ABSTRACT

Background and Aims: Treatment strategies for hepatocellular carcinoma have been advanced. The aim of this study was to compare the change of the prognosis between hepatitis B-related hepatocellular carcinoma (B-HCC) and hepatitis C-related hepatocellular carcinoma (C-HCC) in the last two decade.

Methods: We enrolled 166 B-HCC patients who underwent percutaneous ablation between 1990 and 2009. Patients were divided into three groups according to the treatment time period: 1990-1995 (cohort 1, n=19), 1996-2002 (cohort 2, n=49), 2003-2009 (cohort 3, n=98). We enrolled 1,219 C-HCC patients who underwent percutaneous ablation during the same period (n=190, 413 and 616, respectively.). Interferon and nucleos(t)ide analog use was investigated. Prognosis was evaluated for each cohort using the Kaplan-Meier method and a multivariate Cox proportional hazard regression model.

Results: Two (11%), twenty-four (49%) and eighty (82%) B-HCC patients received nucleos(t)ide analogs during the follow-up period in cohorts 1-3, respectively. Among them 1, 18, and 62 patients achieved viral remission, respectively. Thirty-four (18%), thirty-five (8%), and eighty-four (14%) C-HCC patients received interferon therapy, respectively. The 5-year B-HCC ($p<0.001$) survival rates were 52.6, 61.1, and 81.6% for cohorts 1-3, respectively. Whereas, the survival rates were 55.6, 58.8, and 61.1% for C-HCC ($p=0.12$), respectively. The B-HCC prognosis improved dramatically (hazard ratio [HR] of 0.30 for cohort 3 vs. 1; 95% CI, 0.16-0.58; $p<0.001$) over time, whereas the prognosis of C-HCC improved moderately (HR 0.75; 95% CI, 0.61-0.93; $p=0.01$).

Conclusions: The prognosis of B-HCC has improved dramatically over time, whereas that of C-HCC has improved moderately.

Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide, and is the leading cause of cancer death [1]. HCC usually develops in patients with chronic liver diseases, often related to infection with hepatitis B or C virus [2-4]. Close surveillance of high-risk patients with advanced diagnostic modalities has increased the rate of early cancer detection and potentially curative treatments [5, 6]. Even after locally curative treatments, HCC frequently recurs due to hepatocarcinogenesis in the remaining liver tissue and intrahepatic cancer spread [7, 8]. In many cases, liver function deteriorates due to chronic liver disease progression and repeated treatments. Liver transplantation can treat HCC and liver dysfunction [9], but it is often unfeasible due to the shortage of donor organs, and it is not a realistic option for patients >70 years old [10, 11].

To improve HCC prognosis in viral hepatitis patients, antiviral therapy is administered following curative treatment. It has been reported that nucleos(t)ide analogues (NA) in hepatitis B-related HCC (B-HCC) and interferon (IFN)-based therapy in hepatitis C-related HCC (C-HCC) had beneficial effects in terms of preventing recurrence and preserving liver function [12-14]. However, these trials enrolled only selected patients with specific conditions. It is not well documented whether the prognosis outside of clinical trials actually improved following radical percutaneous therapy.

We evaluated the effects on the prognosis of HCC patients following radical percutaneous therapy in the past two decades with a focus on antiviral therapy in B-HCC and C-HCC.

Materials and Methods

Patients

This retrospective study was conducted according to the ethical guidelines for epidemiological research designed by the Japanese Ministry of Education, Culture, Sports, Science, and Technology and the Ministry of Health, Labor, and Welfare. The study design was included in a comprehensive protocol for retrospective studies at the University of Tokyo Hospital, Department of Gastroenterology, and was approved by the University of Tokyo Medical Research Center Ethics Committee (approval number, 2058).

Between 1990 and 2009, a total of 1,908 patients with treatment-naïve HCC were admitted to the Department of Gastroenterology at the University of Tokyo Hospital. All patients were registered in a prospectively collected computerized database, and the study was based on data until the end of December 2012. Among these patients, 1,596 were initially treated for primary HCC with radical percutaneous tumor ablation (PTA) using either percutaneous ethanol injection therapy (PEIT), percutaneous microwave coagulation therapy (PMCT), or radiofrequency ablation (RFA). Of these patients, 1,385 (B-HCC/ C-HCC =166/1219) were positive for either hepatitis B surface (HBs) antigen or HCV antibody. Those positive for both were excluded from the study. Patients were divided into three groups according to the initial treatment year: 1990-1995 (cohort 1), 1996-2002 (cohort 2), and 2003-2009 (cohort 3).

