of coagulation necrosis compared with standard RFA.[9,12] In a previous study, we used an RITA 500PA (RITA Medical Systems) and an expandable electrode (model 30). However, our procedure can be performed equally well using other RF systems.

In this study, we investigated the efficacy of balloon-occluded RFA, using a cool RF single electrode. The Cool-tip RF system is a powerful generator compared with the RITA 500PA. In fact, a necrotic area of up to 3 cm in diameter produced with a cool RF single electrode has been observed in tumors.[6] Therefore, we expected a much larger necrotic area than we achieved before to be achieved with balloon-occluded RFA using the RITA500PA and an expandable electrode (model 30). In our previous study, the greatest long-axis and short-axis dimensions of the coagulation area in balloon-occluded RFA using the RITA 500PA and an expandable electrode (model 30) were 36.6 ± 3.8 mm and 30.1 ± 6.0 mm, respectively.[12] In our current study, the greatest dimension of the area coagulated by balloon-occluded RFA using a cool RF electrode (CT-2030) was significantly larger (greatest long-axis dimension, 47.6 ± 7.8 mm; greatest short-axis dimension, 33.4 ± 7.5 mm) than that coagulated by standard RFA (greatest long-axis dimension, 35.3 ± 4.7 mm; greatest short-axis dimension, 25.9 ± 3.7 mm; $P = 0.002$ for greatest long-axis dimension; $P = 0.041$ for greatest short-axis dimension), with the same thermal ablation times. We also demonstrated that balloon-occluded RFA using another RF electrode increased the area of coagulation necrosis compared with standard RFA. We could achieve a much larger necrotic area compared with that in balloon-occluded RFA using an expandable electrode. It is also possible to perform balloon-occluded RFA using a cool RF electrode for large HCC nodules (>3 cm in diameter). In this study, nine HCC nodules (nine patients) measured more than 3 cm in diameter. The largest diameter was 53 mm. Although we required a few needle insertions (mean, 2.1), combined balloon-occluded RFA using a cool RF single electrode and angio-CT assistance[9] techniques could achieve one-session treatment for four large HCC nodules in four patients.

Balloon-occluded RFA is a simple and easy technique. However, we do not always succeed with this technique because of variant vascular anatomy or irregular shape of the hepatic artery. Therefore, we also designed RFA with balloon microcatheter occlusion of the hepatic artery (balloon-microcatheter-occluded RFA). Using the same thermal ablation times for balloon-microcatheter-occluded RFA and standard RFA, there was a significant difference in the greatest short-axis dimension (balloon-microcatheter-occluded RFA, 31.5 ± 4.6 mm; standard RFA, 25.9 ± 3.7 mm; $P = 0.022$), but not in the greatest long-axis dimension (balloon-microcatheter-occluded RFA, 38.3 ± 5.7 mm; standard RFA, 35.3 ± 4.7 mm; $P = 0.285$). We think that the coagulation necrosis obtained with balloon-microcatheter-occluded RFA is insufficient. The first reason is the small balloon size of the microcatheter. The balloon size is 4 mm in outer diameter. On the other hand, the balloon size of the 5-Fr catheter used in the balloon-occluded RFA procedure is 9 mm in outer diameter. Thus, balloon-microcatheter-occluded RFA may not prevent the cooling effect exerted by the arterial flow, compared with balloon-occluded RFA. The second reason is variant vascular anatomy. In two of the five such patients, the right hepatic artery was supplied from the superior mesenteric artery. Therefore, when the right hepatic artery was occluded by means of the balloon microcatheter, the arterial flow in the right lobe was supplied through an anastomosis. Thus, we think that a sufficient effect could not be obtained because a cooling effect remained in the tumor. Balloon-occluded RFA (or balloon-microcatheter-occluded RFA) may not be indicated for patients with separate flow in the liver. In addition, there are some disadvantages of balloon-microcatheter-occluded RFA. First, this technique is troublesome. In fact, we need to exchange the 5.0-Fr catheter for a 5.1-Fr catheter to insert the balloon microcatheter and to exchange the balloon microcatheter for an ordinary microcatheter to perform angio-CT assistance.[9] Second, we cannot inject contrast medium because of the small inner luminal diameter (0.38 mm) of the balloon microcatheter. Therefore, further development of the balloon microcatheter will be required. This is a preliminary report and we need further study with a greater number of patients.

Complications after RFA for hepatic tumors have been reported. The rate of major complications for the treatment of hepatic tumors ranged from 0% to 12.7%.[24] The rate of major complications in our treatments (balloon-occluded RFA and balloon-microcatheter-occluded RFA) was 9.1%. Because the rate of major complications was relatively high, we should limit the indications of RFA with balloon occlusion of the hepatic artery. At this time, we think that patients who have HCC in peripheral sites of the liver, with favorable liver reserve capacity, are suitable candidates for these procedures, because of the larger areas of coagulation. However, we cannot refer to adequate indications for these procedures because of the small patient population and the short follow-up periods. Further studies with more patients and longer follow-up periods are needed to investigate adequate indications.

In conclusion, balloon-occluded RFA using a cool RF single electrode is superior to standard RFA. In addition, the coagulation area obtained with balloon-occluded RFA using a cool RF single electrode is larger

than that obtained with balloon-occluded RFA using the RITA 500PA and an expandable electrode (model 30). Balloon-occluded RFA using a cool RF single electrode may be indicated for patients with large HCC nodules. Furthermore, we also reported balloon-occluded RFA using a balloon microcatheter (balloon-microcatheter-occluded RFA) for the treatment of HCC. Although further development of the balloon microcatheter is required, this technique may have the potential to become widespread.

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Report of the 16th follow-up survey of primary liver cancer

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Abstract

In the 16th nationwide follow-up survey of primary liver cancer, 19,920 patients were newly registered as patients with primary liver cancer at 795 medical institutions in Japan over a period of 2 years (from January 1, 2000 to December 31, 2001). Of these patients, 94.5% had hepatocellular carcinoma (HCC) and 3.6% had intrahepatic cholangiocarcinoma (ICC). In addition, 21,268 follow-up patients were registered, and a valid response rate of 75.6% was obtained in these follow-up patients. In this study, epidemiological and clinicopathological factors, diagnosis and treatment were investigated in patients who were newly registered in the 16th follow-up survey. As additional statistics, the cumulative survival rates of newly registered patients in the 11th to 16th follow-up surveys were calculated for each histological type (HCC, ICC and combined HCC and ICC) by background factor(s) and treatment, respectively. Furthermore, in patients with HCC, the cumulative survival rates were calculated for several types of treatment (hepatectomy, local ablation therapy and transcatheter arterial chemoembolization). It is anticipated that this follow-up survey will contribute to future research and medical practice for primary liver cancer.

Keywords: Follow-up survey; Hepatocellular carcinoma; Intrahepatic cholangiocarcinoma; Combined hepatic carcinoma; Cumulative survival rate

1. Introduction

Since 1965, the Liver Cancer Study Group of Japan (LCSGJ) has conducted 15 nationwide follow-up surveys of primary liver cancer in patients in member hospitals and cooperative institutions in Japan, to promote research and medical practice in the treatment of liver cancer [1–9]. The 16th Nationwide Follow-up Survey of Primary Liver Cancer was conducted over a 2-year period (from January 1, 2000 to December 31, 2001), and 19,920 patients with primary liver cancer were newly registered from 795 institutions. Of these patients, 94.5% had hepatocellular carcinoma (HCC) and 3.6% had intrahepatic cholangiocarcinoma (ICC). In addition, 21,268 follow-up patients were registered and a valid response rate of 75.6% was obtained in these follow-up patients. The newly registered patients were investigated using items related to epidemiological and clinicopathological factors, diagnosis and treatment. Furthermore, the cumulative survival rates of newly registered patients in the 11th to 16th follow-up surveys were calculated for histological type, background factors and treatment.

2. Materials and methods

2.1.1. Basic statistics

The subjects were 19,920 patients with primary liver cancer who underwent treatment or autopsy during a 2-year period (from January 1, 2000 to December 31, 2001) in 795 institutions in Japan. Doctors in the institutions completed a form developed by the Follow-up Survey Committee of

Abbreviations: HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; combined HCC and ICC, combined hepatocellular and cholangiocarcinoma; AFP, alpha-fetoprotein; PIVKA-II, protein induced by Vitamin K absence or antagonist-II

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Table 1
Classification of primary liver cancer

Diagnosis	Male (n=14226)	Female (n=5694)	Total (n=19920)
HCC	13557	5270	18827 (94.51)
ICC	431	293	724 (3.63)
Combined	86	33	119 (0.60)
Cystadenocarcinoma	24	19	43 (0.22)
Hepatoblastoma	13	14	27 (0.14)
Sarcoma	6	5	11 (0.06)
Others	109	60	169 (0.85)

HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; combined: combined hepatocellular and cholangiocarcinoma. Values in parentheses are in percent.

the LCSGJ (Chairperson: Yoshio Yamaoka). Table 1 shows a breakdown of the cancer by histological type. When there was an inconsistency between the clinical, pathological and autopsy diagnoses, the autopsy diagnosis and the pathological diagnosis were given first and second priority, respectively. As far as possible, the data are shown as raw data prior to processing. The results in the tables are categorized into HCC, ICC and combined HCC and ICC, for which more than 100 new cases were registered in this follow-up survey. The abbreviations in the tables conform to the "The General Rules for the Clinical and Pathological Study of Primary Liver Cancer", 2nd English ed. [10].

2.1.2. Additional statistics

The cumulative survival rates of newly registered patients in the 11th to 16th follow-up surveys whose final prognosis was determined to be survival or death (excluding patients with unknown outcomes) were calculated for each histological type (HCC, ICC and combined HCC and ICC) by background factors and treatment. Furthermore, the cumulative survival rates of patients with HCC were calculated for each treatment (hepatectomy, local ablation therapy and transcatheter arterial embolization).

3. Results

3.1.1. Causes of death during the study period

In patients with HCC, the death rate due to cancer was 57.2% and death rates due to hepatic failure, gastrointestinal bleeding and rupture of esophagogastric varices were 26.2, 2.7 and 4.9%, respectively. Of the patients who did not survive, 48 (1.6%) died within 30 days after surgery. These represented 0.9% of the 5374 patients who underwent surgery. In patients with ICC, the death rates due to cancer and hepatic failure were 84.7 and 11.3%, respectively. In patients with combined HCC and ICC, the death rate due to cancer was 75.0% (Table 2).

Table 2
Causes of death

	HCC	ICC	Combined
Alive	15256	422	69
Total deaths of between 2000 and 2001	3048	275	44
Cancer death	1744 (57.2)	233 (84.7)	33 (75.0)
Hepatic failure	798 (26.2)	31 (11.3)	9 (20.5)
Gastrointestinal bleeding	82 (2.7)	4 (1.5)	0 (0.0)
Rupture of esophageal varices	150 (4.9)	1 (0.4)	0 (0.0)
Rupture of tumor	226 (7.4)	2 (0.7)	2 (4.5)
Operative death	48 (1.6)	4 (1.5)	0 (0.0)
Other causes	311	17	3
Unknown	128	5	3

HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; combined: combined hepatocellular and cholangiocarcinoma. Values in parentheses are in percent.

