Meeting Report

First International Symposium of Current Issues for Nationwide Survey of Primary Liver Cancer in Korea, Taiwan and Japan

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common malignant neoplasm in the world and causes nearly 500,000 deaths per year (1). This cancer is attributable mainly to hepatic B virus (HBV) infection in sub-Saharan Africa and Asia, and C virus (HCV) in Japan, Europe, and the USA. The prognosis still remains poor because of the advanced stage of cancer and associated hepatic impairment at diagnosis and because of the high recurrence rate.

The 1st International Symposium of Current Issues for Nationwide Survey of Primary Liver Cancer in Korea, Taiwan and Japan was held at the 42nd Annual Meeting of Liver Cancer Study Group of Japan in Tokyo on 6–7 July 2007. In this symposium, dedicated discussion was carried out by Drs B.I. Choi, C.K. Wang, I. Ikai and K. Okita (chair person) regarding the basic and clinical studies that were mainly based on the data by the Liver Cancer Study Group founded in these countries (Table 1), and more precise current issues and perspectives have been clarified in the following sections. The continuous promotion of the research and clinical study is now desired with dynamic and subtle future planning.

CURRENT ISSUES FOR NATIONWIDE SURVEY OF PRIMARY LIVER CANCER IN KOREA

In Korea, nationwide statistical data on patients who have received therapy for primary liver cancer or its natural history did not exist. Moreover, various local treatment methods for HCC such as percutaneous alcohol injection therapy, microwave coagulation therapy and radiofrequency ablation therapy are being performed without a period of verification of consensus. This has led to a lack of uniformity in establishing not only the diagnosis but also the initial mode of therapy for primary liver cancer among various institutions and has resulted in a tendency toward conflict rather than synergy among the various diagnosis and treatment modalities. Therefore, there exists a strong need for a national cancer registry for primary liver cancer. Fortunately, as the first step, the Korean Liver Cancer Study Group (KLCSG) was established in June of 1999 to arrive at a consensus and hence overcome these problems, and to establish an environment for co-operation between institutions (2). The total membership of KLCSG in 2006 was 247. Scientific meetings are held five times a year including three-monthly conferences, one single-topic conference and one annual meeting. ‘The general rules for the study of primary liver cancer’, which successfully laid down the groundwork for a national cancer registry was published in June of 2001. The second edition was published in 2004.

EPIEMIOLOGY

In Korea, there are two cancer registry systems. One is a national cancer registry from the epidemiologic aspect and the other is a cancer registry based on liver cancer study...
group from a clinical aspect. Korea cancer central registry was established in 1980, and is a hospital-based cancer registry. The headquarters of the Korea cancer central registry is in the National Cancer Center. The other cancer registry is the primary liver cancer registry of KLCSG. The cancer registry committee of KLCSG was formed in June 2003. In June 2004, a database form for cancer registry was decided. In October 2005, cancer registration was started. As at June 2006, the number of registered patients was 6199 (3).

Ten major cancers in Korea are summarized (Figure 1). Liver cancer is the third most prevalent cancer in males and the sixth in females, with 18 and 7% of total cancers respectively. More than 10,000 new cases are currently diagnosed annually, with an age-adjusted Korean male and female

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**Table 1.** Background of the Liver Cancer Study Group, epidemiology, and clinical study of primary liver cancer among Korea, Taiwan, and Japan

<table>
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<th>Item</th>
<th>Korea</th>
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<td>A. Background of the Liver Cancer Study Group</td>
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<tr>
<td>1. Liver Cancer Study Group founded in</td>
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<td>2. Registration system started in</td>
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<td>1978</td>
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<td>4. No. of registered patients</td>
<td>6,200</td>
<td>~26,000</td>
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<td>B. Epidemiology</td>
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<td>6. No. of patient death/year</td>
<td>10,000</td>
<td>7,000</td>
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<td>C. Etiology</td>
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<td>16%</td>
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<td>11. Tumor marker</td>
<td>AFP</td>
<td>AFP, AFP-L3 or PIVKA-II</td>
<td>AFP, AFP-L3 &amp; PIVKA-II</td>
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<td>Ultrasound</td>
<td>Ultrasound</td>
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<td>43–59%</td>
<td>53%</td>
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<td>14. Percutaneous ethanol injection (PEI)</td>
<td>40–50%</td>
<td>52% (&lt;3 cm)</td>
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<td>15. Radiofrequency ablation (RFA)</td>
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<td>74% (3ys, &lt;4 cm) vs 55% by PEI</td>
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<td>16. Transarterial chemoembolization (TACE)</td>
<td>20–40%</td>
<td>12%</td>
<td>21%</td>
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<td>LFT, PT, INR</td>
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<td>G. Cancer staging system by</td>
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<td>modified UICC/AJCC</td>
<td>modified UICC/AJCC</td>
<td>New TNM proposed by LCSGJ (2000)</td>
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<td>H. Integration of liver function and cancer stage</td>
<td>CLIP, JIS</td>
<td>JIS, CLIP, TKY</td>
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<td>I. Guideline published in</td>
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LFT, liver function test; PT, prothrombin time; INR, international normalized ratio; UICC/AJCC, International Union Against Cancer/American Joint Committee on Cancer; CLIP, the Cancer of the Liver Italian Program; JIS, Japan Integrated Staging score; TKY, Tokyo score.