Inclusion criteria for PTA were as follows: (1) surgical resection was not indicated or patients preferred nonsurgical therapy; (2) serum total bilirubin concentration < 3 mg/dL; (3) platelet count $\geq 50\times10^3$ /μl for RFA or $\geq 40\times10^3$ /μl for PEIT and PMCT; (4) prothrombin activity ≥ 50% for RFA and PMCT or ≥ 35% for PEIT. Exclusion criteria were as follows: (1) presence of vascular invasion or extrahepatic metastasis; (2) tumor not visualized ultrasonographically or not accessible percutaneously; (3) refractory ascites; (4) past history

of choledochojejunostomy or sphincterotomy in cases of PMCT and RFA; (5) tumor and gastrointestinal tract adhesion in cases of PMCT and RFA. In general, we performed PTA on Child-Pugh class A or B patients with a single tumor ≤ 5 cm in diameter or three or fewer tumors ≤ 3 cm in diameter. In more severe cases, we performed PTA on patients for a possible cure or for prolongation of life [15].

Diagnosis of HCC

HCC was diagnosed by dynamic CT or MRI with hyperattenuation in the arterial phase and washout in the late phase considered diagnostic [16]. When the diagnosis of HCC was not definite on CT or MRI, ultrasound-guided tumor biopsy was performed and a pathological diagnosis was made based on the Edmondson-Steiner criteria [17].

Follow-up

To detect recurrent HCC in the early stages, serum α-fetoprotein (AFP), lectin-reactive AFP, and des-γ-carboxy-prothrombin (DCP) levels were measured monthly, and CT or MRI and ultrasonography was performed every four months. Chest CT or bone scintigraphy was performed if extrahepatic metastasis was suspected. PTA was used for recurrent HCC treatment if the patient met the indication criteria. The choice of PTA modalities depended on the time period: PEIT was the only modality used before 1994, PMCT was used between 1995 and 1998, and RFA was applied after 1999 and remains the principal treatment. If multiple recurrent nodules were not treatable with PTA, transarterial chemoembolization (TACE) was performed.

Interferon therapy

IFN therapy was considered after curative treatment for C-HCC when patients met the following criteria: (1) HCC was well controlled with percutaneous therapy; (2) positive serum HCV-RNA (3) a platelet count above 75,000 /μl; (4) Child-Pugh classification A or B; (5) the patient was younger than 75 years old, and (6) no severe comorbidities were present such as cardiovascular disease or uncontrolled diabetes. IFN therapy was performed on patients who agreed to treatment after being fully informed of benefits and side effects. HCV-RNA was quantitatively measured with the Amplicore HCV-RNA Monitor Kit Version 2.0 (Roche Diagnostics Systems, Indianapolis, IN, USA) or the COBAS TaqMan HCV auto (Roche Diagnostics Systems, Indianapolis, IN, USA). HCV-RNA seronegativity was qualitatively confirmed with the Amplicore HCV-RNA Monitor Kit- version 2.0 or the COBAS TaqMan HCV auto (Roche Diagnostics Systems, Indianapolis, IN, USA). Sustained virologic response (SVR) was defined as undetectable HCV-RNA levels for more than 6 months after cessation of IFN therapy. Interferon therapy regimens included: interferon monotherapy, interferon plus ribavirin, peginterferon monotherapy, and peginterferon plus ribavirin.

Nucleos(t)ide analogue (NA) therapy

NA was administered to patients without advanced liver fibrosis if they had both elevated alanine aminotransferase (ALT) levels (≥31 IU/L) and elevated HBV DNA levels (≥4 log copies/mL). It was used in advanced fibrosis patients with elevated HBV-DNA levels (≥3 log copies/mL). The HBV DNA serum levels were quantified by a transcription mediated amplification (TMA) assay which can quantify 3.7–8.7 log copies/mL, a COBAS Amplicor HBV Monitor Test (Roche Diagnostic) which can quantify 2.6–7.6 log copies/mL, or a COBAS TaqMan HBV Test v2.0 (Roche Diagnostics) which can quantify 2.1–9.0 log

copies/mL. Virologic responses were defined as follows: remission when HBV-DNA remained undetectable throughout therapy, breakthrough when there was a ≥1 HBV-DNA log copy increase from a nadir or redetection of serum HBV DNA at levels at least tenfold the lower detection limit of the assay after achieving undetectable levels, and no response when HBV DNA was always detectable. NA therapy was initiated with entecavir (ETV) or, when ETV was not yet available, lamivudine (LAM). When viral breakthrough or no response was suspected, adefovir (ADV) was administered in addition to LAM or ETV. In our analysis, only responses to the initial therapy were considered.

