TABLE 5. Summary of Articles on Outcome After Selection for LDLT in Adults

Reference No.	16	17	18	19	20	21	22	23	Current study
Year	2000	2004	2004	2005	2000	2001	2002	2002	2005
Country	USA	Hong Kong	Germany	Spain	USA	USA	Germany	Turkey	Japan
Analysis was on recipients or donors	Recipients	Recipients	Donors and recipients	Recipients	Donors	Donors	Donors	Donors	Recipients
No. of patients evaluated	100	51*	297	121					533
Rejection due to recipient issue	51 (51%)	0	101 (34%)	60 (50%)					165 (31%)
Patient declined	4 (4%)	NA	8 (3%)	36 (30%)					15 (3%)
Patient underwent DDLT	8 (8%)	6 (12%)	15 (5%)	14 (12%)					1 (0.2%)
Unable to find donor	24 (24%)	26 (51%)	0†	17 (14%)					45 (8%)
Donor not suitable	10 (10%)	5 (10%)	107 (55%)	23 (19%)					74 (14%)
No. of LDLTs	15 (15%)	21 (41%)	89 (30%)	21 (17%)					249 (47%)
No. of donors evaluated			622		126	66	148	85	
Donor declined			NA		2 (2%)	10 (15%)	NA	NA	
Psychosocial issue			26 (4%)		2 (2%)	NA	7 (8%)	NA	
No. of donors undergoing surgery			89 (14%)		35 (28%)‡	15 (23%)	46 (31%)	27 (32%)	

Abbreviations: LDLT, living donor liver transplantation; DDLT, deceased donor liver transplantation; NA, not applicable.
*Patients with hepatocellular carcinoma only.
†Only patients with potential donors were analyzed in this study.
‡Right liver graft only.

traindicated in 26 potential donors. In addition, 23 donors withdrew from the program during and after formal evaluation.

Recipient Outcome after Rejection for LDLT

Of 142 patients who were denied LDLT for medical reasons, 9 sought out another transplant program: 2 received LDLT in Japan and 1 received DDLT abroad (Fig. 1). Among the 119 transplant candidates who were rejected due to donor-related issues, 8 patients registered for the DDLT list; 1 received a DDLT, 1 received a domino transplantation at our center, 3 died, and 3 awaited for DDLT. Seven patients underwent DDLT at centers abroad, and 1 with an ABO-mismatched volunteer donor underwent LDLT at another center in Japan.

DISCUSSION

In this analysis, 249 (47%) of the referred potential recipients underwent LDLT. This ratio is higher than those (15-30%) of previous reports.[16,18,19] The differences are partly due to differences in availability of deceased donors. In most of the centers, potential transplant candidates were primarily registered for the DDLT waiting list, and were offered LDLT as an alternative. In contrast, patients in our study may have already been selected by their referring physician according to the availability of potential donors. The selection bias might have reduced the rejection ratio in our hospital (Table 5).

A total of 165 (31%) candidates were rejected due to recipient issues and this proportion was comparable with other studies.[16,18,19] Advanced HCC was the most common reason for rejection in the present analysis. Tumor number and size are restricted by our inclusion criteria, but not in the other LDLT programs in Japan[25,26] or in other countries.[17,27] Among the patients rejected due to advanced HCC in our program, some sought other institutions at home and abroad. The next most common cause of rejection was poor general condition, including multiorgan failure other than liver disease. The indications for LDLT are similar to those for DDLT, which is in contrast with Western countries where a balance needs to be achieved between the candidate's liver disease severity and the adequacy of a partial graft for transplantation. Russo and Brown[28] proceeded with LDLT in candidates with Model for End-Stage Liver Disease scores between 11 and 25.

After identifying the 368 potential recipients suitable for LDLT, we then investigated donor issue for rejection. Of the 368 patients, 249 (68%) underwent procedure. In contrast to previous reports[16,17] in which approximately half of the LDLT candidates had no potential donor, only 70 (19%) of 368 patients were rejected due to the lack of suitable donor candidates. There is usually a higher number of potential donors than recipients; the ratio of donors and adult recipients is 2.1.[18] Our analysis lacked this information because we identified primary donor candidates who were formally evaluated at our center. In many cases, 1 donor candidate was already selected among multiple family members at the time of referral.