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![Figure 1. Incidence of ten major cancers in Korea [cited from Park and Kim (4)]. NHL, non-Hodgkin lymphoma.](image-url)
incidence of 45.0 and 12.0 per 100 000 population. In Korea, around 10 000 people die from liver cancer every year. The mortality rate is 24/100 000/year (4).

In terms of the incidence of pathologic type of primary liver cancer in Korea, HCC counts for 75%, while unclassified malignant neoplasm for 16%. However, most unclassified cancers are HCC so it probably comprises 90% of primary liver cancer in Korea, while cholangiocarcinoma comprises 4.3% (4).

HCC is the fifth most common cause of cancer and its incidence is increasing worldwide because of the dissemination of HB and HC virus infection (5). Risk factors of HCC in Korea are mainly chronic liver disease. HBV infection is 74%, HCV infection 9% and alcohol 7% (4).

SCREENING AND DIAGNOSIS

HCC is one of the few cancers with well-defined major risk factors. In 80% of cases, HCC develops in cirrhotic livers. Liver cirrhosis is the long-term result of chronic viral infection and is the strongest predisposing factor of HCC in Korea. Early detection of HCC in patients with high risk is therefore important to achieve better results of treatment. In 2001, recommendation guidelines for early detection of HCC were proposed by the Korean Society of Hepatology (6). Based upon these guidelines a national liver cancer screening program was started in 2003. This screening program was for patients with high risk and low socioeconomic status, and included checking alpha-fetoprotein (AFP) and hepatic ultrasound (US) every 6 months.

With regard to imaging protocol for HCC, recent advances in liver imaging techniques have facilitated the detection of small HCCs.

Recent progression of noninvasive imaging technology includes various techniques of harmonic US imaging with several kinds of US contrast agents, multidetector computed tomography (MDCT), and rapid high-quality magnetic resonance (MR) technique with new, tissue-specific contrast agents. These techniques seem to have a strong potential for improving detection and characterization of HCC (7).

Routine image protocol of HCC in Korea requires that screening is done by US, the standard technique is triple phase CT, the complementary study is dynamic MRI and the pre-operative technique is angio-CT or SPIO-enhanced MRI.

Modified UICC is recommended for staging of primary liver cancer by KLCSG. Child–Pugh classification is the most popular reference of liver function. According to the data from National Cancer Center in Korea, stage III is the most common followed by stage IVa and II (4).

TREATMENT

Unfortunately, there are no available data of a nationwide survey in Korea because the KLCSG is still in the early stages. Recently, one executive committee member of KLCSG searched literature of Korean data and reviewed Korean data during the past 3 years (8).

Among primary treatment modalities for HCC in Korea, transarterial chemoembolization (TACE) is the most popular, followed by surgery and local ablation therapy such as radiofrequency (RF), or percutaneous ethanol injection (PEI).

During the past several years, surgical techniques have also improved in Korea. Several reports in terms of surgical treatment of HCC revealed that morbidity was 10%, mortality 1–2% and transfection rate 7%, and the 5-year survival rate was 50–60%, similar to that of Japan (8). Living donor liver transplantation is becoming popular in Korea due to refinements of the technique and good results (9). According to one recent study with retrospective non-population based consecutive 312 case series including 75 cadaver donor liver transplantation (CDLT) and 237 living donor liver transplantation (LDLT) from 1992 to 2002 from four institutions, it showed that overall the 3-year survival rate was 73% in LDLT and 61% in CDLT (8).