Statistical analysis

Data are presented as means and standard deviations or as medians and interquartile ranges (IQR) for quantitative variables. Qualitative variables are given as numbers and percentages. Statistical analysis of differences between B-HCC and C-HCC was conducted using Student's *t*-test or the Mann–Whitney U test for continuous variables, and the chi-square test for categorical variables. The Jonckheere–Terpstra and the Cochran–Armitage trend tests for continuous and categorical variables, respectively, were used to evaluate the relevance of trends between cohorts.

Survival time was defined as the interval between the first PTA and death or the last visit to outpatient clinic up to December 31, 2012. Survival curves were drawn by the Kaplan–Meier method and compared using the log-rank test. Prognostic relevance for treatment cohorts was analyzed in each virus group using multivariate Cox proportional hazard regression models adjusted for baseline variables that were significant in the univariate analyses. Statistical analyses were performed using R 2.13.0 (http://www.R-project.org). All tests for differences were two-tailed, and a p value less than 0.05 was considered to indicate a significant difference.

Results

Patient profiles

Baseline characteristics from initial presentation are shown in Table 1. C-HCC patients were on average 8 years older than B-HCC patients. The proportion of males was higher in B-HCC patients (78 vs. 62%, $p<0.001$). C-HCC patients had lower serum albumin concentrations, higher ALT levels, lower platelet counts, and the proportion of Child-Pugh class A was lower in C-HCC patients (80 vs. 69%, $p=0.005$). B-HCC patients had higher DCP levels and the mean tumor size tended to be larger (26.5 vs. 24.7 mm, $p=0.08$). There was no significant difference in the number of tumors between the B-HCC and C-HCC groups.

Patients were divided into three groups based on the year of the initial treatment, and 209, 462, and 714 patients belonged to cohorts 1-3, respectively. Baseline characteristics of B-HCC and C-HCC patients stratified by cohorts are shown in Table 1. The mean age increased for both B-HCC and C-HCC, and the proportion of male patients decreased for C-HCC in more recent cohorts. ALT levels decreased, platelet counts increased, and the proportion of Child-Pugh class A patients increased in later cohorts for C-HCC, but not among B-HCC patients. The mean tumor size decreased, but there were no significant differences in AFP levels and tumors among the cohorts for both B-HCC and C-HCC. After the introduction of RFA, there was a noted transition from PEIT to RFA during the study period.

Antiviral effect

The proportion of B-HCC patients treated with NA during the follow up period increased in all cohorts from 11% in cohort 1 to 82% in cohort 3 ($p<0.001$). A total of 27 patients (one in cohort 2 and 26 in cohort 3) started NA therapy prior to HCC diagnosis, and 79 patients began NA therapy during HCC treatment. The median (IQR) intervals between HCC

treatment and NA therapy initiation were 5.45 (5.45–15.1), 2.63 (1.39–5.99), and 0.91 years (0.06–1.58) in cohorts 1-3, respectively. Virologic remission was achieved in 1 (50%), 18 (75%), and 62 (78%) patients in cohorts 1-3, respectively. Viral breakthrough was observed in 1 (25%), 6 (25%), and 18 (23%) patients, respectively. Rescue therapy (LAM and ADV in 22 patients, ETV monotherapy in 2 patients) was initiated, and 22 patients (92%) achieved undetectable HBV DNA levels (<2.6 log copies/ml).

The proportion of C-HCC patients who received IFN therapy during HCC treatment remained consistently low: 34 (18%), 35 (8%), and 84 (14%) patients in cohorts 1-3, respectively. SVR was achieved in 13 (38%), 13 (37%), and 31 (37%) patients. The median (IQR) intervals between initial HCC treatment and IFN therapy in cohorts 1–3 were 0.32 (0.10–1.48), 2.20 (0.53–3.91), and 0.69 years (0.30–1.47), respectively.

Prognosis

Of the 1,385 patients (B-HCC/C-HCC=166/1219) in the current study, 868 (71/797) died during the observation period and 83 (6.0%) were lost to follow up. The cause of death included: tumor progression in 475 (49/426), hepatic failure in 205 (12/193), and unrelated causes in 188 (10/178), as shown in Table 2. Deaths due to hepatic failure caused by bile duct injury following RFA were included: one patient in cohort 3 with B-HCC and two patients in cohort 3 with C-HCC. Death in B-HCC patients was mainly from tumor progression (p=0.02). More C-HCC patients succumbed to unrelated liver conditions, and the proportion of liver-unrelated deaths in C-HCC patients tended to increase over time (p=0.09). The 5-year survival rates of B-HCC patients in cohorts 1–3 were 52.6, 61.1, and 81.6%, respectively (Figure 1). The 5-year survival rates of C-HCC patients in cohorts 1-3 were 55.6, 58.8, and 61.1% (Figure 2). B-HCC patient survival improved significantly over time (p<0.001), whereas C-HCC survival did not (p=0.12).