The major causes of donor rejection were medical contraindication and refusal. The medical evaluation process has been reported by different authors, and is divided into 3 to 6 phases.[16,18-23,29] The noninvasive initial screening process excludes 20 to 40% of potential donors.[18,20,22,23] The percentage of donors who undergo the operation among candidates varies from 14 to 32%.[18,20-23] In a review of transplant programs in the

United States, an average of 45% of evaluated donors was eventually accepted.[10] This percentage was based on a questionnaire survey, however, and might not reflect the entire cohort of the potential donors evaluated.

In the present study, refusal to donate occurred in 23 cases; 18 of them refused to donate during the evaluation and 5 declined after completion of the medical evaluation for donation. It is difficult to determine if the donors changed their mind for psychosocial reasons. At the initial screening, potential donors with psychosocial problems required psychiatric consultation. During the evaluation process, coordinators were open to donor question or complaints. Published reports also suggest that refusal occurs during all phases of the evaluation. Valentin-Gamazo et al.[18] reported that psychologic evaluation is required twice for all potential donors during the evaluation process. In their series, 26 donors rejected the surgery after psychologic assessment; 21 were excluded after the first consultation, and 5 after the second consultation. In Trotter et al.,[16] 2 potential donors refused donation after it was determined that they were medically acceptable for donation. These results suggest that the autonomy of the decision of the donor should be protected even after completing the entire evaluation process. In contrast, the recipient and family are coerced to some degree after being informed about LDLT, and thus it remains uncertain as to whether physicians should offer liver transplantation to all potential patients. While surgical techniques and perioperative procedures continue to be refined, the importance of a precise approach to psychosocial problems in donors should be pursued.

In summary, we report the process of the recipient evaluation for LDLT and its outcome in a single-center experience. Although approximately half of the evaluated patients successfully underwent LDLT in our program, the patients we evaluated were already selected before referral, specifically after decision making to be a donor among family members. To save more patients requiring liver transplantation who are not able to find living donors, the role of DDLT should be reacknowledged in our society.

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Step-wise progression of fibrosis toward hepatocellular carcinoma and its resolution

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Abstract

The incidence of hepatocellular carcinoma (HCC) is increasing in various countries in the world. In particular, a rapid and major increase has been observed in Japan since mid 1970s, and the increment was attributable mainly to hepatitis C virus (HCV)-related HCC. While HCC incidence now seems to be at a peak, epidemiological studies indicated that HCV spread in Japan occurred mostly in the 1950s and 1960s. The interval between the two peaks represents incubation period for HCC development, the risk of which increases gradually with progression of liver fibrosis. These data suggest an imminent outbreak of HCC in countries where HCV spread took place more recently. In this chapter, we summarized the natural course of chronic hepatitis C as experienced in Japan, emphasizing its relation to HCC development, and the outcome of HCC prevention by interferon monotherapy in the 1990s.

Epidemiology of hepatocellular carcinoma and chronic hepatitis C

Hepatocellular carcinoma (HCC) is a common malignancy worldwide, where chronic viral hepatitis, either by hepatitis B virus (HBV) or hepatitis C virus (HCV), plays a major role in etiology. Geographically, the prevalence of HBV infection varies widely, and the virus is the main causative agent of HCC in places where HBV infection is highly prevalent, such as in East and Southeast Asia and sub-Saharan Africa (Bosch *et al.*, 1999). Chronic HBV infection is acquired mainly through the vertical mother-neonate transmission at labor, and the prevalence of chronic hepatitis B, together with the incidence of HBV-related HCC, has probably remained relatively constant in each area until the recent introduction of neonate immunization (Chang *et al.*, 2000). In contrast, the prevalence of HCV infection has actually increased in several regions (Wasley & Alter, 2000; El-Serag *et al.*, 2003). Japan, located in Far East Asia, suffered from HBV infection with a moderate prevalence rate, about 2% in general population, until neonate immunization began in 1980s. However, the mortality due to primary liver cancer, mostly HCC, has

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been steadily increasing since mid 1970s, and more than tripled in the fourth quarter of the last century. In particular, HCC occurring in patients with so-called non-A non-B chronic hepatitis was conspicuous. Following the discovery of HCV in 1989 (Choo *et al.,* 1989), it was soon found that most HCC patients with non-A non-B chronic hepatitis did have HCV infection, whether or not they had received blood transfusion previously (Saito *et al.,* 1990). At present, 75% - 80% of HCC patients in Japan have HCV infection while 10% - 15% have HBV infection (Shiratori *et al.,* 1995a).