TACE is the most frequently performed procedure for HCC, with 10 000–15 000 procedures performed per year (10). Recently, RF ablation therapy (RFA) for HCC is becoming more popular. The 5-year survival rates of patients with HCC who underwent non-surgical therapy such as PEI, TACE and RFA have reached 46%, 15% and 58%, respectively, according to several recent studies (8, 10).

PRACTICE GUIDELINES

However, the KLCSG attempted to establish guidelines for the diagnosis and treatment of HCC in conjunction with the Korean National Cancer Center. In 2003, a tentative practice guideline was proposed by the task force team and this guideline was published in the second edition of the general rules for the study of primary liver cancer in June 2004, after several consensus meetings with hepatologists, hepatic surgeons, radiologists and pathologists (11).

If HCC is suspected by AFP and US in surveillance program, further studies are indicated including history taking, physical examination, liver battery, AFP and 3-phase CT. Optional studies include additional US, dynamic MRI, hepatic angiography and tumor marker. Some of these studies confirm HCC while some are not definite.

For confirmed HCC, staging should be performed and according to the status and clinical situation, appropriate treatment should be applied. In Korea, there is no nationwide survey database for the diagnosis and treatment of HCC.

In the near future, the nationwide survey database should be completed the KLCSG and will thus be able to help improve the prognosis of HCC patients in Korea.

(by B.I. Choi, The Korean Liver Cancer Study Group)

PRIMARY LIVER CANCER IN TAIWAN

The population of Taiwan is 23 million and about 7000 deaths from HCC and 1000 cases of liver cirrhosis deaths
from HBV and HCV-related liver disease are reported annually. In comparison, about 30,000 HCC patients per year die in Japan.

Primary liver cancer, including HCC and cholangiocarcinoma, are the leading cause of cancer death in Taiwan (12). It has ranked first among cancer mortality in men and second in women since 1980s.

Cholangiocarcinoma was less common than HCC. The cause of most cholangiocarcinoma was associated with hepato- lithiasis and infection with a parasite known as the liver fluke (13). HCC almost accounts for 95% of primary liver cancer. The major pathway of hepatocarcinogenesis is through HBV or HCV infection, chronic hepatitis and cirrhosis to HCC. The prevalence rates of HBsAg and anti-HCV are 15–20% and 1–3% respectively, in the general population. Dual infection with HBV and HCV is around 3–12% in patients with chronic hepatitis B in Taiwan. Overall, 90% of cases of HCC are attributable to persistent viral infections with either HBV (55–60%) or HCV (30–35%). The frequency of HCC with underlying liver cirrhosis in our study was 80% (14).

The surveillance tests commonly used in patients at risk for HCC are periodic US examination of the liver and measurement of serum AFP concentration, with serum AFP level > 400 ng/ml as a complementary method for the diagnosis of HCC. However, in 35–45% of HCC patients, the AFP level may be normal. Additional sensitive serum marker to improve the early detection of small HCC, including lectin-reactive alpha-fetoprotein (AFP-L3) and des-gamma-carboxyl-prothrombin (DCP/PIVKA-II). Our recent study suggested that the accuracy, sensitivity and specificity of DCP were higher than AFP in detecting HCC (81.9%, 77% and 86.4% versus 68.5%, 59% and 77.3%, respectively) (15). However, its use as a surveillance test has not been well established. The definite diagnosis of HCC was made by histology, especially 1–2 cm of liver lesion. However, a liver tumor in 2 imaging modalities such as US, contrast enhanced ultrasonography (CEUS), enhanced CT, MRI, SPIO-MRI and/or angiography, with high AFP > 400 ng/ml also is diagnostic.

Tumor staging, which is the basis for therapeutic management, included the Okuda system, the Cancer of the Liver Italian Program (CLIP) score, the Barcelona Clinic Liver Cancer (BCLC) staging system, Japan Integrated Scoring system and TNM (tumor-node-metastasis) staging system. All available models have based on two factors influencing outcome: the underlying liver function and the extensiveness of the tumor. As the clinical presentation of HCC is tremendously heterogeneous, the prognosis in relation to treatment should be further evaluated.