Predictors of survival

The factors of "antiviral therapy" and "initial treatment modality" were strongly correlated with cohorts. The two confounding factors were excluded from univariate and multivariate analysis in order to examine the prognostic improvement of HCC over time.

In the univariate analysis, the following factors were significantly associated with a poorer prognosis: lower platelet count, higher DCP levels, poorer Child-Pugh class, larger tumor size, number of tumors, and earlier cohort groups in B-HCC patients (Table 3). Older age, lower platelet count, higher AFP and DCP levels, poorer Child-Pugh class, larger tumor size, and number of tumors were associated with a poorer prognosis for C-HCC (Table 4). In the multivariate analysis, the prognosis for B-HCC, adjusted for clinical factors significant in the univariate analysis, improved dramatically with time (hazard ratio [HR] of cohort 3 vs. cohort 1: 0.30; 95% CI, 0.16–0.58; $p<0.001$). C-HCC showed moderate improvement (HR of cohort 3 vs. cohort1: 0.75; 95% CI, 0.61–0.93; $p=0.01$).

Discussion

The current study demonstrated that the prognosis of B-HCC has improved dramatically with time, whereas that of C-HCC showed only moderate improvement. As for B-HCC patients, the potential mechanism behind this drastic improvement may involve several factors. First, the tumor size at initial diagnosis decreased, likely due to advances in imaging modalities for surveillance. Second, the proportion of patients initially treated with RFA increased. We and other researchers reported that RFA provides better local HCC control than PEIT [18-20], and the introduction of RFA might have improved survival. Third, NA therapy could maintain liver function during the clinical course and facilitated repeated treatment for recurrent tumors [21-23]. Of special note is the feasibility of NA therapy, which can be introduced in decompensated patients to improve liver function [24-26]. Even patients with viral breakthrough were almost completely controlled by the addition of NAs. In the current study, the number of deaths due to liver failure did not decrease significantly (Table 2). This could be because the total mortality was low. Among the four patients that died from liver failure in cohort 3, two patients rejected NA therapy despite its indication. The other patient developed liver failure in spite of NA therapy because of bile duct injury following RFA [27]. Another patient died from liver failure with pleural effusion.

The improvement in C-HCC prognosis was moderate. C-HCC patients could also have benefited from the aforementioned imaging and therapeutic advances. Alternatively, C-HCC patient age strongly affected survival. In Japan, the majority of C-CH patients acquired the virus in the 1950s and 1960s, and new infections have been extremely rare since 1990 [28]. Therefore, C-CH and C-HCC patients in Japan are of advanced age [29]. The 5.8-year difference in mean ages between cohorts 1 and 3 corresponds to a 7.3% decline in the 5-year survival rate under the assumption of a hazard ratio of 1.04 per year and 60% of the baseline

survival rate. These older patients were more likely to have liver-unrelated mortality than younger patients in cohorts 1 and 2 (Table 2).

The difference in antiviral therapy feasibility may explain the difference in the survival improvement in the two groups. Compared to NAs, which can be administered even to B-HCC patients with impaired hepatic function without serious adverse effects, IFN-based therapies are associated with a higher adverse effect rate and a lower SVR rate, especially with advanced liver fibrosis. Moreover, SVR rates decreased in older patients [30]. Several studies have reported the survival benefits of IFN therapy following HCC treatment [12, 31-33]. Five year survival rates of interferon groups were 68-91 % [31, 33]. In this study five year survival rate of C-HCC patients treated with interferon based therapy during HCC treatment was actually 87.1% (95% CI; 81.9-92.7) (data not shown).But the indication seems to be fairly limited in daily practice, especially in those patients for whom hepatic resection was not indicated because of impaired liver function or medical comorbidities. In this study, the proportion of C-HCC patients who received IFN therapy after HCC treatment remained low (~13% in all cohorts; the proportion who achieved SVR was even lower). Safer and more effective HCV regimens may improve the prognosis of C-HCC [34-36]. A previous study also revealed the improved prognosis of B-HCC over time. However that study included patients treated with surgery, ablation therapies and TACE. In this study we limited patients initially treated with ablation therapies, which could reduce the influence of the difference of treatment modalities and could focus the effect of antiviral therapies [37].

