liver failure, gastrointestinal bleeding and infection, in the order of their incidences.[17,47]

National efforts to reduce the occurrence of HCC

In 1980, Ministry of Health and Welfare and the National Cancer Center performed a "National Cancer Registration Program", which intended to promote a national effort to exactly compute the statistics for the annual report of cancer prevalence in Korea. In 1996, "National R&D Program for Cancer Control" was started to support the R&D activities of the industry, academia and research institutes. In 2001, in conjunction with the National Cancer Center, the Korean Liver Cancer Study Group (KLCSG) made recommendations for the early detection of HCC so curative treatments could be applied as early as possible. In 2003, "National Cancer Screening Program", which was initially introduced for stomach, cervix, and breast cancer in 1999, was extended to HCC for high-risk subjects with low socioeconomic status. Practice guideline for diagnosis and treatment of HCC, which was enacted in 2004,[30] was revised by the efforts of KLCSG and the National Cancer Center in 2009.[68] At present, the National Cancer Control Institute, which was reorganized in 2005, is working with the aim to be a world-class cancer control policy institute. Besides, nationwide screening for HBsAg and anti-HCV for the whole population, universal vaccination for HBV in children, routine screening for HBsAg and anti-HCV of all blood products are all preventive efforts currently enforced in Korea to reduce the incidence of HCC.

Future perspectives

The reports from Korea, in comparison with those from other countries such as Japan[69] and the United States,[70] show distinct differences in the features of HCC, including its incidence, risk factors, survival and mortality rates. International collaboration between Korea and other countries for clinico-epidemiologic research should be encouraged to precisely understand the reasons for these differences, and eventually to provide the specific measures for managing HCC in diverse etiologic situations.

Recently, sorafenib, a potent multikinase inhibitor, was introduced into the treatment of advanced HCC as a molecular targeted therapy,[71-74] but its therapeutic effect was limited and had a room for more improvement. Definite clarification in the molecular and cellular levels of hepatitis virus-associated hepatocellular carcinogenesis might be necessary to provide insights into the advanced therapeutic and preventive approaches for HCC in Korea, where the majority of HCC originate from chronic HBV and HCV infections.

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