All of the therapeutic methods of HCC, including surgical resection, liver transplantation, living donor liver transplantation (LDLT), non-surgical treatment with local ablation therapy and transcatheter arterial embolization (TAE, TACE), are widely applied in Taiwan. Surgical resection has been considered as the optimal treatment, but only a small proportion (less than 15%) of patients could be qualified for surgery and there is a high rate of recurrence. The 5-year survival rate of HCC patients after curative resection has usually been less than 50% over the last 20 years. The common causes of death were tumor recurrence and complications of liver cirrhosis. Liver transplantation has been successful in the treatment of limited cases of HCC. The major limitation is the lack of cadaveric grafts. Therefore, liver transplantation has been advocated as a salvage treatment for unresectable HCC in Taiwan (16). Living-donor liver transplantation, which first developed in Japan in the early 1990s, has provided a solution to the severe lack of cadaveric grafts (17). However, the selective criteria still need to be developed in this area. As a result, various local ablation therapies have been proposed and accepted as main modalities for treating patients with HCC.

PEI is considered the most easily performed and effective modality of direct ablation therapy for HCC. In our series of study, in the patients with HCC smaller than 5 cm, the cumulative survival rates at 1, 3 and 5 years were 98%, 80% and 52% respectively. RFA is being considered as an effective therapy for HCC. In a recent report, a randomized-controlled trial (RCT) for HCC less than 4 cm from Taiwan, RFA has a slightly higher rate of complete necrosis than PEI (96% versus 88%). The 3-year survival rate was also significantly higher in HCC patients receiving RFA than those receiving PEI (74% versus 55%) (18).

TACE is a major palliative treatment for unresectable HCC. Recently, a nationwide, multicenter study from four medical centers in Taiwan reported that the 1-, 3- and 5-year survival rates for patients who underwent TACE alone were significantly higher than those underwent supportive treatment (60.2, 39.3 and 11.5% versus 37.3, 17.6 and 2%, respectively) (19). However, several studies have shown a superior effect of combination therapy with TACE and PEI compared with either monotherapy for the treatment of advanced HCC (14). We had investigated the long-term survival and prognostic factors of 208 HCC patients treated with TACE/PEI combination therapy. The 1-, 3- and 5-year survival rates were significantly increased to 88, 65 and 47% respectively in the Taipei City Hospital. Multivariate analysis showed that the stage of cirrhosis (Child’s class B or C versus class A) was the only factor that significantly affected the survival rate.

Radiotherapy alone was thought to have a limited role in the treatment of intrahepatic malignancy because of the low tolerance to whole organ irradiation. Intensity-modulated radiotherapy (IMRT) is the most recent technical advance in external beam photon radiation therapy. The ability to deliver high radiation doses can maintain or even reduce the risk of normal liver toxicity. A recent report from Taiwan showed that use of IMRT achieved a large dose reduction to the spinal cord and at least similar organ-sparing results for kidneys and stomach. IMRT significantly reduced the dose in normal tissue, but significantly increased the mean dose to the tumor target, as compared with three-dimensional conformal radiotherapy (3D-CRT) (20).
The use of systemic chemotherapy in the management of HCC is limited by the fact that most patients have cancer and liver cirrhosis. The most widely used chemotherapeutic drugs for HCC were 5-FU, doxorubicin and cisplatin. However, the response rates were usually unsatisfactory. Hence, new agents with new mechanisms, such as molecular targeting therapy and anti-angiogenetic therapy, need to be developed in the future.

Because HCC is closely associated with HBV, many Asian countries have adopted mass vaccination programs since the 1980s. A nationwide hepatitis B vaccination program was implemented in Taiwan in July 1984. The average annual incidence of HCC in children 6–14 years of age declined from 0.70 per 100 000 children between 1981 and 1986 to 0.57 between 1986 and 1990, and to 0.36 between 1990 and 1994 \(P < 0.01\) (21). Since the institution of Taiwan’s program of universal hepatitis B vaccination, the incidence of hepatocellular carcinoma in children has declined. However, the incidence of HCC among adults should continue to be monitored after the hepatitis B mass-vaccination program.

By using periodic examinations of serum AFP and abdominal US every 6 months, HCC can be detected and treated earlier. However, because of the increasing incidence of HCC worldwide, new therapies for HCC will continue to be needed.