About 40% of HCC patients positive for HCV in Japan have a history of blood transfusion, and the frequency distribution of the time of receiving blood transfusion shows a prominent peak around the year 1960. After World War II ended in 1945, there was an outbreak of psycho-stimulant abuse in Japan, mainly with methamphetamine administered intravenously. HCV was thought to be first spread among these injecting-drug users. In the mean time, the public health insurance system was rapidly organized, covering virtually the whole population, and the opportunities for receiving major surgery with blood transfusion were considerably enlarged. However, a blood bank system based on voluntary blood donation was yet to be established, and the blood supply depended heavily on paid blood donors. Unfortunately, injecting-drug users not infrequently acted also as paid blood donors, which accelerated viral spread into general population (Yoshizawa, 2002). Reuse of syringes and needles in medical practice may have also played a role in the viral spread. Subsequently, post-transfusion hepatitis became a major public concern in the 1960s, and commercial blood banks were entirely abolished by 1969, to be succeeded by the Japanese Red Cross Society, whose blood supply was totally based on voluntary blood donation. Reuse of syringes and needles was strongly discouraged in medical practice in the 1970s. Although HCV transmission through blood transfusion continued until the establishment of a sensitive HCV detection system in the early 1990s, horizontal HCV transmission started to decline in the 1970s, and persons younger than 50 years of age at present have a substantially lower prevalence of HCV infection than older persons.

In Japan, there was an interval of about 20 years between the spread of HCV, which peaked in the 1950s and 1960s, and the commencement of the increase in HCC incidence, which occurred in the late 1970s. This trend is reaching a plateau now but has not yet started to decline. In contrast, in the United States, HCV spread is thought to have started in the mid 1960s, mainly among injecting-drug users, and the viral transmission was thought to have lasted until the 1990s. In the United States, HBV prevalence has been low and HCC used to be relatively uncommon. However, the incidence of HCC is now increasing, most of which is due to chronic hepatitis C (El-Serag *et al.,* 2003). In fact, the prevalence of HCV infection among the general population in the United States is estimated at about 2%, which is similar to that in Japan. Considering the interval of about 20 years between the peak of HCV spread of the two countries, it is strongly suspected that the incidence of HCC is bound to rise further in the United States in the near future. In Europe, where HCC used to be relatively rare, countries are now confronted with the increasing incidence of HCV-related HCC (Deuffic-Burban *et al.,* 2004).

Progression of fibrosis and hepatocellular carcinoma

HCV-related HCC occurred mainly in patients with advanced liver fibrosis, usually cirrhosis, and these patients developed HCC 25 - 30 years after receiving blood transfusion if they have a history. It can be assumed, consequently, that fibrosis progresses slowly in chronic hepatitis C, but this is to be demonstrated in prospective studies. Currently, histopathologic examination of liver biopsy specimen is still the gold standard in the evaluation of liver fibrosis, and the degree of liver fibrosis is classified into five categories (Desmet *et al.,* 1994): F0 (no fibrosis), F1 (slight fibrosis), F2 (moderate fibrosis), F3 (severe fibrosis), and F4 (cirrhosis). Poynard *et al.,* (1997) examined the relationship between liver histology and the period after blood transfusion in a cross-sectional study among 2,235 chronic hepatitis C patients, and estimated the progression rate of liver fibrosis stage to be 0.133 unit/year. They also showed that the progression was more rapid in alcohol drinkers (0.168 unit/year) and that male patients showed a higher rate than female patients (0.154 unit/year versus 0.111 unit/year). Mathurin *et al.* (2000) showed that the progression of fibrosis was slower (0.05 unit/year) in patients with persistently normal serum aminotransferase levels. As for a prospective study, the authors and colleagues analyzed, as a project of the IHIT (Inhibition of Hepatocarcinogenesis by Interferon Therapy) study (see below), the progression rate of liver fibrosis by directly comparing liver biopsy specimens taken from the same patients at an interval of 3.7 years on average (range 1 - 10 years) (Shiratori *et al.,* 2000). A total of 106 patients with chronic hepatitis C, who had not received interferon therapy, were included in the study. The average progression rate, defined as the change in fibrosis staging score divided by the interval between two biopsies, was found to be 0.10 ± 0.02 unit/year. Thus, both a large-scale cross-sectional study and a prospective cohort study showed similar results, indicating that the progression of liver fibrosis is indeed slow in chronic hepatitis C: it would take about 40 years, on average, for cirrhosis to be established. However, Poynard *et al.* (2001), analyzing a large cohort of untreated patients with a reliably estimated duration of infection, demonstrated that prognosis of fibrosis is not linear but dependent mainly on age and the duration of infection and can be divided into four successive periods with very slow, slow, intermediate, and rapid progression rates.