The current study had a number of limitations. First, because this was not a controlled study, we could not identify the exact cause of the improved prognosis. Second, because our hospital is a tertiary care center and the study population consisted of patients with early tumor stages, the results may have been subject to selection bias. The proportion of patients diagnosed with HCC during close surveillance in our hospital like a tertiary care

institution was lower for B-HCC than C-HCC (26 vs. 35%, p=0.03) (data not shown), which might result in a larger tumor size with B-HCC on initial presentation. Third, the observation period for cohort 3 was relatively short, which could be associated with insufficient statistical precision.

In conclusion, the prognosis of B-HCC has improved dramatically over time, whereas that of C-HCC has improved moderately.

References

1 Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer. 2010 Dec 15;127: 2893-917.
2 Simonetti RG, Camma C, Fiorello F, et al. Hepatitis C virus infection as a risk factor for hepatocellular carcinoma in patients with cirrhosis. A case-control study. Ann Intern Med. 1992 Jan 15;116: 97-102.
3 Tsukuma H, Hiyama T, Tanaka S, et al. Risk factors for hepatocellular carcinoma among patients with chronic liver disease. N Engl J Med. 1993 Jun 24;328: 1797-801.
4 Kiyosawa K, Umemura T, Ichijo T, et al. Hepatocellular carcinoma: recent trends in Japan. Gastroenterology. 2004 Nov;127: S17-26.
5 Zoli M, Magalotti D, Bianchi G, Gueli C, Marchesini G, Pisi E. Efficacy of a surveillance program for early detection of hepatocellular carcinoma. Cancer. 1996 Sep 1;78: 977-85.
6 Yuen MF, Cheng CC, Lauder IJ, Lam SK, Ooi CG, Lai CL. Early detection of hepatocellular carcinoma increases the chance of treatment: Hong Kong experience. Hepatology. 2000 Feb;31: 330-5.
7 Kim YS, Rhim H, Cho OK, Koh BH, Kim Y. Intrahepatic recurrence after percutaneous radiofrequency ablation of hepatocellular carcinoma: analysis of the pattern and risk factors. Eur J Radiol. 2006 Sep;59: 432-41.
8 Okuwaki Y, Nakazawa T, Shibuya A, et al. Intrahepatic distant recurrence after radiofrequency ablation for a single small hepatocellular carcinoma: risk factors and patterns. J Gastroenterol. 2008;43: 71-8.
9 Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996 Mar 14;334: 693-9.
10 Neuberger J, James O. Guidelines for selection of patients for liver transplantation in the era of donor-organ shortage. Lancet. 1999 Nov 6;354: 1636-9.
11 Wiesner RH. Patient selection in an era of donor liver shortage: current US policy. Nat Clin Pract Gastroenterol Hepatol. 2005 Jan;2: 24-30.
12 Singal AK, Freeman DH, Jr., Anand BS. Meta-analysis: interferon improves outcomes following ablation or resection of hepatocellular carcinoma. Aliment Pharmacol Ther. 2010 Oct;32: 851-8.
13 Shen YC, Hsu C, Chen LT, Cheng CC, Hu FC, Cheng AL. Adjuvant interferon therapy after curative therapy for hepatocellular carcinoma (HCC): a meta-regression approach. J Hepatol. 2010 Jun;52: 889-94.
14 Wong JS, Wong GL, Tsoi KK, et al. Meta-analysis: the efficacy of anti-viral therapy in prevention of recurrence after curative treatment of chronic hepatitis B-related hepatocellular carcinoma. Aliment Pharmacol Ther. 2011 May;33: 1104-12.
15 Teratani T, Yoshida H, Shiina S, et al. Radiofrequency ablation for hepatocellular carcinoma in so-called high-risk locations. Hepatology. 2006 May;43: 1101-8.
16 Torzilli G, Minagawa M, Takayama T, et al. Accurate preoperative evaluation of liver mass lesions without fine-needle biopsy. Hepatology. 1999 Oct;30: 889-93.
17 Edmondson HA, Steiner PE. Primary carcinoma of the liver: a study of 100 cases among 48,900 necropsies. Cancer. 1954 May;7: 462-503.
18 Shiina S, Teratani T, Obi S, et al. A randomized controlled trial of radiofrequency ablation with ethanol injection for small hepatocellular carcinoma. Gastroenterology. 2005 Jul;129: 122-30.
19 Livraghi T, Goldberg SN, Lazzaroni S, Meloni F, Solbiati L, Gazelle GS. Small hepatocellular carcinoma: treatment with radio-frequency ablation versus ethanol injection. Radiology. 1999 Mar;210: 655-61.
20 Lencioni RA, Allgaier HP, Cioni D, et al. Small hepatocellular carcinoma in cirrhosis: randomized comparison of radio-frequency thermal ablation versus percutaneous ethanol injection. Radiology. 2003 Jul;228: 235-40.
21 Liaw YF, Sung JJ, Chow WC, et al. Lamivudine for patients with chronic hepatitis B and advanced liver disease. N Engl J Med. 2004 Oct 7;351: 1521-31.
22 Dienstag JL, Goldin RD, Heathcote EJ, et al. Histological outcome during long-term lamivudine therapy. Gastroenterology. 2003 Jan;124: 105-17.