3.1.2. Past history

Of the patients with HCC, 77.4 and 62.6% had a past history of chronic hepatitis and liver cirrhosis, respectively, while 19.0 and 9.9% of ICC patients and 58.3 and 29.9% of patients with combined HCC and ICC had this history, respectively. Of patients with HCC, 14.2% of patients with concomitant chronic hepatitis were treated with interferon therapy and 30.1 and 23.5% of the HCC patients had a past history of blood transfusion and habits of alcohol intake, respectively.

3.1.3. Clinical diagnosis

Clinical diagnosis of primary liver cancer in patients with HCC was made at an average age of 64.8 years in males and 68.5 years in females. For patients with ICC, the corresponding average ages were 65.2 years in males and 67.9 years in females. The average age has increased in every survey. The male to female ratios for the HCC and ICC patients were 2.84 and 1.50, respectively.

In patients with HCC, the level of liver injury at the time of diagnosis based on the liver damage classification of the LCSGJ was class A, B and C in 58.1, 32.9 and 9.0% of patients, respectively, whereas 69.3, 23.3 and 7.4% of HCC patients were in Child–Pugh Class A, B and C categories, respectively (Table 3). In this study, factors related to the criteria for LCSGJ liver damage classification and the Child–Pugh Score were included in the investigation items. The concordance rate for the LCSGJ liver damage classification reported from institutions and that estimated from the investigation items was 84.0% and the equivalent concordance rate for the Child–Pugh Class was 87.2%.

Of the HCC patients, 34.5, 36.7 and 28.8% had serum alpha-fetoprotein (AFP) levels of <15, 15–199 and 200 ng/mL or more, respectively, while 38.4, 14.1 and 47.5% of patients with HCC had a protein induced by Vitamin K absence or antagonist-II (PIVKA-II) level of <40, 40–99

Table 3
Clinical profile

	HCC	ICC	Combined
Diagnosis	$n=37222$	$n=1381$	$n=220$
Computed tomography	13609 (36.6)	526 (38.1)	86 (39.1)
Magnetic resonance imaging	3164 (8.5)	141 (10.2)	18 (8.2)
Ultrasonogrphy	10956 (29.4)	394 (28.5)	57 (25.9)
Selective angiography	7344 (19.7)	153 (11.1)	39 (17.7)
Histopathological finding	1837 (4.9)	113 (8.2)	17 (7.7)
Others	312 (0.8)	54 (3.9)	3 (1.4)
Encephalopathy	$n=17827$	$n=690$	$n=110$
None	16938 (95.0)	684 (99.1)	109 (99.1)
Mild	658 (3.7)	2 (0.3)	1 (0.9)
Coma occasionally	231 (1.3)	4 (0.6)	0 (0.0)
Acites	$n=17981$	$n=688$	$n=107$
Absent	15494 (86.2)	618 (89.8)	103 (96.3)
Slight	1511 (8.4)	26 (3.8)	1 (0.9)
Moderate	976 (5.4)	44 (6.4)	3 (2.8)
Serum bilirubin (mg/mL)	$n=18007$	$n=674$	$n=107$
<2.0	16070 (89.2)	546 (81.0)	102 (95.3)
2.0~3.0	1149 (6.4)	26 (3.9)	1 (0.9)
≧3.1	788 (4.4)	102 (15.1)	4 (3.7)
Serum albumin (g/dl)	$n=17642$	$n=650$	$n=106$
<2.8	1472 (8.3)	44 (6.8)	3 (2.8)
2.8–2.9	966 (5.5)	20 (3.1)	6 (5.7)
3.0–3.5	5180 (29.4)	143 (22.0)	21 (19.8)
>3.5	10024 (56.8)	443 (68.2)	76 (71.7)
ICG R_{15} (%)	$n=12460$	$n=409$	$n=81$
≦14	4112 (33.0)	267 (65.3)	40 (49.4)
15–24	3693 (29.6)	86 (21.0)	27 (33.3)
25–40	3043 (24.4)	34 (8.3)	12 (14.8)
>40	1612 (12.9)	22 (5.4)	2 (2.5)
Prothrombin activity (%)	$n=16139$	$n=578$	$n=99$
<40	326 (2.0)	11 (1.9)	0 (0.0)
40–49	426 (2.6)	8 (1.4)	3 (3.0)
50–70	3753 (23.3)	56 (9.7)	25 (25.3)
71–80	3403 (21.1)	89 (15.4)	18 (18.2)
>80	8231 (51.0)	414 (71.6)	53 (53.5)
Platelet count ($\times 10^4/mm^3$)	$n=17927$	$n=666$	$n=105$
<3.0	164 (0.9)	3 (0.5)	1 (1.0)
3.0–4.9	1037 (5.8)	7 (1.1)	2 (1.9)
5.0–9.9	6046 (33.7)	44 (6.6)	15 (14.3)
10.0–14.9	5320 (29.7)	111 (16.7)	38 (36.2)
15.0–19.9	2906 (16.2)	152 (22.8)	27 (25.7)
≧20.0	2454 (13.7)	349 (52.4)	22 (21.0)
Liver damage classificaiton by LCSGJ	$n=15682$	$n=553$	$n=95$
A	9117 (58.1)	439 (79.4)	67 (70.5)
B	5161 (32.9)	82 (14.8)	27 (28.4)
C	1404 (9.0)	32 (5.8)	1 (1.1)
Child–Pugh classification	$n=16840$	$n=577$	$n=99$
A	11676 (69.3)	465 (80.6)	82 (82.8)
B	3920 (23.3)	81 (14.0)	16 (16.2)
C	1244 (7.4)	31 (5.4)	1 (1.0)
AFP (ng/mL)	$n=17538$	$n=500$	$n=105$
<15	6042 (34.5)	426 (85.2)	49 (46.7)
≦199	6437 (36.7)	52 (10.4)	31 (29.5)
≦399	1103 (6.3)	4 (0.8)	6 (5.7)
≦999	1076 (6.1)	8 (1.6)	9 (8.6)
≦9999	1654 (9.4)	7 (1.4)	3 (2.9)
≦99999	851 (4.9)	3 (0.6)	7 (6.7)
≧100000	375 (2.1)	0 (0.0)	0 (0.0)
AFP-L_3 (%)	$n=5094$	$n=72$	$n=26$
ND	1729 (33.9)	48 (66.7)	4 (15.4)
<5.0	1090 (21.4)	9 (12.5)	6 (23.1)
≦9.9	440 (8.6)	1 (1.4)	1 (3.8)
≦14.9	280 (5.5)	0 (0.0)	1 (3.8)
≦19.9	139 (2.7)	3 (4.2)	1 (3.8)
≧20.0	1416 (27.8)	11 (15.3)	13 (50.0)
PIVKA-II (mAU/mL)	$n=15377$	$n=333$	$n=89$
<40	5908 (38.4)	266 (79.9)	40 (44.9)
≦99	2165 (14.1)	15 (4.5)	20 (22.5)
≦299	1954 (12.7)	18 (5.4)	15 (16.9)
≦499	765 (5.0)	7 (2.1)	2 (2.2)
≦999	947 (6.2)	6 (1.8)	3 (3.4)
≦2999	1202 (7.8)	12 (3.6)	2 (2.2)
≦9999	942 (6.1)	5 (1.5)	5 (5.6)
≧10000	1494 (9.7)	4	2 (2.2)
CEA (ng/mL)	$n=6990$	$n=606$	$n=86$
<2.5	3007 (43.0)	205 (33.8)	34 (39.5)
≦4.9	2414 (34.5)	154 (25.4)	23 (26.7)
≦9.9	1269 (18.2)	78 (12.9)	17 (19.8)
≦19.9	210 (3.0)	54 (8.9)	6 (7.0)
≦49.9	59 (0.8)	47 (7.8)	1 (1.2)
≦99.9	13 (0.2)	23 (3.8)	1 (1.2)
≧100	18 (0.3)	45 (7.4)	4 (4.7)
CA 19-9 (U/mL)	$n=5173$	$n=600$	$n=77$
<37	3138 (60.7)	164 (27.3)	31 (40.3)
≦99	1410 (27.3)	96 (16.0)	19 (24.7)
≦299	482 (9.3)	87 (14.5)	12 (15.6)
≦999	106 (2.0)	68 (11.3)	6 (7.8)
≦2999	16 (0.3)	67 (11.2)	5 (6.5)
≦9999	11 (0.2)	46 (7.7)	3 (3.9)
≧10000	10 (0.2)	72 (12.0)	1 (1.3)

HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; combined: combined hepatocellular and cholangiocarcinoma; ICG R_{15}: indocyanine green retention rate at 15 min; AFP: alpha-fetoprotein; AFP-L_3: lectin-reactive alpha-fetoprotein; PIVKA-II: protein induced by Vitamin K absence-II; CEA: carcinoembrionic antigen; CA 19-9: carbohydrate antigen 19-9. Values in parentheses are in percent.

and 100 mAU/mL or more, respectively. Serum levels of lectin-reactive alpha-fetoprotein (AFP-L3) fraction, a newly determined item in this study, was recorded in approximately 29% of patients whose AFP was determined and 36% of the patients had an AFP-L3 fraction of 10% or more. In patients with ICC, 40.8% had a carcinoembryonic antigen level of 5.0 ng/mL or more and 72.7% had a carbohydrate antigen 19-9 level of 37 U/mL or more (Table 3).

In tests related to hepatitis B virus, the percentages of hepatitis B virus surface antigen-positive patients were 15.5, 6.1 and 18.4% in patients with HCC, ICC and combined HCC and ICC, respectively, and the percentages of anti-hepatitis C virus antibody-positive patients were 71.8, 20.9 and 53.8%, respectively (Table 4).

Regarding the maximum tumor size, which was determined using diagnostic imaging, 32.3% of the patients with HCC had tumors of size 2 cm or less and in 78.2% of patients,

Table 4
Hepatitis B and C virus-associated antigen and antibody

	HCC	ICC	Combined
HBsAg	$n=17959$	$n=670$	$n=103$
Negative	15156 (84.4)	629 (93.9)	84 (81.6)
Positive	2790 (15.5)	41 (6.1)	19 (18.4)
Undetermined	13 (0.1)	0 (0.0)	0 (0.0)
HBsAb	$n=6050$	$n=184$	$n=42$
Negative	4837 (80.0)	153 (83.2)	30 (71.4)
Positive	1164 (19.2)	31 (16.8)	12 (28.6)
Undetermined	49 (0.8)	0 (0.0)	0 (0.0)
HBcAb	$n=4621$	$n=120$	$n=33$
Negative	2188 (47.3)	78 (65.0)	16 (48.5)
Positive	2372 (51.3)	40 (33.3)	17 (51.5)
Undetermined	61 (1.3)	2 (1.7)	0 (0.0)
HBeAg	$n=3824$	$n=99$	$n=21$
Negative	3267 (85.4)	93 (93.9)	20 (95.2)
Positive	535 (14.0)	6 (6.1)	1 (4.8)
Undetermined	22 (0.6)	0 (0.0)	0 (0.0)
HBeAb	$n=3701$	$n=98$	$n=22$
Negative	1892 (51.1)	65 (66.3)	8 (36.4)
Positive	1717 (46.4)	32 (32.7)	14 (63.6)
Undetermined	92 (2.5)	1 (1.0)	0 (0.0)
HCVAb	$n=18216$	$n=670$	$n=106$
Negative	5121 (28.1)	527 (78.7)	49 (46.2)
Positive	13080 (71.8)	140 (20.9)	57 (53.8)
Undetermined	15 (0.1)	3 (0.4)	0 (0.0)

HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; combined: combined hepatocellular and cholangiocarcinoma. Values in parentheses are in percent.

the tumor size was 5 cm or less. The corresponding numbers in patients with ICC were 10.9 and 56.1%, respectively. Of the tumors, 56.8 and 74.7% were solitary in patients with HCC and ICC, respectively (Table 5). In patients with HCC, 91.7% had a tumor stain and esophagogastric varices of F2 or RC (+) or higher were found in 45.7%.