70% - 80% of HCC patients positive for HCV have cirrhosis in the background liver, and the majority of the rest have liver fibrosis at stage F3. The proportion of patients with advanced fibrosis is greater among HCV-related HCC patients than among HBV-related HCC (Shiratori *et al.,* 1995a; Takano *et al.,* 1995). These facts, combined with the slow progression of liver fibrosis in chronic hepatitis C, are compatible with the observed interval of 20 - 30 years between HCV transmission through blood transfusion and HCC development. Moreover, these data also suggest a strong association between the degree of fibrosis and the risk of HCC development in chronic hepatitis C. Of course, accurate assessment of the risk of HCC in association with the degree of liver fibrosis requires prospective observation.

In 1994, we set up a national surveillance program for HCC occurrence among chronic hepatitis C patients, designated as the IHIT study (Yoshida *et al.,* 1999). About 3,000 patients with chronic hepatitis C, who underwent liver biopsy at one of the participating institutions, were enrolled and regularly checked for HCC development. Among these

patients, about 2,500 were treated with interferon monotherapy, and the other 500 remained untreated for various reasons and served as controls. In 1999, we published the first data obtained from the cohort, showing that interferon therapy was significantly associated with reduced risk of HCC (see below). Here, we summarize the prospectively observed HCC incidence rates among the untreated chronic hepatitis C patients. The study included 490 patients who were not treated with interferon, of whom 270 were men and 220 were women, with an average age of 53.6 ± 11.2 years. During a median follow-up of 4.01 years, HCC developed in 59 of the 490 patients. Annual incidence rates as calculated by the person-year method were 0.45%, 1.99%, 5.34%, and 7.88% for the liver fibrosis stage F0/F1, F2, F3, and F4, respectively. Multivariate analysis revealed that age and male gender were also significant risk factors for HCC development. A Cox's proportional hazard model analysis, adjusting for sex and age, revealed risk ratios for HCC development, relative to fibrosis stage F0/F1, to be 4.43 (95% confidence interval: 1.70 - 11.5) at stage F2, 13.10 (5.19 - 33.0) at stage F3, and 24.01 (9.64 - 59.8) at stage F4 (cirrhosis).