23 Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. Hepatology. 2010 Sep;52: 886-93.
24 Villeneuve JP, Condreay LD, Willems B, et al. Lamivudine treatment for decompensated cirrhosis resulting from chronic hepatitis B. Hepatology. 2000 Jan;31: 207-10.
25 Shim JH, Lee HC, Kim KM, et al. Efficacy of entecavir in treatment-naive patients with hepatitis B virus-related decompensated cirrhosis. J Hepatol. 2010 Feb;52: 176-82.
26 Kim WR, Terrault NA, Pedersen RA, et al. Trends in waiting list registration for liver transplantation for viral hepatitis in the United States. Gastroenterology. 2009 Nov;137: 1680-6.
27 Kondo Y, Shiina S, Tateishi R, et al. Intrahepatic bile duct dilatation after percutaneous radiofrequency ablation for hepatocellular carcinoma: impact on patient's prognosis. Liver Int. 2011 Feb;31: 197-205.
28 Yano K, Tamada Y, Yatsuhashi H, et al. Dynamic epidemiology of acute viral hepatitis in Japan. Intervirology. 2010;53: 70-5.
29 Yoshizawa H, Tanaka J, Miyakawa Y. National prevention of hepatocellular carcinoma in Japan based on epidemiology of hepatitis C virus infection in the general population. Intervirology. 2006;49: 7-17.
30 Oze T, Hiramatsu N, Yakushijin T, et al. Indications and limitations for aged patients with chronic hepatitis C in pegylated interferon alfa-2b plus ribavirin combination therapy. J Hepatol. 2011 Apr;54: 604-11.
31 Hagihara H, Nouso K, Kobayashi Y, et al. Effect of pegylated interferon therapy on intrahepatic recurrence after curative treatment of hepatitis C virus-related hepatocellular carcinoma. Int J Clin Oncol. 2011 Jun;16: 210-20.
32 Hung CH, Lee CM, Wang JH, Tung HD, Chen CH, Lu SN. Antiviral therapy after non-surgical tumor ablation in patients with hepatocellular carcinoma associated with hepatitis C virus. J Gastroenterol Hepatol. 2005 Oct;20: 1553-9.
33 Shiratori Y, Shiina S, Teratani T, et al. Interferon therapy after tumor ablation improves prognosis in patients with hepatocellular carcinoma associated with hepatitis C virus. Ann Intern Med. 2003 Feb 18;138: 299-306.
34 Chayama K, Takahashi S, Toyota J, et al. Dual therapy with the nonstructural protein 5A inhibitor, daclatasvir, and the nonstructural protein 3 protease inhibitor, asunaprevir, in hepatitis C virus genotype 1b-infected null responders. Hepatology. 2012 Mar;55: 742-8.
35 Poordad F, Lawitz E, Kowdley KV, et al. Exploratory study of oral combination antiviral therapy for hepatitis C. N Engl J Med. 2013 Jan 3;368: 45-53.
36 Zeuzem S, Soriano V, Asselah T, et al. Faldaprevir and deleobuvir for HCV genotype 1 infection. N Engl J Med. 2013 Aug 15;369: 630-9.
37 Nouso K, Kobayashi Y, Nakamura S, et al. Evolution of prognostic factors in hepatocellular carcinoma in Japan. Aliment Pharmacol Ther. 2010 Feb 1;31: 407-14.

Table 1. Patient Profile According to Viral Infection and Year of Treatment.