3.1.4. Main treatment

The main treatment was newly investigated in this survey. In patients with HCC, 31.3, 26.8 and 36.4% had undergone

Table 5
Tumor characteristics by imaging studies

	HCC	ICC	Combined
Tumor size by imaging studies (cm)	$n=17559$	$n=586$	$n=105$
≦1	797 (4.5)	11 (1.9)	1 (1.0)
≦2	4872 (27.7)	53 (9.0)	11 (10.5)
≦3	4273 (24.3)	94 (16.0)	22 (21.0)
≦5	3797 (21.6)	171 (29.2)	22 (21.0)
≦10	2759 (15.7)	210 (35.8)	38 (36.2)
≦15	679 (3.9)	31 (5.3)	10 (9.5)
≦20	177 (1.0)	6 (1.0)	0 (0.0)
≦25	58 (0.3)	3 (0.5)	0 (0.0)
>25	147 (0.8)	7 (1.2)	1 (1.0)

Table 5 (*Continued*)

	HCC	ICC	Combined
Number of tumors by imaging studies	$n=17981$	$n=620$	$n=108$
1	10205 (56.8)	463 (74.7)	61 (56.5)
2	3140 (17.5)	37 (6.0)	17 (15.7)
3	1526 (8.5)	16 (2.6)	7 (6.5)
4	604 (3.4)	9 (1.5)	2 (1.9)
5	257 (1.4)	6 (1.0)	3 (2.8)
≧6	2249 (12.5)	89 (14.4)	18 (16.7)
Portal vein invasion by imaging studies	$n=16466$	$n=529$	$n=101$
Vp0	14164 (86.0)	330 (62.4)	78 (77.2)
Vp1	472 (2.9)	40 (7.6)	6 (5.9)
Vp2	497 (3.0)	59 (11.2)	5 (5.0)
Vp3	871 (5.3)	81 (15.3)	7 (6.9)
Vp4	462 (2.8)	19 (3.6)	5 (5.0)
Hepatic vein invasion by imaging studies	$n=15605$	$n=488$	$n=94$
Vv0	14855 (95.2)	429 (87.9)	88 (93.6)
Vv1	255 (1.6)	19 (3.9)	3 (3.2)
Vv2	239 (1.5)	26 (5.3)	3 (3.2)
Vv3	256 (1.6)	14 (2.9)	0 (0.0)
Bile duct invasion by imaging studies	$n=15317$	$n=500$	$n=94$
B0	14897 (97.3)	265 (53.0)	84 (89.4)
B1	159 (1.0)	58 (11.6)	1 (1.1)
B2	127 (0.8)	64 (12.8)	6 (6.4)
B3	89 (0.6)	69 (13.8)	2 (2.1)
B4	45 (0.3)	44 (8.8)	1 (1.1)
Distant metastases by imaging studies			
Lung	314	34	2
Bone	249	22	1
Adrenal gland	71	2	1
Lymph node	233	102	15
Brain	24	1	0
Peritonieum	46	20	1
Others	46	9	1
Esophageal or gastric varices	$n=6109$	$n=49$	$n=20$
F1, RC(−)	3318 (54.3)	27 (55.1)	13 (65.0)
F2 or RC(+)	2385 (39.0)	21 (42.9)	7 (35.0)
Rupture	406 (6.6)	1 (2.0)	0 (0.0)

HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; combined: combined hepatocelluar and cholangiocarcinoma; Vp0: absence of invasion of (or tumor thrombus in) the portal vein; Vp1: invasion of (or tumor thrombus in) distal to the second-order branches of the portal vein, but not of the second-order branches; Vp2: invasion of (or tumor thrombus in) second-order branches of the portal vein; Vp3: invasion of (or tumor thrombus in) first-order branches of the portal vein; Vp4: invasion of (or tumor thrombus in) the main trunk of the portal vein and/or contralateral portal vein branch to the primarily involved lobe; Vv0: absence of invasion of (or tumor thrombus in) the hepaticl vein; Vv1: invasion of (or tumor thrombus in) peripheral branches of the hepatic vein; Vv2: invasion of (or tumor thrombus in) the right, middle or left hepatic vein, the inferior right hepatic vein or the short hepatic vein; Vv3: invasion of (or tumor thrombus in) the inferior vena cava; B0: absence of invasion of the bile ducts; B1: invasion of (or tumor thrombus in) the third-order or more peripheral branches of the bile duct, but not of second-order branches; B2: invasion of (or tumor thrombus in) the second-order branches of the bile duct; B3: invasion of (or tumor thrombus in) the first-order branches of the bile duct; B4: invasion of (or tumor thrombus in) the common hepatic duct. Values in parentheses are in percent.

Table 6
Main treatment

	HCC	ICC	Combined
Surgery	5304 (31.3)	346 (65.7)	71 (72.4)
Local ablation therapy	4546 (26.8)	26 (4.9)	5 (5.1)
Transcatheter arterial chemoembolization	6168 (36.4)	28 (5.3)	14 (14.3)
Chemotherpy	777 (4.6)	93 (17.6)	6 (6.1)
Others	146 (0.9)	34 (6.5)	2 (2.0)
Best suppotive care	1618	169	16

HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; combined: combined hepatocelluar and cholangiocarcinoma. Values in parentheses are in percent.

surgery (hepatectomy and liver transplantation), local ablation therapy and transcatheter arterial embolization, respectively. In patients with ICC, 65.7 and 17.6% had undergone surgery (hepatectomy) and chemotherapy, respectively, and in patients with combined HCC and ICC, 72.4 and 14.3% had undergone surgery (hepatectomy) and transcatheter arterial chemoembolization, respectively (Table 6).

3.1.5. Surgery

From a macroscopic analysis of the resected specimens, 56.7% of HCC was of the simple nodular type and 59.3% of ICC was of the mass forming type. These types were the most common. Macroscopic results from the resected specimens are shown in Table 7. In patients with HCC, tumors of size 2 cm or below, 2–5 and 5–10 cm were found in 20.0, 51.5 and 19.7% of patients, respectively, and 71.3% of the

Table 7
Operative findings or macroscopic pathological characteristics of surgical specimen

	HCC	ICC	Combined
Tumor size (cm)	$n=5174$	$n=322$	$n=67$
≦1	101 (2.0)	9 (2.8)	0 (0.0)
≦2	933 (18.0)	27 (8.4)	8 (11.9)
≦3	1268 (24.5)	50 (15.5)	8 (11.9)
≦5	1399 (27.0)	96 (29.8)	20 (29.9)
≦10	1020 (19.7)	119 (37.0)	27 (40.3)
≦15	336 (6.5)	20 (6.2)	4 (6.0)
≦20	72 (1.4)	0 (0.0)	0 (0.0)
≦25	24 (0.5)	1 (0.3)	0 (0.0)
>25	21 (0.4)	0 (0.0)	0 (0.0)
Number of tumors	$n=5202$	$n=325$	$n=67$
1	3707 (71.3)	263 (80.9)	36 (53.7)
2	798 (15.3)	21 (6.5)	16 (23.9)
3	283 (5.4)	7 (2.2)	5 (7.5)
4	109 (2.1)	2 (0.6)	1 (1.5)
5	45 (0.9)	1 (0.3)	2 (3.0)
>5	260 (5.0)	31 (9.5)	7 (10.4)
Tumor extent	$n=5116$	$n=324$	$n=65$
Hs	2105 (41.1)	54 (16.7)	11 (16.9)
H1	1331 (26.0)	98 (30.2)	20 (30.8)
H2	1253 (24.5)	123 (38.0)	27 (41.5)
H3	286 (5.6)	35 (10.8)	4 (6.2)
H4	141 (2.8)	14 (4.3)	3 (4.6)
Growth type	$n=5042$	$n=307$	$n=61$
Eg	4634 (91.9)	147 (47.9)	44 (72.1)
Ig	408 (8.1)	160 (52.1)	17 (27.9)
Capsule formation	$n=5078$	$n=304$	$n=64$
Fc(−)	1124 (22.1)	276 (90.8)	39 (60.9)
Fc(+)	3954 (77.9)	28 (9.2)	25 (39.1)
Capsule infiltration	$n=3846$	$n=27$	$n=25$
Fc-inf(−)	2093 (54.4)	13 (48.1)	12 (48.0)
Fc-inf(+)	1753 (45.6)	14 (51.9)	13 (52.0)
Septum formation	$n=4789$	$n=281$	$n=63$
Sf(−)	2120 (44.3)	261 (92.9)	41 (65.1)
Sf(+)	2669 (55.7)	20 (7.1)	22 (34.9)
Serosal invasion	$n=5039$	$n=310$	$n=66$
S0	3916 (77.7)	172 (55.5)	38 (57.6)
S1	850 (16.9)	97 (31.3)	23 (34.8)
S2	197 (3.9)	39 (12.6)	5 (7.6)
S3	76 (1.5)	2 (0.6)	0 (0.0)
Lymph node metastasis	$n=4698$	$n=321$	$n=59$
Absent	4613 (98.2)	215 (67.0)	48 (81.4)
Present	85 (1.8)	106 (33.0)	11 (18.6)
Portal vein invasion	$n=5130$	$n=320$	$n=64$
Vp0	4322 (84.2)	208 (65.0)	47 (73.4)
Vp1	419 (8.2)	30 (9.4)	9 (14.1)
Vp2	150 (2.9)	42 (13.1)	5 (7.8)
Vp3	176 (3.4)	35 (10.9)	2 (3.1)
Vp4	63 (1.2)	5 (1.6)	1 (1.6)
Hepatic vein invasion	$n=5072$	$n=309$	$n=63$
Vv0	4766 (94.0)	260 (84.1)	54 (85.7)
Vv1	165 (3.3)	17 (5.5)	6 (9.5)
Vv2	90 (1.8)	21 (6.8)	3 (4.8)
Vv3	51 (1.0)	11 (3.6)	0 (0.0)
Hepatic arterial invasion	$n=4404$	$n=266$	$n=54$
Va0	4367 (99.2)	241 (90.6)	52 (96.3)
Va1	31 (0.7)	9 (3.4)	2 (3.7)
Va2	3 (0.1)	14 (5.3)	0 (0.0)
Va3	3 (0.1)	2 (0.8)	0 (0.0)
Bile duct invasion	$n=5097$	$n=305$	$n=65$
B0	4939 (96.9)	153 (50.2)	54 (83.1)
B1	104 (2.0)	53 (17.4)	5 (7.7)
B2	26 (0.5)	62 (20.3)	3 (4.6)
B3	14 (0.3)	26 (8.5)	2 (3.1)
B4	14 (0.3)	11 (3.6)	1 (1.5)
Intrahepatic metastasis	$n=5037$	$n=327$	$n=67$
IM0	3838 (76.2)	242 (74.0)	43 (64.2)
IMs	128 (2.5)	6 (1.8)	1 (1.5)
IM1	425 (8.4)	27 (8.3)	8 (11.9)
IM2	422 (8.4)	31 (9.5)	7 (10.4)
IM3	224 (4.4)	21 (6.4)	8 (11.9)
Peritoneal dissemination	$n=5061$	$n=330$	$n=67$
Absent	5023 (99.2)	309 (93.6)	65 (97.0)
Present	38 (0.8)	21 (6.4)	2 (3.0)
Surgical margine	$n=4808$	$n=315$	$n=63$
Presence of cancer invasion	522 (10.9)	53 (16.8)	11 (17.5)
Absence of cancer invasion	4286 (89.1)	262 (83.2)	52 (82.5)
Non-cancerous portion	$n=4871$	$n=304$	$n=64$
Normal liver	516 (10.6)	222 (73.0)	12 (18.8)