When we submitted these results to a medical journal, a certain reviewer, presumably from a western country, commented that the observed HCC incidence rates were extremely high, and possibly due to localized conditions specific to Japan. Indeed, while most studies in Japan concerning HCC incidence among HCV-positive cirrhotic patients showed an annual incidence rate of 6% - 8% (Nishiguchi *et al.,* 1995; Ikeda *et al.,* 1999; Nishiguchi *et al.,* 2001), similar studies performed in the United States or European countries reported much lower rates of about 3% (Colombo *et al.,* 1991; Fattovich *et al.,* 1997; Niederau *et al.,* 1998; Serfaty *et al.,* 1998). In 2004, we reported an updated analysis on HCC development among the IHIT cohort (Yoshida *et al.,* 2004). We then calculated the annual incidence rates of HCC among interferon non-responders as stratified by sex and age (the number of untreated patients were too small to calculate stratified incidence rates, but multivariate analysis indicated that the risk of HCC was not different between the two groups). The results showed that the incidence rate of HCC was strongly dependent not only on liver fibrosis stage but also on the age and sex of patients. For example, Japanese male cirrhotic patients between the ages of 40 and 49 years had an annual incidence rate of 4.3% and female patients under similar conditions had a rate of 2.2%. In this age-group, the annual incidence rate of HCC in Japan was not much different from that reported from western countries. On the other hand, cirrhotic patients over 60 years of age showed much higher incidence rate; as high as 12.5% among male patients and 6.4% among female ones. As described above, typical patients with chronic hepatitis C in Japan contracted HCV around 1960 and are now older than 60 years of age. Thus, the difference in annual HCC incidence rates between Japan and western countries is probably explainable by the difference in the age of patients. This interpretation strongly suggests further increase in HCC incidence to come in countries where HCV infection is prevalent among younger persons at present.

Interferon therapy for chronic hepatitis C

Interferon, once thought to be an omnipotent antiviral agent, was used against HBV infection in 1970s. In 1980s, while HCV was yet to be discovered, several attempts were made to treat non-A non-B post-transfusion hepatitis with interferon, on the well-

grounded assumption that a virus, or viruses, was causative (Hoofnagle *et al.,* 1986). Following the discovery of HCV, it was shown that interferon was indeed effective against HCV infection in a subgroup of patients, leading to persistent normalization of serum aminotransferase levels (Hoofnagle & Di Bisceglie, 1997). Following the advent of a sensitive and specific HCV-RNA detection system, it is known that interferon therapy against chronic hepatitis C may lead to sustained virologic response, which is clinically synonymous with viral eradication. Consensus nowadays is that HCV will not reappear if HCV-RNA is negative in serum 24 weeks after the cessation of interferon administration. Serum aminotransferases levels usually normalize along with the sustained virologic response. Histologic examination of the liver reveals rapid amelioration of necro-inflammatory changes.

In 1992, interferon monotherapy was licensed by the Ministry of Health and Welfare of Japan for use in chronic hepatitis C. The major concern for hepatologists was whether interferon therapy would reduce the risk of HCC, which we recognized as by far the most important sequela of chronic hepatitis C. Thus, the authors and colleagues set up the IHIT study, officially started in 1994, to survey HCC among a large-scale cohort, focusing on the effect of interferon therapy on the incidence rate of HCC. Interferon therapy in Japan in 1990s was usually based on interferon-alpha monotherapy, although interferon-beta was sometimes used instead. The duration of interferon administration was limited to 6 months at the longest by the national health insurance policy, but the dose could be varied according to the patient's condition and doctor's judgment, which tended to be higher than the dose used in the United States and European countries at that period. In our cohort, the median total dose was 480 MU and the median duration of administration was 160 days, and the interferon monotherapy resulted in sustained virologic response in 789 (33.5%) of 2357 patients who were treated and assessed for virologic outcome (Yoshida *et al.,* 1999).

Among the cohort of 2890 patients, a total of 148 developed HCC during the follow-up (median, 4.3 years). Risk factors for HCC development were assessed with Cox's proportional hazard regression model, and sex, age, and liver fibrosis stage were found to be significant independent risk factors. When the presence or absence of interferon therapy was included in the model, interferon therapy was also shown to be significant, with a risk ratio (treatment versus no treatment) of 0.516 (95% confidence interval: 0.358 - 0.742, $p < 0.001$). In other words, interferon therapy with an overall sustained virologic response rate of 33.5% reduced the risk of HCC by half. As a matter of fact, the risk of HCC differed between sustained virologic responders and non-responders. When the two groups were separately compared with the untreated group as the reference, the risk ratio for HCC development was 0.197 (95% confidence interval: 0.099 - 0.392, $P < 0.001$) among the sustained virologic responders and 0.631 (0.434 - 0.918, $p = 0.016$) among the non-responders. It appeared that interferon therapy suppressed HCC development even among non-responders. However, about 10% of patients in the non-responder group showed sustained biochemical response, i.e., sustained normalization of serum aminotransferase levels and others had aminotransferase levels decreased, although not normalized, as compared to the levels before interferon therapy. We divided interferon-treated patients into three groups based on serum alanine aminotransferase (ALT) levels after interferon therapy: normalized; remained less than two times the upper limit of