Variables	B-HCC					C-HCC				
	Total (n=166)	Cohort 1 (n=19)	Cohort 2 (n=49)	Cohort 3 (n=98)	p	Total (n=1219)	Cohort 1 (n=190)	Cohort 2 (n=413)	Cohort 3 (n=616)	p
Age (years)	59.8±9.7	52.4±8.8	60.1±9.5	61.0±9.4	0.002	68.1±8.0	63.3±8.2	67.7±7.1	69.9±7.9	<0.001
Male gender	129 (78)	17 (89)	35 (75)	77 (79)	0.71	756 (62)	137 (72)	263 (64)	356 (58)	<0.001
Albumin (g/dl)	3.8±0.5	3.7±0.6	3.7±0.5	3.9±0.5	0.02	3.6±0.5	3.5±0.5	3.6±0.4	3.6±0.5	<0.001
ALT (IU/L)	39 (27-56)	39 (35-79)	36 (27-58)	39 (26-51)	0.21	58 (38-88)	79 (53-112)	66 (48-94)	59 (43-79)	<0.001
Platelet count ($\times 10^3/\mu l$)	13.1±5.9	11.2±4.5	12.7±5.4	13.6±6.3	0.20	10.9±5.0	9.9±4.4	10.7±4.7	11.3±5.4	<0.001
AFP >100 ng/ml	39 (23)	2 (11)	13 (27)	24 (24)	0.36	254 (21)	35 (18)	99 (24)	120 (19)	0.72
DCP >100 mAU/mL*	35 (22)	0 (0)	9 (18)	26 (27)	0.01	156 (13)	16 (10)	56 (14)	84 (14)	0.25
Child–Pugh class A	133 (80)	13 (68)	39 (80)	73 (74)	0.89	843 (69)	98 (52)	289 (70)	456 (74)	<0.001
Single tumor	103 (62)	13 (68)	33 (67)	80 (82)	0.06	725 (59)	113 (59)	240 (58)	372 (60)	0.65
Tumor size (mm)	26.5±11.1	27.0±13.6	28.9±12.9	25.1±9.3	0.16	24.8±10.8	26.6±13.7	26.4±12.1	23.2±8.4	<0.001
Antiviral therapy	106 (64)	2 (11)	24 (49)	80 (82)	<0.001	153 (13)	34 (18)	35 (8)	84 (14)	0.68
Viral response	81 (76)	1 (50)	18 (75)	62 (78)	0.51	89 (37)	13 (38)	13 (37)	31 (37)	0.90
Initial treatment modality†										

PEIT	34 (20)	18 (95)	16 (33)	0 (0)	<0.001	334 (27)	184 (97)	149 (36)	1 (0.2)	<0.001
PMCT	7 (4)	1 (5)	6 (12)	0 (0)	0.02	43 (3.5)	6 (3)	37 (9)	0 (0)	<0.001
RFA	128 (77)	0 (0)	30 (61)	98 (100)	<0.001	863 (71)	0 (0)	248 (60)	615 (99.8)	<0.001

NOTE. Values are means ± SD, medians (interquartile range), or numbers (%)

* Serum DCP level was missing in 8 B-HCC patients in cohort 1 and in 22 patients in cohort 1, 6 in cohort 2, and 4 in cohort 3 with C-HCC.

† Including overlap.

AFP, α-fetoprotein; ALT, alanine transaminase; DCP, des-γ-carboxy-prothrombin; PEIT, percutaneous ethanol infection therapy; PMCT, percutaneous microwave coagulation therapy; RFA, radiofrequency ablation.

Table 2. Cause of Death.

Group (n)	Total deaths	Tumor progression (%)	Liver failure (%)	Liver-unrelated (%)
B-HCC (166)	71	49 (69.0)	12 (16.9)	10 (14.1)
Cohort 1 (19)	17	13 (76.5)	4 (23.5)	0 (0)
Cohort 2 (49)	29	18 (62.1)	4 (13.8)	7 (24.1)
Cohort 3 (98)	25	18 (72)	4 (16)	3 (12)
C-HCC (1219)	797	426 (53.5)	193 (24.2)	178 (22.3)
Cohort 1 (190)	171	90 (52.6)	51 (29.8)	30 (17.5)
Cohort 2 (413)	333	191 (57.4)	66 (19.8)	76 (22.8)
Cohort 3 (616)	293	145 (49.5)	76 (25.9)	72 (24.6)

Table 3. Univariate and Multivariate Analysis of Overall Survival for B-HCC.