Table 7 (*Continued*)

	HCC	ICC	Combined
Chronic hepatitis/liver fibrosis	2041 (41.9)	47 (15.5)	32 (50.0)
Liver cirrhosis	2314 (47.5)	35 (11.5)	20 (31.3)
Extent of hepatic resection	*n*=5003	*n*=318	*n*=65
Hr0	1654 (33.1)	24 (7.5)	9 (13.8)
HrS	1127 (22.5)	26 (8.2)	16 (24.6)
Hr1	990 (19.8)	38 (11.9)	10 (15.4)
Hr2	1057 (21.1)	185 (58.2)	25 (38.5)
Hr3	129 (2.6)	45 (14.2)	5 (7.7)
Liver transplantation	46 (0.9)	0 (0.0)	0 (0.0)
Lymphnode dissection	*n*=4895	*n*=314	*n*=60
Not performed	4713 (96.3)	115 (36.6)	41 (68.3)
Performed	182 (3.7)	199 (63.4)	19 (31.7)
Residual cancer	*n*=5015	*n*=323	*n*=65
Absent	4628 (92.3)	281 (87.0)	54 (83.1)
Present	387 (7.7)	42 (13.0)	11 (16.9)
Distant metastases	*n*=5139	*n*=326	*n*=67
Absent	5060 (98.5)	315 (96.6)	66 (98.5)
Present	79 (1.5)	11 (3.4)	1 (1.5)
TNM stage by LCSGJ	*n*=5088	*n*=329	*n*=68
I	811 (15.9)	19 (5.8)	6 (8.8)
II	2391 (47.0)	91 (27.7)	18 (26.5)
III	1212 (23.8)	89 (27.1)	21 (30.9)
IV A	571 (11.2)	55 (16.7)	15 (22.1)
IV B	103 (2.0)	75 (22.8)	8 (11.8)

HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; combined: combined hepatocelluar and cholangiocarcinoma; Hs: cancer limited to one subsegment; H1: cancer limited to one segment; H2: cancer limited to two segments; H3: cancer limited to three segments; H4: cancer involving more than three segments; expansive growth (Eg): well demarcated border; infiltrative growth (Ig): poorly demarcated border; Fc(−): absence of capsule formation; Fc(+): presence of capsule formation; Fc-inf(−): absence of cancerous infiltration of the tumor capsule; Fc-inf(+): presence of cancerous infiltration of the tumor capsule; Sf(−): absence of formation of a fibrous septum within the tumor; Sf(+): presence of fibrous septum wihin the tumor; S0: absence of invation of the serosa; S1: tumor invasion of the serosa; S2: tumor invasion of adjacent organs (enter name of organ involved); S3: tumor rupture with intraperitoneal bleeding; Vp0 – Vp4, Vv0 – Vv3, B0 – B4: findings of vascular and bile duct invasion described in Table 5 was observed histologically; Va0: absence of invasion of the hepatic artery; Va1: invasion distal to the second-order branches of the hepatic artery, but not of the second-order branches; Va2: invasion of the second oreder branches of the hepatic artery; Va3: invasion of the left or right hepatic artery or the proper hepatic artery; lM0: absence of intrahepatic metastasis; lM1: intrahepatic metastasis within the subsegment in which the principal tumor is located; lM2: intrahepatic metastasis in two segments; lM3: intrahepatic metastasis to three or more segments; Hr0: resection of less than one subsegment (Couinaud's segment); HrS: resection of one subsegment (Couinaud's segment); Hr1: resection of one segment (anterior, posterior, medial or left lateral sebmentectomy); Hr2: resection of two segments (right or left lobectomy or central bisegmentectomy); Hr3: resection of three segments (right or left trisegmentectomy). Values in parentheses are in percent.

tumors were solitary. Vascular invasions in the portal vein, hepatic vein and bile duct were found in 15.8, 6.0 and 3.1% of patients, respectively. Regarding findings in non-cancerous parts of the liver, normal liver, chronic hepatitis/liver fibrosis and liver cirrhosis were found in 10.6, 41.9 and 47.5% of patients, respectively. The extent of surgical resection was Hr0, HrS, Hr1, Hr2 and Hr3 in 33.1, 22.5, 19.8, 21.1 and 2.6% of patients, respectively. Liver transplantation, which was a new item recorded in this survey, was performed in 46 patients with HCC. In patients with ICC, tumors of size 2 cm or below, 2–5 and 5–10 cm were found in 11.2, 45.3 and 37.0% of patients, respectively, and 80.9% of the tumors were solitary. Normal liver was found in 73.0% of the ICC patients.

3.1.6. *Local ablation therapy*

Of patients with HCC, 38.8% underwent local ablation therapy. Ethanol injection therapy, microwave coagulation therapy and radiofrequency ablation therapy were given to 41.2, 17.7 and 40.2% of these patients, respectively, with

Table 8
Local ablation therapy

	HCC	ICC	Combined
	n=15262	*n*=543	*n*=88
Not performed	9344 (61.2)	503 (92.6)	70 (79.5)
Performed	5918 (38.8)	40 (7.4)	18 (20.5)
EIT	2437 (41.2)	8 (20.0)	4 (22.2)
MCT	1048 (17.7)	16 (40.0)	6 (33.3)
RFA	2380 (40.2)	14 (35.0)	8 (44.4)
Others	53 (0.9)	2 (5.0)	0 (0.0)
	n=5858	*n*=40	*n*=18
Percutaneous	4930 (84.2)	25 (62.5)	9 (50.0)
Others	928 (15.8)	15 (37.5)	9 (50.0)
Number of tumors	*n*=5769	*n*=38	*n*=18
1	4201 (72.8)	29 (76.3)	17 (94.4)
2	1017 (17.6)	5 (13.2)	0 (0.0)
3	364 (6.3)	2 (5.3)	0 (0.0)
4	98 (1.7)	2 (5.3)	0 (0.0)
5	37 (0.6)	0 (0.0)	0 (0.0)
>5	52 (0.9)	0 (0.0)	1 (5.6)
Tumor size (cm)	*n*=5603	*n*=38	*n*=17
≦1	531 (9.5)	4 (10.5)	3 (17.6)
≦2	2515 (44.9)	11 (28.9)	5 (29.4)
≦3	1602 (28.6)	10 (26.3)	2 (11.8)
≦5	699 (12.5)	7 (18.4)	4 (23.5)
≦10	149 (2.7)	4 (10.5)	3 (17.6)
≦15	23 (0.4)	1 (2.6)	0 (0.0)
≦20	41 (0.7)	1 (2.6)	0 (0.0)
≦25	25 (0.4)	0 (0.0)	0 (0.0)
>25	18 (0.3)	0 (0.0)	0 (0.0)
Efficacy evaluation	*n*=5253	*n*=36	*n*=17
CR	3958 (75.3)	22 (61.1)	8 (47.1)
PR	978 (18.6)	7 (19.4)	7 (41.2)
MR	149 (2.8)	5 (13.9)	0 (0.0)
NC	95 (1.8)	2 (5.6)	2 (11.8)
PD	73 (1.4)	0 (0.0)	0 (0.0)

HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; combined: combined hepatocelluar and cholangiocarcinoma; EIT: ethanol injection therapy; MCT: microwave coagulation therapyl; RFA: radiofrequency ablation therapy; CR: complete response; PR: partial response; MR: minor response; NC: no change; PD: progressive disease. Values in parentheses are in percent.

Table 9
Transcatheter arterial embolization

	HCC	ICC	Combined
	$n=15784$	$n=549$	$n=89$
Not performed	7654 (48.5)	501 (91.3)	67 (75.3)
Performed	8130 (51.5)	48 (8.7)	22 (24.7)
Lipiodol	1972 (24.3)	16 (33.3)	9 (40.9)
Embolic material	180 (2.2)	4 (8.3)	0 (0.0)
Lipiodol + embolic material	5907 (72.7)	26 (54.2)	13 (59.1)
Others	71 (0.9)	2 (4.2)	0 (0.0)
	$n=7971$	$n=47$	$n=22$
Without anticancer agents	598 (7.5)	4 (8.5)	2 (9.1)
With anticancer agent	7373 (92.5)	43 (91.5)	20 (90.9)
Extent of embolization	$n=7567$	$n=47$	$n=22$
Less than one segment	2178 (28.8)	10 (21.3)	2 (9.1)
One segment to one lobe	3171 (41.9)	25 (53.2)	8 (36.4)
More than one lobe	1508 (19.9)	6 (12.8)	4 (18.2)
Whole liver	710 (9.4)	6 (12.8)	8 (36.4)
Efficacy evaluation	$n=6707$	$n=42$	$n=22$
CR	1822 (27.2)	5 (11.9)	1 (4.5)
PR	2797 (41.7)	10 (23.8)	7 (31.8)
MR	729 (10.9)	6 (14.3)	5 (22.7)
NC	804 (12.0)	14 (33.3)	7 (31.8)
PD	555 (8.3)	7 (16.7)	2 (9.1)

HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; combined: combined hepatocelluar and cholangiocarcinoma; CR: complete response; PR: partial response; MR: minor response; NC: no change; PD: progressive disease. Values in parentheses are in percent.

percutaneous treatment being given in 84.2% of these cases. In the 15th survey, only 6.0% of patients who underwent local ablation therapy received radiofrequency ablation therapy, suggesting a marked increase in the use of this treatment. Of these patients, 72.8% had one tumor, 54.4% had a tumor of size 2 cm or less, and 28.6% had a tumor of 2–3 cm. Treatment outcomes of complete response (CR) and partial response (PR) occurred in 75.3 and 18.6% of patients, respectively (Table 8).