normal; and higher. The risk of HCC development, as relative to the untreated group, was 0.197 (0.104 - 0.375, $P < 0.001$), 0.358 (0.206 - 0.622, $P < 0.001$), and 0.910 (0.616 - 1.344, $p > 0.2$) in each group, respectively. These results suggested that the reduction in risk of HCC after interferon therapy was mainly associated with amelioration of liver inflammation while viral eradication in itself was not a prerequisite. Reduction in HCC incidence after interferon therapy was demonstrated also by other cohort studies (Imai *et al.,* 1998; Kasahara *et al.,* 1998; Ikeda *et al.,* 1999) and a randomized controlled trial (Nishiguchi *et al.,* 1995) performed in Japan in 1990s.

It should be mentioned, however, that active hepatitis may recrudesce not infrequently in patients with persistent viremia whose aminotransferase level in serum was once normalized after interferon therapy, which is probably accompanied by reverting risk of HCC. In fact, the risk ratio for HCC between non-sustained virologic response and no treatment increased from 0.631 (95% confidence interval: 0.434 - 0.918, $p = 0.016$) in 1999 to 0.835 (0.625 - 1.125, $p = 0.221$) in the more recent, no longer retaining statistical significance (Yoshida *et al.,* 2004). This change may have reflected recrudescence of active hepatitis in biochemical responders, demonstrating that sustained virologic response should be the primary goal of antiviral therapy.

Quantifying the benefit of interferon therapy

Since we set up the IHIT study, there have been advances in interferon therapy against chronic hepatitis C, namely, the introduction of PEG (polyethylene glycol) interferon and the combination with ribavirin (Reichard *et al.,* 1998), and they were accompanied by substantial improvement of sustained virologic response rate. In most countries, the combination of PEG interferon and ribavirin is now the standard treatment for chronic hepatitis C (Manns *et al.,* 2001; Fried *et al.,* 2002). In Japan, however, the combination therapy is yet to be licensed as of 2004, and the effect of the combination therapy on HCC development cannot be measured at present. However, we can estimate, based on reports from abroad and the results of clinical trials, the probability of achieving sustained virologic response in each patient. For example, patients with genotype Ib HCV infection with high virus load, the most resistant to interferon therapy, showed sustained response rates of lower than 10% to conventional interferon monotherapy (Shiratori *et al.,* 1995b), but are thought to have response rates higher than 50% to the combination therapy. With the estimated sustained response rate, we can assess the benefit of antiviral therapy in terms of HCC suppression based on the actual incidence rates as stratified by the response to interferon and other risk factors, namely, sex, age, and liver fibrosis stage. Thus, we examined the HCC incidence rate in each category and, also considering life expectancy based on the sex and age-ranked mortality in the general population, calculated the difference in lifetime probability of developing HCC, which is equal to the difference in HCC-free survival with and without attaining sustained virologic response (Yoshida *et al.,* 2004). Prior estimation of the difference can be obtained by multiplying the result by the expected sustained virologic response rate.

Qualitatively speaking, the results were just as expected: the benefit was greater when a patient was younger; liver fibrosis was more advanced; and the efficacy of antiviral protocol was better. Quantitatively, however, the benefit varied immensely according to each

patient's conditions. For example, a patient older than 60 years of age with stage F1 fibrosis gained less than one year elongation of HCC-free survival with sustained virologic response. In this case, indication for treatment may be questionable if we also consider untoward effects as well as socioeconomic efficiency. On the other hand, a 30 year old male with stage F3 liver fibrosis gained as long as 12.4 years by attaining sustained virologic response. With the same sustained virologic response rate, the difference between the two cases in cost-effectiveness is as large as 20-fold.