Variables	Univariate		Multivariate	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Male gender	1.53 (0.80-2.92)	0.20		
Age	1.004 (0.98-1.03)	0.78		
ALT (IU/L)	1.003 (1.00-1.06)	0.11		
Platelet count (1×10^4/μl)	0.95 (0.90-0.99)	0.02	0.95 (0.90-1.00)	0.049
AFP >100 ng/ml	1.16 (0.69-1.97)	0.58		
DCP >100 mAU/mL	2.01 (1.16-3.46)	0.01	1.00 (1.00-1.001)	0.68
Child–Pugh class				
A	1		1	
B	2.55 (1.53-4.25)	<0.001	1.47 (0.78-2.77)	0.23
Tumor size (mm)	1.03 (1.01-1.05)	0.007	1.04 (1.02-1.06)	<0.001
Tumor number > 1	2.03 (1.26-3.28)	0.003	2.08 (1.22-3.55)	0.007
Cohort 1	1		1	
Cohort 2	0.56 (0.30-1.02)	0.06	0.58 (0.31-1.08)	0.09
Cohort 3	0.30 (0.16-0.56)	<0.001	0.30 (0.16-0.58)	<0.001

HR, hazard ratio; CI, confidence interval; AFP, α-fetoprotein; ALT, alanine transaminase; DCP, des-γ-carboxy-prothrombin.

Table 4. Univariate and Multivariate Analysis of Overall Survival for C-HCC.

	Univariate		Multivariate	
Variables	HR (95% CI)	*p*	HR (95% CI)	*p*
Male gender	1.02 (0.85-1.14)	0.81		
Age	1.03 (1.02-1.04)	<0.001	1.04 (1.03-1.05)	<0.001
ALT (IU/L)	1.00 (1.00-1.001)	0.35		
Platelet count ($1\times10^4/\mu l$)	0.98 (0.96-0.99)	0.001	0.98 (0.96-1.00)	0.02
AFP >100 ng/ml	1.52 (1.28-1.79)	<0.001	1.41 (1.19-1.68)	<0.001
DCP >100 mAU/mL	1.71 (1.40-2.09)	<0.001	1.31 (1.04-1.64)	0.02
Child–Pugh class				
A	1		1	
B	1.82 (1.58-2.11)	<0.001	1.69 (1.44-1.99)	<0.001
Tumor size (mm)	1.02 (1.02-1.03)	<0.001	1.02 (1.01-1.02)	<0.001
Tumor number > 1	1.12 (1.06-1.19)	<0.001	1.21 (1.05-1.39)	0.01
Cohort 1	1		1	
Cohort 2	0.86 (0.72-1.04)	0.12	0.78 (0.64-0.96)	0.02
Cohort 3	0.82 (0.67-0.99)	0.04	0.75 (0.61-0.93)	0.01

HR, hazard ratio; CI, confidence interval; AFP, α-fetoprotein; ALT, alanine transaminase; DCP, des-γ-carboxy-prothrombin.

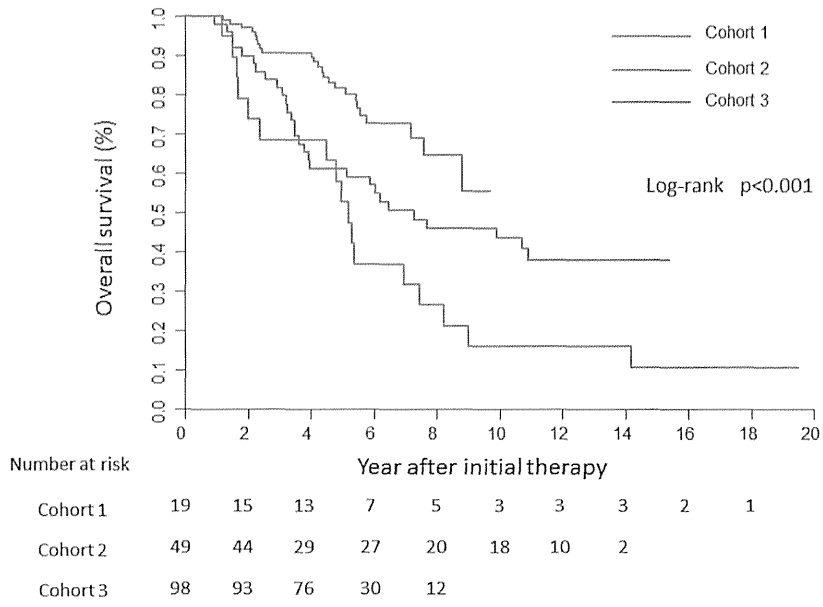

Figure 1. Overall survival in B-HCC patients according to the cohort. The survival rates at 1, 3, 5, and 7 years were 100, 68.4, 52.6 and 31.6% in cohort 1, 98.0, 81.6, 61.1 and 50.4% in cohort 2, and 100, 90.6, 81.6, and 72.7% in cohort 3, respectively.