(by C.K. Wang et al., The Liver Cancer Study Group of Taiwan)

CURRENT ISSUES IN A NATIONWIDE SURVEY OF PRIMARY LIVER CANCER IN JAPAN

More than 34 000 people in Japan die each year due to primary liver cancer. Primary liver cancer is the third leading cause of death in males and the fourth in females among malignant neoplasm. The Liver Cancer Study Group of Japan (LCSGJ) was founded in 1967 in order to promote the basic research and to advance clinical practice of the primary liver cancer. An important project in the LCSGJ is a nationwide follow-up survey of patients with primary liver cancer in Japan. The results of the first survey were reported at the 5th annual meeting of the LCSGJ in 1969. The first four surveys were conducted retrospectively. A prospective registration system was developed after the fifth survey for new patients and follow-up surveys were made every other year. The 17th survey (conducted between 2002 and 2003) is the most recent in the database and its results were reported in 2006 (22). So far, approximately 140 000 cases have been registered in the LCSGJ database. Approximately 95% of these cases are classified as HCC and another 3.6% are classified as intrahepatic cholangiocarcinoma. A small number of patients with combined hepatocellular and cholangiocarcinoma, cystadenocarcinoma and hepatoblastoma is also registered. Using this database, the LCSGJ conducted several studies concerning the epidemiology, diagnosis, treatment and prognosis of primary liver cancer (23–32).

EPIDEMIOLOGY AND DIAGNOSIS OF HEPATOCELLULAR CARCINOMA

In the fifth survey (conducted between 1978 and 1979), the mean age of patients with HCC was 57 years old. This value increased in each subsequent survey. The mean age of patients with HCC increased over the ensuing 24 years to 67 years old in the 17th survey (22). It is well known that the condition is more prevalent in males, but the ratio of male to female patients decreased from 4.5:1 in the fifth survey to 2.5:1 in the 17th survey. In this last survey, 15.5% of the patients with HCC were positive for HBsAg and 71.8% were positive for anti-HCV. Throughout the past 10 years, the ratio of patients with hepatitis B and C infection did not change.

Published in Japan in 2005, the Clinical Practice Guidelines for Hepatocellular Carcinoma recommend conducting periodical evaluations using tumor markers (AFP, PIVKA-II and AFP-L3) and ultrasonography for surveillance of HCC in high risk patients with HBV and/or HCV infection. When any tumor markers are elevated or any nodular lesion in the liver is detected by ultrasonography, a dynamic CT and/or a dynamic MRI is recommended to make a definitive diagnosis of HCC. In the 17th survey (22), 64% of the patients had an AFP level of 15 ng/mL or more, 59% had a PIVKA-II level of 40mAU/mL or more and 31% had an AFP-L3 fraction of 15% or more. Advances in the screening program have led to an increase in the number of patients with small HCC. The last survey also revealed that 32% of newly registered patients with HCC had tumors measuring 2 cm or less in size.

TREATMENT OF HEPATOCELLULAR CARCINOMA

In 1970, the only therapeutic modalities for HCC were hepatic resection and systemic chemotherapy. By 1980, the medical community had witnessed the increased occurrence of TACE and local ablation therapies. Liver transplantation for HCC became a viable treatment option in 2000. Now, one third of patients are treated by hepatic resection, one third are treated by local ablation therapy, one third receive TACE, while a few patients are treated by other therapies.

The 5-year survival rate of patients who underwent hepatic resection between 1978 and 1989 was only 35%. It improved approximately 20% over the following 15 years and eventually reached a rate of 53% between 1992 and 2003. Operative mortality rate decreased to less than 1% during this time.

There are three kinds of local ablation therapies: PEI, microwave coagulation therapy (MCT) and RFA. Registration of patients who underwent PEI, MCT and RFA began in 1988, 1992 and 1998, respectively. Due to its therapeutic efficacy, the use of RFA is increasing significantly and the use of PEI is decreasing. In the 17th survey, 66% of
patients were treated by RFA. When local ablation therapy was utilized, more than half of target tumors were less than 2 cm, but a small number of larger tumors were also treated. More than 90% of PEI and RFA treatments were conducted by a percutaneous approach, but two thirds of MCT were conducted surgically. Of all the local ablation therapies, 84% were done percutaneously. The 5-year survival rates of patients who underwent PEI, MCT and RFA between 1992 and 2003 were 39, 49 and 57%, respectively.

The 17th survey also revealed that more than half of the patients treated by TACE had multiple tumors (22). In 75% of the TACE treatments, lipiodol emulsion and gelatin sponges were used as embolization materials, and segmental embolization was performed in approximately 70% of the cases. The 5-year survival rate in patients who underwent TACE with and without a gelatin sponge between 2002 and 2003 was 23 and 16%, respectively. In addition, the 17th survey also reported an increasing number of patients treated by various new therapeutic modalities, such as liver transplantation. However, the nationwide survey database does not contain a sufficient amount of data to evaluate the outcome of patients treated by these new modalities.