Table 10
Microscopic pathological findings of surgical or biopsy specimen

	HCC	ICC	Combined
Capsule formation	$n=4982$	$n=289$	$n=64$
fc(−)	1215 (24.4)	263 (91.0)	46 (71.9)
fc(+)	3767 (75.6)	26 (9.0)	18 (28.1)
Capusle infiltration	$n=3672$	$n=22$	$n=18$
fc-inf(−)	1129 (30.7)	8 (36.4)	4 (22.2)
fc-inf(+)	2543 (69.3)	14 (63.6)	14 (77.8)
Septum formation	$n=4613$	$n=265$	$n=64$
sf(−)	1614 (35.0)	247 (93.2)	34 (53.1)
sf(+)	2999 (65.0)	18 (6.8)	30 (46.9)
Serosal invasion	$n=4738$	$n=293$	$n=65$
s0	4051 (85.5)	184 (62.8)	45 (69.2)
s1	504 (10.6)	80 (27.3)	14 (21.5)
s2	121 (2.6)	26 (8.9)	6 (9.2)
s3	62 (1.3)	3 (1.0)	0 (0.0)
Lymph node metastasis	$n=3411$	$n=284$	$n=50$
Absent	3341 (97.9)	165 (58.1)	36 (72.0)
Present	70 (2.1)	119 (41.9)	14 (28.0)
Portal vein invasion	$n=4920$	$n=300$	$n=65$
vp0	3409 (69.3)	162 (54.0)	30 (46.2)
vp1	1100 (22.4)	82 (27.3)	27 (41.5)
vp2	178 (3.6)	31 (10.3)	5 (7.7)
vp3	180 (3.7)	19 (6.3)	2 (3.1)
vp4	53 (1.1)	6 (2.0)	1 (1.5)
Hepatic vein invasion	$n=4829$	$n=289$	$n=63$
vv0	4200 (87.0)	222 (76.8)	48 (76.2)
vv1	509 (10.5)	45 (15.6)	11 (17.5)
vv2	79 (1.6)	16 (5.5)	4 (6.3)
vv3	41 (0.8)	6 (2.1)	0 (0.0)
Hepatic arterial invasion	$n=3981$	$n=225$	$n=46$
va0	3948 (99.2)	211 (93.8)	45 (97.8)
va1	29 (0.7)	6 (2.7)	1 (2.2)
va2	1 (0.0)	6 (2.7)	0 (0.0)
va3	3 (0.1)	2 (0.9)	0 (0.0)
Bile duct invasion	$n=4855$	$n=272$	$n=66$
b0	4684 (96.5)	121 (44.5)	50 (75.8)
b1	116 (2.4)	73 (26.8)	12 (18.2)
b2	30 (0.6)	43 (15.8)	3 (4.5)
b3	16 (0.3)	17 (6.3)	1 (1.5)
b4	9 (0.2)	18 (6.6)	0 (0.0)
Intrahepatic metastasis	$n=4610$	$n=288$	$n=59$
im0	3533 (76.6)	209 (72.6)	35 (59.3)
ims	131 (2.8)	4 (1.4)	1 (1.7)
im1	466 (10.1)	28 (9.7)	10 (16.9)
im2	310 (6.7)	34 (11.8)	10 (16.9)
im3	170 (3.7)	13 (4.5)	3 (5.1)
Surgical margine	$n=4607$	$n=292$	$n=65$
Presence of cancer invasion	592 (12.9)	56 (19.2)	12 (18.5)
Absence of cancer invasion	4015 (87.1)	236 (80.8)	53 (81.5)
Non-cancerous portion	$n=5156$	$n=292$	$n=68$
Normal liver	393 (7.6)	201 (68.8)	11 (16.2)
Chronic hepatitis or liver fibrosis	2239 (43.4)	58 (19.9)	29 (42.6)
Liver cirrhosis	2524 (49.0)	33 (11.3)	28 (41.2)
Liver fibrosis	$n=2826$	$n=152$	$n=36$
F0 (normal)	243 (8.6)	95 (62.5)	9 (25.0)
F1	416 (14.7)	18 (11.8)	6 (16.7)
F2	494 (17.5)	10 (6.6)	5 (13.9)
F3	470 (16.6)	6 (3.9)	2 (5.6)
F4 (liver cirrhosis)	1203 (42.6)	23 (15.1)	14 (38.9)

HCC: hepatocellular carcinoma; ICC: intrahepatic cholangiocarcinoma; combined: combined hepatocelluar and cholangiocarcinoma; fc, fc-inf, sf, s, vp0 – vp4, vv0 – vv3, va0 – va3, b0 – b4, im0 – im3: findings described in Tables 5 and 7 were observed histologically; F1: fibrosis expansion of portal tract; F2: bridging fibrosis formation; F3: bridging fibrosis fromation accompanying lobular distortion. Values in parentheses are in percent.

3.1.7. Transcatheter arterial embolization

Transcatheter arterial embolization was conducted in 51.5% of patients with HCC. Of these patients, lipiodol alone and lipiodol + embolic material were used in 24.3 and 72.7% of patients, respectively. Anticancer agents were given to 92.5% of these patients concomitantly. Regarding the extent of embolization, less than one segment, one segment to one lobe, more than one lobe and the whole liver were treated in 28.8, 41.9, 19.9 and 9.4% of patients, respectively. Treatment outcomes of CR and PR occurred in 27.2 and 41.7% of patients, respectively (Table 9).

3.1.8. Chemotherapy

Chemotherapy was given to 16.5% of patients with HCC (CR: 19.9%; PR: 30.2%) and 91.2% of these patients received chemotherapy via the hepatic artery. In patients with ICC, 26.7% underwent chemotherapy (CR: 7.6%; PR: 4.8%), and of these patients 43.5, 32.7 and 22.4% received chemotherapy intraarterially, intravenously and orally, respectively.

3.1.9. Pathological diagnosis

Pathological diagnoses by biopsy alone, resected specimens alone and both biopsy and resected specimens were conducted in 14.7, 31.0 and 1.8% of patients, respectively, and 52.4% of patients were not diagnosed pathologically. Pathological results from biopsy and resected specimens are shown in Table 10. In patients with HCC, well, moderately and poorly differentiated tumor types were found in 33.2, 56.2 and 9.6% of patients, respectively, while in patients with ICC, well, moderately and poorly differentiated tumor types were found in 23.1, 53.4 and 20.0% of patients, respectively. Regarding pathological findings in noncancerous parts of the liver, normal liver, chronic hepatitis/liver fibrosis and liver cirrhosis were found in 7.6, 43.4 and 49.0% of patients, respectively.

3.1.10. Recurrence

During the survey (within 2 years after diagnosis), 31.7% of patients with HCC experienced recurrence of the disease. Transcatheter arterial embolization and local ablation therapy were given to 52.0 and 25.5% of these patients, respectively,

Table 11
Cumulative survival rates (%) of HCC patients treated with hepatic resection (1990–2001)

	n	Year									
		1	2	3	4	5	6	7	8	9	10
All cases	25228	88.2	79.1	70.5	62.3	54.6	48.2	42.1	37.3	32.3	28.9
Tumor size (cm)											
≤2	4871	95.3	90.5	84.5	77.4	69.6	61.8	54.9	48.4	40.8	37.5
2–5	13023	91.5	83.0	73.5	64.5	56.2	49.1	42.3	37.8	32.6	29.1
5–10	4588	80.7	66.7	57.5	49.1	42.5	38.2	33.5	29.0	26.4	22.0
>10	1980	67.8	53.9	45.1	39.0	33.0	29.2	26.8	24.0	23.4	21.6
Tumor number											
1	17869	90.9	83.5	75.6	67.9	60.3	53.6	47.5	42.8	37.5	33.9
2	3828	87.0	75.4	65.5	55.6	47.8	40.8	34.1	27.6	21.5	18.3
≥3	2988	75.6	59.7	48.8	39.1	30.9	26.5	21.7	18.9	16.4	14.2
Portal vein invasion											
Vp0	20650	92.0	84.0	75.3	66.8	58.9	51.8	45.0	39.8	34.6	31.1
Vp1	1877	78.3	63.3	53.9	45.6	37.6	33.9	30.4	28.1	24.4	21.2
Vp2	764	58.8	43.0	36.2	30.0	26.8	23.6	22.2	21.1	19.3	15.5
Vp3 or Vp4	864	50.7	33.3	25.8	22.3	18.5	17.0	15.0	13.1	10.6	10.6
Non-cancerous portion											
Normal liver	2054	87.8	78.8	72.0	66.0	61.4	59.8	55.0	52.0	49.6	48.0
Chronic hepatitis/liver fibrosis	7859	90.7	83.1	75.7	69.0	62.6	57.7	52.2	47.2	42.5	38.8
Liver cirrhosis	11294	87.1	77.3	67.5	58.7	50.0	42.6	35.9	31.1	25.9	23.1
Liver damage classification by LCSGJ											
A	15718	90.4	82.3	74.6	66.6	59.1	52.5	46.9	42.3	37.2	33.7
B	6884	86.0	75.5	65.0	56.2	47.7	41.2	34.5	29.6	23.9	20.6
C	713	73.7	59.8	50.0	42.9	36.4	33.3	27.2	21.4	17.4	14.0
TNM Stage by LCSGJ											
I	3223	96.5	92.9	87.8	80.7	72.9	65.6	58.6	52.9	45.4	42.1
II	10925	93.2	86.3	77.7	69.1	61.1	53.5	46.6	40.9	35.9	31.7
III	5414	84.0	70.3	59.8	50.0	41.8	36.4	30.6	27.3	23.3	19.4
IVA	1569	62.1	45.1	34.7	28.8	24.4	20.9	19.2	14.7	11.7	11.7
IVB	291	56.4	40.8	28.6	23.3	16.3	14.8	12.7	12.7	12.7	12.7

Table 12
Cumulative survival rates (%) of HCC patients treated with local ablation therapy (1990–2001)

	n	Year									
		1	2	3	4	5	6	7	8	9	10
All cases	20805	93.0	80.6	67.1	54.2	43.4	34.6	28.1	22.4	17.8	15.0
Liver damage classification by LCSGJ											
A	10306	95.9	87.3	76.5	64.4	52.8	42.7	35.7	28.8	24.6	21.1
B	7444	92.4	77.4	61.5	47.6	37.1	28.8	23.3	18.4	13.4	12.0
C	1665	80.2	60.2	42.3	29.5	22.5	18.7	12.2	7.2	5.8	2.9
Tumor number											
1	12293	94.4	84.2	72.2	60.7	50.0	40.4	33.3	26.6	21.6	18.2
2	4449	92.8	79.1	65.3	50.6	39.0	30.9	24.0	19.2	15.8	13.1
3	1984	91.7	76.4	59.6	44.0	32.7	24.4	19.8	15.3	9.2	7.7
4	747	89.5	72.0	53.1	38.7	30.4	25.5	18.6	10.8	10.8	8.7
≧5	998	83.2	61.4	44.0	30.6	22.1	16.9	13.8	13.8	7.6	–
Tumor size (cm)											
≦1	1297	97.8	91.8	82.4	72.7	61.5	52.5	46.0	37.8	34.4	26.8
1–2	8904	95.8	87.0	75.1	63.6	52.3	42.1	35.5	29.0	22.5	19.6
2–3	5999	93.0	78.6	63.0	47.7	36.6	27.9	21.3	15.9	12.8	10.0
3–5	2774	88.4	69.8	53.7	39.7	28.5	22.1	15.4	10.4	7.3	6.2
>5	799	74.8	53.1	36.9	28.4	25.1	20.7	12.7	12.7	9.5	–

as treatment for recurrence in the liver. The most frequent organ of distant metastasis was the lung, followed by the bone and lymph nodes. Radiotherapy, systemic chemotherapy and resection were chosen as therapy for recurrence in other organs.

3.1.11. Autopsy

Autopsy was performed in 485 patients, 424 of which were patients with HCC. Liver cirrhosis was found in 80.7% of patients with HCC. Invasion of the portal vein, hepatic vein or bile duct was found in 72.4, 43.1 and 18.4% of patients, respectively. Distant metastasis was most frequently found in the lung (43.3%) and metastasis to the lymph node was also found (28.3%). In patients with ICC, the most frequent distant metastasis sites were the intraperitoneal organs and lymph nodes, in 30.6 and 63.6% of patients, respectively.