Resolution of cirrhosis

Liver cirrhosis used to be recognized as the end stage of various liver diseases regardless of etiology. Underlying this concept was the assumption that liver fibrosis, once established, would never regress. This assumption might have been practically correct in case of chronic hepatitis C when there was no effective antiviral treatment, because chronic HCV infection, once established, will not terminate spontaneously. However, now that potent antiviral therapy has become available, the notion of cirrhosis as the terminal stage may be questioned. Previous studies showed substantial amelioration of liver inflammation after sustained virologic response induced by interferon therapy, although changes in liver fibrosis was less clear in short-term observation (Sobesky *et al.*, 1999). As a project in the IHIT study, we histologically compared liver biopsy specimens that were repeatedly obtained from the same patients (Shiratori *et al.*, 2000). The results obtained from untreated patients were described above, showing that liver fibrosis advanced at about 0.1 unit/year. In the same study, we also analyzed changes in liver histology of sustained virologic responders and of non-responders. Among 183 sustained virologic responders, 108 showed improvement in the stage of liver fibrosis, 73 remained at the same stage, and only 2 revealed worsening. In particular, 7 of the 24 patients diagnosed at F4 fibrosis at the first biopsy were found to be at F2 and 4 others, at F3, indicating that cirrhosis was indeed resolved during 4 years' observation period in 46% of once cirrhotic patients. Necro-inflammatory activity showed more prominent amelioration: activity grading, which had been A0 (no inflammation) in none, A1 (mild inflammation) in 47, A2 (moderate) in 72, and A3 (severe) in 64 at the first biopsy, became A0 in 95, A1 in 74, A2 in 12, and A3 in 2 at the second biopsy. These results clearly showed that liver fibrosis, even at the stage of cirrhosis, will regress if we can suppress necro-inflammatory activity in the liver through viral eradication. The average progression rate of liver fibrosis stage among sustained virologic responders was calculated to be - 0.28 ± 0.03 unit/year, showing definite regression. As we described above, the amelioration of hepatic inflammation and fibrosis in sustained virologic responders is associated with decreased risk of HCC, although the mechanism of HCV-related carcinogenesis nor its suppression by interferon therapy is not well understood. Virologic non-responders showed an intermediate result between the sustained responders and untreated controls, with a fibrosis progression rate of 0.02 ± 0.02 unit/year. While the fibrosis stage regressed in 57/304 (18.8%) patients, it progressed in 74/304 (24.3%) and remained at the same stage in the remaining. This observation may indicate that amelioration of hepatic inflammation during and after (in some patients) interferon administration in virologic non-responders had some beneficial effects on liver fibrosis even in spite of continued infection, as indicated by others (Poynard *et al.*, 2002).

Another possible benefit as a consequence of sustained virologic response is improvement in liver function reservoir. In fact, some western studies, while failing to show the effect of interferon therapy on HCC, did indicate that interferon therapy was effective in suppressing death due to liver failure (Niederau *et al.,* 1998). This discrepancy may reflect the difference in age of patients: HCC occurs first in older patients, while liver failure occurs first in younger patients. Either by suppressing HCC or liver failure, interferon therapy may improve life expectancy of chronic hepatitis C patients. In 2002, we analyzed the effect of interferon therapy on life expectancy among the IHIT cohorts (Yoshida *et al.,* 2002). Life expectancy was compared between the patients and sex and age-matched general population by using standardized mortality rate (SMR), defined as the ratio of the observed number of deaths to the expected number. Overall SMR among untreated chronic hepatitis C patients was 1.9 (95% confidence interval: 1.3 - 2.8), indicating that those patients were twice likely to die as compared to the sex- and age-matched general population. There were 30 cases of death among 459 untreated patients during 5.4 years' observation period, and 23 (77%) were due to liver-related causes of deaths and 7 (23%) were liver unrelated. Among the liver-related deaths, 14 were due to HCC, 8 due to liver failure, and 1 due to variceal rupture. In contrast, SMR was 0.4 (0.1 - 0.7) among 817 sustained virologic responders, where 7 deaths occurred: 1 due to HCC, 1 due to variceal rupture, and 5 due to liver-unrelated causes of death, such as malignancy other than HCC and cardiovascular diseases. No deaths due to liver failure were recorded. Thus, although HCC is the main complication of chronic hepatitis C in Japan, and interferon therapy contributed to prolonged life expectancy chiefly by suppressing HCC development, the therapy also inhibited progression to liver failure, further improving prognosis.