**Prognostic Indicators of Patients with Hepatocellular Carcinoma**

Tumor size is one of the most important prognostic indicators of HCC. The last survey reported the following 5-year survival rates in patients who underwent liver resection: 68% in patients with tumors 2 cm or less, 56% in those with tumors 2–5 cm, 42% in patients with 5–10 cm tumors and 32% in patients with tumors greater than 10 cm. The number of tumors is also an important prognostic factor. In patients with one, two, or three or more tumors, the 5-year survival rates were 59, 46 and 30%, respectively. Portal vein tumor thrombosis is the most significant prognostic indicator and the 5-year survival rates in patients with Vp0, Vp1, Vp2 and Vp3–4 were 58, 39, 24 and 18%, respectively. The liver function is also an important prognostic factor.

Based on these reported results, the LCSGJ proposed a new TNM stage classification in 2000 (33). In this stage classification, tumor category is determined by the tumor diameter, the number of tumors and the presence of vascular or bile duct invasion. To precisely evaluate liver function, the LCSGJ also proposed the degree of liver damage classification to replace the Child–Pugh Classification (33). Both the TNM stage and the degree of liver damage have good stratification ability. TNM staging and the degree of liver damage classification are useful in predicting the prognosis of patients with HCC. Recently, several integrative scoring systems combined tumor status and liver function. The modified JIS score calculated from the TNM stage and the degree of liver damage also has good stratification ability (32).

The treatment algorithm for HCC in the Clinical Practice Guidelines for Hepatocellular Carcinoma recommended that therapeutic modalities should be selected based on a careful assessment of the liver damage classification, the number of tumors, and the size of the tumors. Hepatic resection, local ablation, or TACE are the recommended treatments for patients with mild or moderate liver function. For patients with a severely impaired liver function, the recommended treatment is either liver transplantation or supportive care.

**Future Issues**

We obtained evidence concerning HCC from the nationwide follow-up surveys. In future reports, we will provide information about new modalities for HCC such as RFA, liver transplantation, chemotherapy and chemoprevention. We will also evaluate epidemiological and clinical factors of other primary liver cancers such as intrahepatic cholangiocarcinoma.

(by I. Ikai, The Liver Cancer Study Group of Japan)

**Discussion, Perspective and Conclusions**

In Japan, HCC ranks as the fourth most common cancer and is responsible for over 40 000 deaths annually. Very high incidence of HCC has been reported from Korea and Taiwan. Approximately 80% of the Japanese HCC patients are HCV positive and this is quite different characteristics in comparison with Korea and Taiwan where there are larger populations of HBV positive HCC patients. There is no doubt that hepatologists, oncologists and surgeons in these countries have made an effort to improve the mortality rate of HCC patients. Accordingly, it will be very important to exchange the results brought among those countries. Dr Kenichi Takayasu, President of the 42nd Annual Meeting of Liver Cancer Study Group of Japan (LCSGJ), planned to have an International Symposium entitled ‘Current Issues for Nationwide Survey of Primary Liver Cancer among Korea, Taiwan and Japan’.

Discussions opened in this symposium will be summarized as follows.

**Systematization of Liver Cancer Study Group in Korea, Taiwan and Japan**

Liver Cancer Study Groups have been systematized in each country. Registration of the HCC patients is one of the duties in this study group. In Korea, Taiwan and Japan, 6,200, 26,000 and 140,000 patients respectively have been registered at present. Further analysis of the registered patients promises to provide very important information on future management of HCC.

**Epidemiology**

In order, cancer was the third cause of death in males and the sixth in females in Korea, the first in males and second
in females in Taiwan and the third in males and fourth in females in Japan. Number of patient deaths each year is approximately 10,000 in Korea, 7,000 in Taiwan and 34,000 in Japan. Age adjusted incidence of HCC was 45/100,000 population in males and 12/100,000 in females in Korea, 55.8/100,000 in males and 22.3/100,000 in females in Taiwan, and 37.9/100,000 in males and 16.5/100,000 in females in Japan. Frequency of HCC in primary liver cancer was 85% in Korea, 90–95% in Taiwan and 95% in Japan.