3.2. Additional statistics

3.2.1. HCC

Patients with HCC were categorized by initial treatment (main treatment in the 16th survey), hepatectomy (Table 11), local ablation therapy (ethanol injection therapy, microwave coagulation therapy and radiofrequency ablation therapy) (Table 12) and transcatheter arterial embolization (Table 13), and the cumulative survival rates were calculated for each category. In newly registered patients in the 16th survey, the level of liver injury was estimated from items examined in the investigation.

3.2.2. ICC and combined HCC and ICC

In patients with ICC, the cumulative survival rates were calculated by various factors and for all patients. In patients with combined HCC and ICC, the cumulative survival rates were calculated for all patients (Tables 14 and 15).

Table 13
Cumulative survival rates (%) of HCC patients treated with transcatheter arterial embolization (1990–2001)

	n	Year									
		1	2	3	4	5	6	7	8	9	10
All cases	22910	76.8	57.8	42.5	31.3	23.5	17.5	13.4	10.1	8.1	6.2
Liver damage classification by LCSGJ											
A	10429	84.1	67.5	52.4	40.1	31.1	23.8	19.4	14.1	10.8	8.5
B	8041	75.3	54.8	37.9	26.9	19.9	13.7	9.5	7.4	6.9	5.2
C	2500	55.5	32.0	19.7	13.0	7.6	5.1	3.8	3.3	3.3	–
Tumor number											
1	9125	82.7	67.2	53.1	40.6	31.4	23.9	19.3	14.9	12.3	9.8
2	4476	81.5	62.5	44.4	32.9	24.2	18.1	12.8	10.3	8.0	5.0
3	2525	78.8	55.5	37.0	24.4	18.1	12.5	8.6	6.3	4.5	–
4	1135	79.7	55.3	39.8	29.4	20.3	15.0	10.8	7.8	6.2	6.2
≥5	4871	62.4	39.9	25.6	17.5	12.8	8.9	6.9	4.3	3.6	3.0

Table 14
Cumulative survival rates (%) of ICC patients (1990~2001)

	n	Year									
		1	2	3	4	5	6	7	8	9	10
All cases	3084	48.8	33.0	26.6	22.2	20.3	17.7	15.6	14.9	13.5	12.7
Hepatic resection											
Performed	1364	69.5	52.1	44.0	37.9	34.6	30.6	27.2	25.8	23.0	23.0
Not performed	1720	30.9	16.4	11.3	8.2	7.4	6.1	4.9	4.9	4.9	–
Cases of hepatic resection											
Tumor size (cm)											
≦2	116	86.1	77.4	73.2	66.6	66.6	61.5	49.2	49.2	41.0	41.0
2–5	576	77.3	59.7	51.6	42.5	36.0	31.0	29.3	27.3	22.8	–
5–10	491	61.7	43.4	34.7	31.5	30.7	27.1	24.4	22.7	22.7	22.7
>10	129	51.4	31.8	22.7	19.9	16.6	16.6	16.6	16.6	16.6	–
Tumor number											
1	1014	75.3	58.2	50.5	43.8	41.3	35.8	32.5	31.5	27.4	27.4
2	109	64.0	47.6	36.0	27.5	22.4	22.4	18.0	13.5	13.5	–
≧3	183	41.8	21.2	14.5	13.2	7.5	7.5	5.0	5.0	–	–
Residual tumor											
Absent	676	80.2	63.0	53.4	47.8	43.4	38.8	37.7	35.0	30.1	30.1
Present	469	53.0	33.1	28.0	21.4	20.6	18.4	12.9	12.9	12.9	12.9
Lymphnode metastasis											
Absent	859	79.8	62.9	53.9	46.7	43.6	38.4	34.5	32.6	30.4	30.4
Present	422	50.1	30.1	23.9	20.1	16.8	15.1	11.3	11.3	11.3	–

Table 15
Cumulative survival rates (%) of combined HCC and ICC (1990–2001)

	n	Year									
		1	2	3	4	5	6	7	8	9	10
All cases	473	56.9	40.4	29.8	23.6	18.8	14.5	14.5	14.5	14.5	14.5
Hepatic resection											
Performed	270	68.0	48.2	40.7	33.0	30.3	25.2	25.2	25.2	25.2	25.2
Not performed	203	42.1	30.1	15.1	11.1	5.9	3.5	3.5	3.5	3.5	–

4. Conclusion

The number of patients in Japan with primary liver cancer has increased in every follow-up survey. In the 16th nationwide follow-up survey of primary liver cancer, patients who had undergone liver transplantation for HCC were registered. We hope that the results of this follow-up survey will be helpful in facilitating progress in research and medical practice that will contribute to the treatment of primary liver cancer.

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Efficacy of lamivudine for preventing hepatocellular carcinoma in chronic hepatitis B: A multicenter retrospective study of 2795 patients

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Abstract

A retrospective survey of Japanese patients histologically diagnosed with chronic hepatitis B was conducted to determine the effectiveness of lamivudine in preventing hepatocellular carcinoma (HCC). Of the 2795 patients who satisfied criteria for analysis after treatment from any of 30 medical institutions, 657 had received lamivudine and the remaining 2138 had not. A Cox regression model with liver biopsy as the starting point revealed seven factors related to HCC: lamivudine therapy, gender, family clustering of hepatitis B, age at liver biopsy, hepatic fibrosis stage, serum albumin level, and platelet count. In a matched case-controlled study, 377 patients in a lamivudine-treated group and 377 matched patients in a non-treated group were selected based on their propensity scores. The mean follow-up period was 2.7 years in the lamivudine group and 5.3 years in the control group. In the lamivudine group, HCC occurred in four patients (1.1%) with an annual incidence rate of 0.4%/(patient/year), whereas in the control group HCC occurred in 50 patients (13.3%) for a rate of 2.5%/(patient/year). A comparison of the cumulative HCC incidence between the two groups by the Kaplan–Meier method showed a significantly lower incidence of HCC in the lamivudine group ($p < 0.001$). These findings suggest that lamivudine effectively reduces the incidence of HCC in patients with chronic hepatitis B.

Keywords: Chronic hepatitis B; Hepatocellular carcinoma; Anti-viral treatment; Lamivudine

1. Introduction

An estimated 350 million people worldwide are chronically infected with the hepatitis B virus (HBV), most in southeast Asia [1,2]. In this region, infection occurs during infancy, including that through mother–child transmission. Infected persons with HBV are initially asymptomatic, and

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active hepatitis emerges years later. In most patients, seroconversion from hepatitis Be antigen (HBeAg) to antibody to HBeAg (HBeAb) occurs spontaneously with age. At the same time, the virus levels decrease and hepatitis abates. Some patients, however, remain positive for HBeAg, and in those patients the hepatitis virus persists at high levels, resulting in the progression to hepatic cirrhosis, and the onset of hepatocellular carcinoma (HCC) in a high percentage of such patients [3–5]. The number of HBV carriers is decreasing in Japan and some other countries as a result of the prevention of mother–child transmission through the use of HBV vaccines and/or high-potency antibody to hepatitis B surface antigen (HBsAb) human immunoglobulin (HBIG) [6]. Even in these countries, however, only persons born after 1986 are protected by vaccination, and many chronic hepatitis B patients still need treatment. In the past, it was not easy to manage chronic hepatitis B using anti-viral agents such as interferon. In recent years, however, the development of lamivudine, a nucleoside analogue that inhibits reverse transcriptase, has drastically changed the treatment of hepatitis B [7–9]. By virtue of this inhibitory ability, lamivudine was developed as an anti-viral agent against human immuno-deficiency virus (HIV). It was later also found to be effective against HBV because HBV is a member of the Hepadnaviridae family, which utilizes reverse transcriptase in its replication process [10]. Lamivudine was found to inhibit the replication of HBV, reduce hepatitis, and improve liver histological findings in long-term treatment [11]. It is also useful when hepatitis B becomes severe due to acute exacerbation, as well as in the treatment of liver cirrhosis associated with symptoms of hepatic failure, such as ascites and edema [12–16]. However, a number of problems are associated with lamivudine therapy, such as relapse of hepatitis due to the appearance of YMDD mutant viruses and the difficulty of estimating the optimal time to discontinue the treatment [17,18]. In addition, until recently no adequate studies had been conducted to determine whether or not lamivudine inhibits the onset of hepatic cancer, even though it is known to slow the progression of histological changes in the liver. This lack of research is attributable partly to the need for long-term follow-up of a large number of patients and partly to the difficulty of conducting clinical trials. We conducted a multicenter study of a large number of registered patients to evaluate the effects of lamivudine on the course of hepatitis B and the onset of HCC. The data obtained were analyzed in a matched case-controlled study.

2. Materials and methods

2.1. Study design

The Inuyama Hepatitis Study Group designed this multicenter retrospective study to determine whether or not lamivudine is effective in preventing HCC. The subjects were Japanese patients with hepatitis B who were diagnosed with chronic liver disease by liver biopsy after 1980 and were followed up until March 2002. Each patient completed a questionnaire containing 16 items in four categories: background factors: date of birth, sex, family clustering of hepatitis B, and alcohol consumption during follow-up (80 g or more per day as ethanol); examination and test items: date of liver biopsy, grade and stage of histological findings of the liver, hepatitis Be antigen (HBeAg), antibody to HBeAg (HBeAb), albumin, asparate aminotransferase (AST), alanine aminotransferase (ALT), and platelet counts; clinical outcomes: the presence or absence of HCC during the follow-up period and the date of onset if present; lamivudine therapy: the presence or absence of lamivudine therapy during the follow-up period, and the date of initiation and duration of therapy if provided. The study was allowed by the review board of each participating institution. The names, ID numbers, and all other information that would directly identify individual patients were deleted to protect their privacy.

2.2. Patients

The present study included 3022 patients with chronic hepatitis B who underwent liver biopsy at any of 30 medical institutions after 1980. No patient had superinfection with hepatitis C virus and HIV. Two hundred and twenty-seven patients who had not answered the question about lamivudine treatment were excluded from the study. This left a total of 2795 patients for analysis. Among them, 657 patients had received lamivudine therapy and 2138 patients had not.

Histological findings of the liver were scored with respect to the grade of inflammation and stage of hepatic fibrosis according to the New Inuyama Histological Criteria [19] by a pathologist at each institution.

2.3. Lamivudine treatment

The lamivudine treatment group consisted of 657 patients who had received lamivudine therapy (100 mg/day). The median lamivudine treatment period was 18.9 months. Lamivudine therapy was continued until the end of the follow-up period in 45% of the patients.

2.4. Matched case-controlled study

In our analysis of the relationship between lamivudine therapy and hepatic carcinogenicity, the starting point was the day of liver biopsy. However, many patients in the lamivudine group (279 patients or 41.4%) initiated lamivudine therapy more than 2 years after liver biopsy, making them inappropriate subjects for the evaluation of the effects of lamivudine on hepatic carcinogenicity. For this reason, 377 patients who started lamivudine therapy within 2 years after liver biopsy were selected for analysis from the 657 patients in the lamivudine group. The interval from liver biopsy to lamivudine therapy was 5.8 ± 9.0 months, and the treatment

period was 23.1 ± 19.0 months (range 3–96 months). For the control group, seven factors were selected on the basis of the propensity scores from the 2138 patients who had not received lamivudine: age at the time of liver biopsy, gender, family clustering of hepatitis B, stage of hepatic fibrosis, serum albumin level, and platelet count. On that basis, 377 matching patients were selected for the control group [20].