Antiviral therapy after treating HCC

In the previous sections, we described the natural course and treatment of chronic hepatitis C as experienced in Japan, focusing especially on its relation to HCC development. When viewing both chronic hepatitis C and HCC as in the continuum of a clinical entity, HCV infection, there are two other levels of therapeutic intervention. The first is the prevention of HCV transmission. Although effective vaccination against HCV is lacking, interferon therapy is known to be effective against acute HCV infection, inhibiting the establishment of chronicity (Omata *et al.,* 1991; Jaeckel *et al.,* 2001). In addition, infection control procedures in medical practice, and also among injecting-drug users, have helped to suppress HCV spread and should continue to do so.

On the other end of the continuum is the treatment of HCC, although we could not detail it here. In brief, there have been marked advances in diagnostic imaging, such as ultrasonography, computed tomography, and magnetic resonance imaging, for the detection of HCC. In particular, contrast-enhanced imagings have enabled us to conduct accurate differential diagnosis of liver tumors, and HCC can now be often diagnosed at early stages (Kudo, 1999). Moreover, there have also been advances in surgical and medical treatments for HCC. Partial hepatectomy can be performed safely provided that liver function is well preserved, and medical ablation can be used even in the face of moderately impaired liver function (Shiina *et al.,* 1993; Livraghi *et al.,* 1999). Consequently, we can often remove HCC lesions completely, either by surgical resection or medical ablation. However, recurrence of HCC is known to be extremely frequent after

apparently curative surgical or medical removal of the primary tumor, which is reported to be 60% - 80% at 5 years. The majority of intrahepatic recurrence appears in locations distant from the primary tumor, and it is a conspicuous characteristic of HCC recurrence that it continues to occur even after a longer interval (Adachi *et al.,* 1995; Sakon *et al.,* 2000). In this sense, HCC can rarely be cured completely. Indeed, the background liver disease remains unchanged after treatment of HCC, and the risk of *de novo* HCC is still high. Thus, liver transplantation may be an ideal option, and candidate recipients with small HCC (Mazzaferro *et al.,* 1996) are now given a priority in the current donor organ distribution system. Since liver transplantation is outside the scope of this chapter, we will not further elaborate except for mentioning the scarcity of donor organs worldwide.

Alternatively, the combination of complete removal of HCC lesions and concomitant eradication of HCV may eventually equal liver transplantation. Between 1993 and 1997, we enrolled 74 patients with HCV-related HCC after percutaneous ethanol injection therapy into a randomized controlled trial, where 49 received interferon therapy and 25 did not (Shiratori *et al.,* 2003). Eligibility criteria included complete ablation of all HCC nodules, as confirmed on contrast-enhanced computed tomography, and a low virus load, considering the limited efficacy of interferon monotherapy available then. The patients in the treatment group received interferon-alpha for up to 48 weeks, and sustained virologic response was achieved in 14 of them. Other 7 patients obtained normalization of serum aminotransferase levels. Abdominal ultrasonography and computed tomography were regularly repeated and, when recurrence was found, additional treatments were given whenever possible. The end points were HCC recurrence and death. The cumulative incidence rate of HCC recurrence was 24%, 76%, and 92% at 1, 3, and 5 years, respectively, in the control group and 24%, 69%, and 80% in the interferon-treated group. The difference between the groups, as a whole, was not statistically significant, although the cumulative incidence curves appeared to diverge with time. The rates of second or third recurrence were lower in the interferon group. The cumulative survival rate in the interferon group was 68% at 5 years and 53% at 7 years, while in the untreated group it was 48% and 23%, respectively. In addition, the cumulative survival rate among the sustained virologic responders was further better, 78% at 5 years and 68% at 7 years. Thus, interferon therapy after treating primary HCC was beneficial in prolonging survival especially in sustained virologic responders. Interferon therapy after surgical resection of HCC was also reported to reduce HCC recurrence (Kubo *et al.,* 2001). Admittedly, these studies were limited by low efficacy of conventional interferon therapy. However, more effective antiviral protocols are available today, and larger clinical studies with updated antiviral protocol would reveal the importance of antiviral therapy after treating HCC.

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