**Etiology**

In Korean HCC patients, the positive rate of HBV was nearly 70% and HCV was 10%. In Taiwan, HBV in HCC patients was positive between 55 and 65%, and HCV was between 30 and 40%, whereas in Japan, HBV was positive in 16% and HCV 72% among HCC patients.

Hepatocarcinogenesis in men is still unclear. Therefore, to understand how HBV and HCV are involved in carcinogenesis at the molecular level, Korea and Japan provide good fields for research.

**Surveillance System**

HCC stems from chronic liver diseases caused by HBV and HCV. Therefore, establishment of a surveillance system plays an important role in early diagnosis and cure of HCC. In Korea, follow-up study using AFP as tumor marker and US for imaging diagnosis has been adopted. Cheap and convenient US study is believed to be a powerful weapon for the surveillance system in detecting HCC. However, concerning tumor markers, in Taiwan and Japan AFP-L3 or PIVKA-II are integrated in the surveillance system.

**Algorithm of Imaging Diagnosis**

An algorithm of imaging diagnosis should be proposed for early detection of HCC. In three countries, an algorithm of imaging diagnosis in combination with US, CT, MRI and IVR-CT has been established. The introduction of an algorithm is quite necessary, but its implementation rate in patient follow-up is not reported in each country.

**Five Year Survival Rate for Each Treatment**

The 5-year survival rate among the patients who received surgical operations was 40–66% in Korea, 43–59% in Taiwan and 53% in Japan. The 5-year survival rate after PEI was between 40 and 50% in Korea, 52% in Taiwan and 39% in Japan. Following RFA, it was between 50 and 60% in Korea, 57% in Japan, while the 3-year survival rate in Taiwan was 74%. However, in the case of TACE for treatment of larger tumors as compared with the lesions for PEI and RFA, the 5-year survival rate was between 20 and 40% in Korea, 12% in Taiwan and 21% in Japan. Interestingly, in Taiwan, a combination with TACE and PEI improved the 5-year survival rate up to 47%.

**Evaluation of Liver Function**

It has been known that the therapeutic effect in HCC is determined by two factors such as tumor factor (number, size and vascular invasion) and liver function. If liver function is reserved well, several modalities including surgery can be applied. Accordingly, it is very important to estimate reserved liver function precisely in each patient prior to starting therapy. In Taiwan, liver function tests and international normalized ratio (INR) have been used for evaluation, while in Japan degree of liver damage is replacing the Child–Pugh classification.

**Staging System**

As described above, the therapeutic effect is determined by tumor factor and liver function in each patient. Therefore, the staging system is important for the decision regarding therapeutic modality. In Korea and Taiwan, modified UICC/AJCC has been adopted and new TNM proposed by the Liver Cancer Study Group of Japan.

**Integrated System**

Evaluation of therapeutic effect is very difficult in HCC, because even if the tumor is solitary and less than 3 cm in size, the prognosis of the patients in ‘Liver Damage C’ is very poor. Accordingly, a system integrating both tumor factors and reserved liver function has been proposed. In Korea and Japan, the Cancer of the Liver Italian Program (CLIP) and Japan Integrated System (JIS) have been used. In addition to CLIP and JIS, the Barcelona Clinic Liver Cancer (BCLC) staging system and Tokyo Score are reported. Sufficient evaluation of these integrated systems has not been performed so far.

**Publication of Guideline for Management**

A guideline for management of HCC based upon data in RCT level is absolutely necessary for the standardization of management system. In Korea, a guideline was published in 2003, and in Japan, in 2005. The difference in guidelines between Korea and Japan was not discussed in this symposium.

**Perspective and Conclusion**

This symposium has disclosed that there is no distinct difference in management of HCC in Korea, Taiwan and Japan. However, for greater improvement of the 5-year survival rate, we must attempt to diagnose HCC at an earlier stage such when there is a smaller size tumor of less than 3 cm in diameter among patients with reserved liver function in good
condition. Of course, we know that there are too many patients with advanced HCC as compared with the patients with early HCC. A high recurrence rate after treatment is also characteristic in HCC management. Accordingly, future issues are promotion of liver transplantation, development of more effective chemotherapeutic agents and chemoprevention.

The first symposium on ‘Current Issues for Nationwide Survey of Primary Liver Cancer among Korea, Taiwan and Japan’ has provided a good opportunity to make clear what is an important issue in the management of HCC in these countries.

(by K Okita)

References