2.5. Statistical analyses

A series of analyses was conducted using the day of liver biopsy as the starting point. Background factors at the time of liver biopsy were compared by the Student's *t*-test (numerical data) or the χ^2 test (categorical data), and differences were regarded as significant if $p < 0.05$ on both sides. Factors related to HCC were analyzed using a Cox regression model. The incidence of HCC was reported as an annual incidence rate (%/(patient/year)).

Because of the large differences in background factors between the lamivudine and control groups, the groups were matched for further analysis of HCC-related factors. For this analysis, all patients who had started lamivudine therapy within 2 years after liver biopsy were selected. The propensity score method was used to select patients from the control group [20]. Matching was done with respect to the HCC-related factors selected using the Cox regression model. After the matching, the incidence of HCC was shown by the Kaplan–Meier method and compared between the groups by the log-rank test. Differences were regarded as significant if $p < 0.05$ on both sides.

3. Results

3.1. Comparison of background factors

Table 1 demonstrates the comparison of background factors at the time of liver biopsy between the lamivudine and control groups. Significant differences were found in the mean age ($p < 0.001$), duration of follow-up ($p < 0.001$), history of IFN therapy ($p < 0.001$), inflammation of the liver ($p < 0.001$), HBeAg ($p < 0.001$), HBeAb ($p = 0.001$), serum albumin level ($p < 0.001$), AST level ($p = 0.011$), and platelet count ($p < 0.001$).

3.2. Evaluation of factors related to hepatic carcinogenicity by univariate analyses

HCC occurred in 31 of the 657 patients (4.7%) in the lamivudine group and in 239 of the 2138 patients (11.2%) in the control group. The mean follow-up periods after liver biopsy were 4.9 and 6.2 years in the lamivudine and control groups, respectively. Thus, the crude incidence of HCC determined was 1.0 and 1.8%/(patient/year) in the lamivudine and control groups, respectively.

Table 2 shows the incidences of HCC in the lamivudine and control groups in an analysis stratified with respect to background factors. In the lamivudine group, HCC did not occur in patients whose histological findings were grade 0 in inflammation and stage 0 in fibrosis, and significant intergroup differences were noted in this respect. No significant differences were observed other than in the histological findings.

3.3. Evaluation of factors related to hepatic carcinogenicity using a multivariate Cox regression model

Factors contributing to the incidence of HCC were analyzed using a Cox regression model (Table 3). The following variables were selected by the forward–backward stepwise selection method: lamivudine therapy (no therapy, $p = 0.002$), gender (male, $p < 0.001$), family history of hepatitis B (present, $p = 0.015$), age at the time of liver biopsy (older than 40 years, $p < 0.001$), stage of liver fibrosis (more than F2, $p < 0.001$), serum albumin level (less than 4.0 g/dL, $p = 0.001$), and platelet count (less than 150,000/μL, $p < 0.001$)). This analysis showed that lamivudine reduces the risk of HCC.

3.4. Evaluation of factors related to hepatic carcinogenicity by a six-factor matched case-controlled study

Matched case-control analyses were performed for six factors (sex, family history of hepatitis B, age at the time of liver biopsy, stage of liver fibrosis, serum albumin level, and platelet count). There were no significant differences in background factors between the groups, as shown in Table 4. The mean follow-up period in the control group (5.3 years) was about twice that in the lamivudine group (2.7 years). In the lamivudine group, HCC occurred in 4 of 377 patients (1.1%), with an annual incidence rate of 0.4%/(patient/year), compared to 50 of 377 patients (13.3%) and 2.5%/(patient/year), respectively, in the control group. A comparison of the cumulative HCC incidence between the two groups by the Kaplan–Meier method showed a significantly lower incidence in the lamivudine group ($p < 0.001$) (Fig. 1).

Next, the background factors were compared between patients with HCC and those without it in the lamivudine and control groups. In the lamivudine group (Table 5), the mean age was significantly higher in patients with HCC than in those without it (55.0 years versus 41.3 years, $p = 0.024$), but there were no significant differences in the other factors. In the control group (Table 6), the mean age was significantly higher in patients with HCC than in those without it (50.6 years versus 40.0 years, $p < 0.001$). Significant differences were also noted in the stage of liver fibrosis ($p < 0.001$), serum albumin level ($p < 0.001$), and platelet count ($p < 0.001$), suggesting that underlying liver disease was more advanced in patients who developed HCC.

Table 1
Comparison of background factors between lamivudine group and control group assessed at the time of liver biopsy

Parameter	Lamivudine group ($n=657$)	Control group ($n=2138$)	p-Value
Gender[a]			
Male	503 (76.6%)	1583 (74.0%)	0.194
Female	154 (23.4%)	555 (26.0%)	
Age (years)[b]	40.9 ± 11.0	37.3 ± 12.4	<0.001
Follow-up period (years)[b]	4.9 ± 4.4	6.2 ± 5.5	<0.001
Family clustering of hepatitis B[a]			
Yes	376 (57.2%)	1085 (50.7%)	0.011
No	242 (36.8%)	924 (43.2%)	
Unknown	39 (5.9%)	129 (6.0%)	
Drinking during the course of the study (>ethanol 80 g/day)			
Yes	69 (10.5%)	359 (16.8%)	<0.001
No	557 (84.8%)	1708 (79.9%)	
Unknown	31 (4.7%)	71 (3.3%)	
IFN therapy[a]			
Yes	269 (40.9%)	812 (38.0%)	<0.001
No	369 (56.2%)	1306 (61.1%)	
Unknown	19 (2.9%)	20 (0.9%)	
Liver histology			
Grade of inflammation[a]			
A0	15 (2.3%)	84 (3.9%)	<0.001
A1	194 (29.5%)	642 (30.0%)	
A2	283 (43.1%)	996 (46.6%)	
A3	142 (21.6%)	389 (18.2%)	
Unknown	23 (3.5%)	27 (1.3%)	
Stage of fibrosis[a]			
F0	12 (1.8%)	49 (2.3%)	0.491
F1	201 (30.6%)	721 (33.7%)	
F2	167 (25.4%)	524 (24.5%)	
F3	171 (26.0%)	491 (23.0%)	
F4	98 (14.9%)	331 (15.5%)	
Unknown	8 (1.2%)	22 (1.0%)	
HBeAg[a]			
+	355 (54.0%)	1272 (59.5%)	<0.001
–	280 (42.6%)	723 (33.8%)	
Unknown	22 (3.3%)	143 (6.7%)	
HBeAb[a]			
+	215 (32.7%)	642 (30.0%)	0.001
–	418 (63.6%)	1330 (62.2%)	
Unknown	24 (3.7%)	166 (7.8%)	
Albumin (g/dL)[b]	4.01 ± 0.49 ($n=629$)	4.14 ± 0.49 ($n=1941$)	<0.001
AST (IU/L)[b]	110.2 ± 131.8 ($n=593$)	94.5 ± 131.5 ($n=2023$)	0.011
ALT (IU/L)[b]	183.4 ± 211.1 ($n=641$)	163.5 ± 234.3 ($n=2022$)	0.056
Platelet count ($\times 1000/mm^3$)[b]	165.4 ± 54.9 ($n=629$)	176.9 ± 59.6 ($n=1931$)	<0.001

[a] Data are expressed as positive numbers (%).
[b] Data are expressed as means ± S.D.

4. Discussion

It is clear that this study has several limitations: it is not prospective, it is not randomized, there is no single regimen of lamivudine, and there is a lack of virological analysis (including that of the HBV genotype and that of YMDD mutations). It would be desirable to conduct a well-designed prospective study using controls. However, because lamivudine has been used in general practice under the insurance system in Japan, it is difficult to conduct a prospective and randomized control study of lamivudine therapy for chronic hepatitis B. In addition, it is ethically unacceptable to leave patients untreated for a long period of time in a control group, because lamivudine has been shown to abate hepatitis and improve histological findings of the liver [12–16].

Table 2
Comparison of the incidence of HCC in relation to each background factor between lamivudine group and control group

Parameter	Category	Group	Total number of patients (number)	No. of patients with HCC (number)	Average follow-up period (year)	Adjusted incidence of HCC (%/year)
Gender	Male	Lamivudine group	503	27	5.0	1.07
		Control group	1583	191	6.4	1.89
	Female	Lamivudine group	154	4	4.3	0.60
		Control group	555	48	5.6	1.54
Age (years)	<30	Lamivudine group	110	2	4.7	0.39
		Control group	642	8	5.9	0.21
	30≦ and <40	Lamivudine group	192	9	5.7	0.82
		Control group	646	52	6.8	1.18
	40≦ and <50	Lamivudine group	206	9	5.3	0.82
		Control group	491	75	6.7	2.28
	50≦	Lamivudine group	149	11	3.3	2.24
		Control group	359	104	5.3	5.47
Duration of lamivudine treatment (years)	<1	Lamivudine group	178	7	5.0	0.79
		Control group	–	–	–	–
	1≦ and <2	Lamivudine group	215	13	4.4	1.37
		Control group	–	–	–	–
	2≦ and <3	Lamivudine group	145	7	4.6	1.05
		Control group	–	–	–	–
	3≦	Lamivudine group	107	4	5.9	0.63
		Control group	–	–	–	–
Family clustering of hepatitis B	No	Lamivudine group	242	10	4.8	0.86
		Control group	924	100	6.4	1.69
	Yes	Lamivudine group	376	20	5.0	1.06
		Control group	1085	128	5.9	2.00
	Unknown	Lamivudine group	39	1	4.4	0.58
		Control group	129	11	8.2	1.04
Drinking during the course of the study (>ethanol 80 g/day)	No	Lamivudine group	557	23	4.8	0.86
		Control group	1708	158	5.8	1.59
	Yes	Lamivudine group	69	7	5.6	1.81
		Control group	359	76	7.8	2.71
	Unknown	Lamivudine group	31	1	3.8	0.85
		Control group	71	5	7.7	0.91
IFN therapy	No	Lamivudine group	369	19	4.2	1.23
		Control group	1306	167	6.0	2.13
	Yes	Lamivudine group	269	12	6.0	0.74
		Control group	812	70	6.5	1.33
	Unknown	Lamivudine group	19	0	2.6	0.00
		Control group	20	2	7.9	1.27
Liver histology Grade of inflammation	A0	Lamivudine group	15	0	9.3	0.00
		Control group	84	8	6.6	1.44
	A1	Lamivudine group	194	4	5.4	0.38
		Control group	642	59	6.4	1.44
	A2	Lamivudine group	283	15	4.9	1.08
		Control group	996	109	6.3	1.74
	A3	Lamivudine group	142	10	3.4	2.07
		Control group	389	52	5.5	2.43
	Unknown	Lamivudine group	23	2	6.1	1.43
		Control group	27	11	8.7	4.68

Table 2 (*Continued*)

Parameter	Category	Group	Total number of patients (number)	No. of patients with HCC (number)	Average follow-up period (year)	Adjusted incidence of HCC (%/year)
Stage of fibrosis	F0	Lamivudine group	12	0	7.2	0.00
		Control group	49	3	5.7	1.07
	F1	Lamivudine group	201	6	6.0	0.50
		Control group	721	29	6.7	0.60
	F2	Lamivudine group	167	8	4.7	1.02
		Control group	524	38	5.8	1.25
	F3	Lamivudine group	171	11	4.0	1.61
		Control group	491	61	6.0	2.07
	F4	Lamivudine group	98	6	3.6	1.70
		Control group	331	99	6.2	4.82
	Unknown	Lamivudine group	8	0	6.7	0.00
		Control group	22	9	8.3	4.93
HBeAg	–	Lamivudine group	280	10	4.2	0.85
		Control group	723	83	6.4	1.79
	+	Lamivudine group	355	19	5.3	1.01
		Control group	1272	134	6.0	1.76
	Unknown	Lamivudine group	22	2	6.2	1.47
		Control group	143	22	7.4	2.08
HBeAb	–	Lamivudine group	418	19	4.9	0.93
		Control group	1330	137	6.0	1.72
	+	Lamivudine group	215	10	4.7	0.99
		Control group	642	75	6.3	1.85
	Unknown	Lamivudine group	24	2	6.1	1.37
		Control group	166	27	7.4	2.20
Albumin (g/dL)	<4.0	Lamivudine group	257	19	4.5	1.64
		Control group	619	113	5.7	3.20
	4.0≦	Lamivudine group	372	9	4.9	0.49
		Control group	1322	90	6.1	1.12
AST (IU/L)	<50	Lamivudine group	187	7	5.7	0.66
		Control group	905	82	6.1	1.49
	50≦ and <100	Lamivudine group	200	14	4.7	1.49
		Control group	572	81	5.9	2.40
	100≦ and <200	Lamivudine group	142	7	5.1	0.97
		Control group	367	31	6.2	1.36
	200≦	Lamivudine group	64	2	4.4	0.71
		Control group	179	15	6.0	1.40
ALT (IU/L)	<50	Lamivudine group	117	5	4.7	0.91
		Control group	570	69	6.1	1.98
	50≦ and <100	Lamivudine group	155	7	4.9	0.92
		Control group	506	60	5.8	2.04
	100≦ and <150	Lamivudine group	109	9	4.7	1.76
		Control group	297	36	5.9	2.05
	150≦	Lamivudine group	260	9	4.8	0.72
		Control group	649	44	6.2	1.09
Platelet count ($\times 1000/mm^3$)	<150	Lamivudine group	254	18	3.8	1.86
		Control group	629	125	5.8	3.43
	150≦	Lamivudine group	375	11	5.3	0.55
		Control group	1302	67	6.1	0.84

Table 3
Estimation of effects of covariates following selection of regressor in Cox regression model

Category	Hazard ratio	95% Confidence interval (CI)	p-Value
Lamivudine therapy			
No	1		
Yes	0.49	0.31–0.77	0.002
Gender			
Male	1		
Female	0.42	0.28–0.62	<0.001
Family clustering of hepatitis B			
No	1		
Yes	1.44	1.08–1.94	0.015
Age at liver biopsy			
<40 y.o.	1		
≧40 y.o.	2.09	1.77–2.48	<0.001
Stage of liver fibrosis			
F0 or F1	1		
F2, F3, or F4	1.43	1.24–1.64	<0.001
Serum albumin level			
<4.0 g/dL	1		
≧4.0 g/dL	0.58	0.43–0.79	0.001
Platelet count			
<150 × 1000/μL	1		
≧150 × 1000/μL	0.53	0.38–0.73	<0.001

In the analysis of retrospective studies, great precautions are required in order to eliminate any bias between lamivudine-treated and non-treated groups. To minimize inter-group bias, we conducted with the cooperation of multiple medical institutions and a large number of patients (n=2795). The effect of lamivudine on HCC was ultimately analyzed in a matched case-controlled study. Because the time of liver biopsy was used as the starting point in our analysis, the analytical results were not expected to appropriately reflect lamivudine's effect if the therapy was started a long time after the biopsy. Therefore, from among the 657 patients who received lamivudine therapy, we selected 377 patients who started lamivudine therapy within 2 years after biopsy. For a control group, the same number of patients (n=377) without lamivudine therapy was selected from the 2138 subjects.

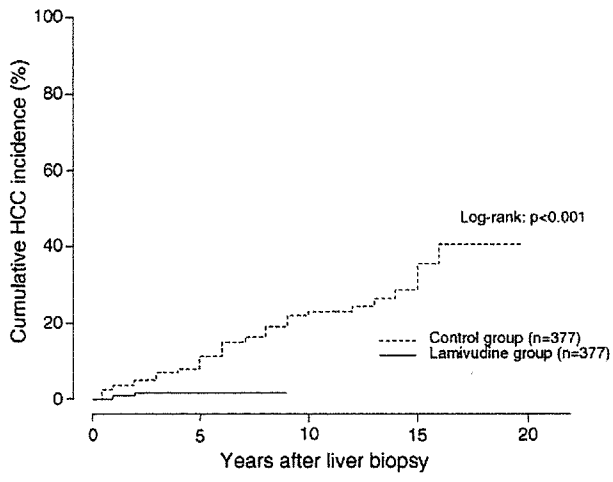

Fig. 1. Comparison of the cumulative HCC incidence between the lamivudine group (solid line) and the control group (broken line) by the Kaplan–Meier method in a case-matched control study. A significant difference was seen between the two groups (p<0.001, log-rank test).

The regimen was not the same in all patients who have been treated by lamivudine. It was transiently discontinued before being recommenced later in some patients, whereas it was uninterrupted throughout the follow-up period in the majority (63%) of subjects in the matched case-controlled study. The duration of lamivudine regimen was not taken into account in the design of our study. Some patients received lamivudine for relatively short periods to improve acute exacerbation of their clinical course in chronic hepatitis B. On the other hand, some patients received lamivudine for the long-term to suppress the development of HCC. In the analysis by a multivariate Cox regression model in all unmatched patients, lamivudine therapy was selected as one of the factors inhibiting the occurrence of HCC. In the matched case-controlled study, the annual occurrence rate of HCC was significantly lower (0.4%/(patient/year)) in the lamivudine group than in the control group (1.8%/(patient/year)), suggesting that lamivudine treatment is effective for inhibiting the occurrence of HCC.

Recently, Liaw et al. conducted a multicenter, centrally randomized, double-blind, placebo-controlled, parallel group study to evaluate the effects of lamivudine on the progression of chronic hepatitis B to hepatic cancer [21]. They randomized 651 patients with histologically confirmed (F3 and F4), compensated hepatic cirrhosis to receive either lamivudine or a placebo at a ratio of 2:1 and continued the treatment for up to 5 years. The study was terminated after a median treatment duration of 32.4 months (range 0–42) owing to a significant difference between the groups in the number of end points reached. The end points were reached by 7.8% of the patients receiving lamivudine and 17.7% of those receiving placebo (hazard ratio for disease progression, 0.45; p=0.001). The Child–Pugh score increased in 3.4% of the patients receiving lamivudine and in 8.8% of those receiving placebo (hazard ratio, 0.45; p=0.02), whereas HCC occurred in 3.9% of those in the lamivudine group and in 7.4% of those in the placebo group (hazard ratio, 0.49: p=0.047). The results of our analysis, which included patients with F0 through F2 hepatic fibrosis, were similar to those of Liaw et al. [21]. Thus, two studies demonstrated that the use of potent anti-viral agents such as lamivudine represents a major advance in the treatment of chronic hepatitis B and slows the progression of severe liver disease to liver cirrhosis as well as HCC.

Both hepatitis B and C are caused by persistent infection with hepatitis viruses, and both have a high probability of resulting in HCC. For this reason, these two diseases have a number of common traits, but some differences have been noted in their relationships with HCC. Among both

Table 4
Comparison of background factors between lamivudine group and control group assessed at the time of liver biopsy (matched case-controlled study)

Parameter	Lamivudine group ($n=377$)	Control group ($n=377$)	p-Value
Gender[a]			
Male	276 (73.2%)	273 (72.4%)	0.806
Female	101 (26.8%)	104 (27.6%)	
Age (years)[b]	41.5 ± 12.0	41.4 ± 12.2	0.950
Follow-up period (years)[b]	2.7 ± 2.1	5.3 ± 4.7	<0.001
Family clustering of hepatitis B[a]			
Yes	238 (63.1%)	242 (64.2%)	0.762
No	139 (36.9%)	135 (35.8%)	
Drinking during the course of the study (>ethanol 80 g/day)[a]			
Yes	38 (10.1%)	62 (16.4%)	0.007
No	333 (88.3%)	314 (83.3%)	
Unknown	6 (1.6%)	1 (0.3%)	
IFN therapy[a]			
Yes	129 (34.2%)	143 (37.9%)	0.046
No	236 (62.6%)	231 (61.3%)	
Unknown	12 (3.2%)	3 (0.8%)	
Liver histology			
Grade of inflammation[a]			
A0	6 (1.6%)	18 (4.8%)	0.001
A1	110 (29.2%)	101 (26.8%)	
A2	157 (41.6%)	186 (49.3%)	
A3	98 (26.0%)	72 (19.1%)	
Unknown	6 (1.6%)	0 (0.0%)	
Stage of fibrosis[a]			
F0	7 (1.9%)	6 (1.6%)	0.647
F1	103 (27.3%)	117 (31.0%)	
F2	95 (25.2%)	97 (25.7%)	
F3	107 (28.4%)	90 (23.9%)	
F4	65 (17.2%)	67 (17.8%)	
HBeAg[a]			
+	193 (51.2%)	220 (58.4%)	0.005
–	178 (47.2%)	141 (37.4%)	
Unknown	6 (1.6%)	16 (4.2%)	
HBeAb[a]			
+	126 (33.4%)	121 (32.1%)	0.030
–	245 (65.0%)	237 (62.9%)	
Unknown	6 (1.6%)	19 (5.0%)	
Albumin (g/dL)[b]	4.00 ± 0.51	4.00 ± 0.52	0.989
AST (IU/L)[b]	118.5 ± 155.4	95.5 ± 126.4	0.031
ALT (IU/L)[b]	191.7 ± 234.8	151.5 ± 180.5	0.009
Platelet count ($\times 1000/mm^3$)[b]	161.7 ± 52.7	164.3 ± 59.5	0.523

[a] Data are expressed as positive numbers (%).
[b] Data are expressed as means ± S.D.

hepatitis B patients and hepatitis C patients, HCC occurs mainly in those with advanced hepatic fibrosis, but the incidence of liver cirrhosis as a background of liver disease is lower in patients with B than in those with C. Furthermore, among hepatitis C patients HCC occurs mainly in those 60 years or older, while among hepatitis B patients it occurs mainly in those under 60 [22–24]. Studies on the cumulative incidence of HCC in hepatitis B patients showed that the HCC incidence increases linearly during the initial 12 years, plateaus, and then increases again in the 17th or 18th year [24,25]. In hepatitis C patients, on the other hand, the HCC incidence shows a continuous, linear increase [26,27]. Various findings obtained to date suggest that these clinical differences are related not only to differences in the hepatitis viral infection route and the timing of infection but also to differences in the mechanisms underlying cancer associated with hepatitis B and C. HCV is an RNA virus, and viral genes are not integrated into the host's genes, whereas HBV is a DNA virus with reverse-transcriptase activity. Thus, HBV genes are often integrated into the host's chromosomes