Hepatology Research 2007; 37: 676–691 doi: 10.1111/j.1872-034X.2007.00119.x

Special Report

Report of the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan†

Iwao Ikai, Shigeki Arii, Masatoshi Okazaki, Kiwamu Okita, Masao Omata, Masamichi Kojiro, Kenichi Takayasu, Yasuni Nakanuma, Masatoshi Makuuchi, Yutaka Matsuyama, Morito Monden and Masatoshi Kudo

The Liver Cancer Study Group of Japan, Kyoto, Japan

In the 17th Nationwide Follow-up Survey of Primary Liver Cancer in Japan, 18 213 individuals were newly registered as patients with primary liver cancer at 645 medical institutions over a period of 2 years (from 1 January 2002 to 31 December 2003). Of these patients, 94.2% had hepatocellular carcinoma (HCC) and 4.1% had intrahepatic cholangiocarcinoma (ICC). In addition, 24 705 follow-up patients were registered in the survey. Epidemiological and clinicopathological factors, diagnosis and treatment were investigated in the newly registered patients, and the cumulative survival rates of newly registered patients in the 12th to 17th follow-up surveys conducted between 1992 and 2003 were calculated for each histological type (HCC, ICC, and combined HCC and ICC) and stratified by background factors and treatment. The data obtained in this follow-up survey should contribute to future research and medical practice for primary liver cancer.

Key words: combined hepatic carcinoma, cumulative survival rate, follow-up survey, hepatocellular carcinoma, intrahepatic cholangiocarcinoma

INTRODUCTION

SINCE 1969, THE Liver Cancer Study Group of Japan (LCSGJ) has conducted 16 nationwide follow-up surveys of primary liver cancer in patients in member hospitals and cooperative institutions in Japan, with the goal of promoting research and clinical treatment of liver cancer.[1–11] The 17th Nationwide Follow-up Survey of Primary Liver Cancer was conducted over a 2-year period from 1 January 2002 to 31 December 2003, and 18 213 patients with primary liver cancer were newly registered at 645 institutions. In addition, 24 705 registered patients were followed up with a valid response rate of 70.0%. Items related to epidemiological and clinicopathological factors, diagnosis and treatment were investigated in the newly registered patients. Cumulative survival rates of newly registered patients in the 12th to 17th follow-up surveys conducted between 1992 and 2003 were calculated for each histological type and based on background factors and treatment.

Correspondence: Dr Iwao Ikai, The Liver Cancer Study Group of Japan, 403 Bear House, 40 Sanno-cho, Shogoin, Sakyo-ku, Kyoto 606-8392, Japan. Email: kangan@nihon-kangan.jp
Received 19 January 2007; accepted 7 March 2007.

†Data the authors present in this article were also published, in the Japanese language, in *Kanzo* 48(3), 2007. Permission granted by the Japan Society of Hepatology.

METHODS

Basic statistics

THE SUBJECTS WERE 18 213 patients with primary liver cancer who underwent treatment or autopsy during a 2-year period from 1 January 2002 to 31 December 2003 at 645 institutions in Japan. Doctors in each institution completed a form developed by the Follow-up Survey Committee of the Liver Cancer Study Group of Japan (chairperson: Masatoshi Kudo). In cases with an inconsistency between the clinical, pathological and autopsy diagnoses, the autopsy and pathological diagnoses were given first and second priority, respectively. Of the 18 213 patients, 94.2% had hepatocellular carcinoma and 4.1% had intrahepatic cholangiocarcinoma (Table 1). The results in the tables are categorized into hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (ICC), and combined HCC and ICC,

Table 1 Classification of primary liver cancer

Diagnosis	Male $n = 13\,017$	Female $n = 5196$	Total $n = 18\,213$
HCC	12 341	4818	17 159 (94.2%)
ICC	470	279	749 (4.1%)
Combined	93	30	123 (0.7%)
Cystadenocarcinoma	15	6	21 (0.1%)
Hepatoblastoma	8	4	12 (0.1%)
Sarcoma	11	8	19 (0.1%)
Others	79	51	130 (0.7%)

Combined, combined hepatocellular and cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma. After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

for which more than 100 newly registered cases appeared in the current follow-up survey. The abbreviations in the tables conform to the *The General Rules for the Clinical and Pathological Study of Primary Liver Cancer, Second English Edition*.[12]

Cumulative survival rate

The cumulative survival rates of newly registered patients in the 12th to 17th 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) and based on different background factors and treatment, including hepatectomy, local ablation therapy, and transcatheter arterial embolization. In the report of the 16th Nationwide Follow-up Survey of Primary Liver Cancer and in prior reports, patients who died due to liver-unrelated causes ('other causes' in Table 2) were considered as censored cases and patients who died due to liver-related events were considered to be uncensored cases. In the present report, however, patients who had died from either liver-related or liver-unrelated causes were considered to be uncensored cases in estimating cumulative survival rates.

RESULTS

Basic statistics

Causes of death during the study period

FOR HCC, THE mortality of newly registered patients during the study period was 15.8%: the death rate due to cancer was 55.1% and death rates due to hepatic failure, gastrointestinal bleeding and rupture of esophagogastric varices were 21.5%, 2.0% and 3.1%, respectively. Of the patients who did not survive, 44 died within 30 days after surgery; these patients represented 0.8% of the 5327 patients who underwent surgery. For

Table 2 Causes of death of patients with primary liver cancer

	HCC	ICC	Combined
Alive	13 946	454	75
Total deaths of between 2002 and 2003	2 700	270	44
Cancer death	1 487 (55.1%)	216 (80.0%)	30 (68.2%)
Hepatic failure	581 (21.5%)	28 (10.4%)	5 (11.4%)
Gastrointestinal bleeding	55 (2.0%)	2 (0.7%)	2 (4.5%)
Rupture of esophageal varices	85 (3.1%)	0 (0.0%)	3 (6.8%)
Rupture of tumor	172 (6.4%)	0 (0.0%)	1 (2.3%)
Operative death	44 (1.6%)	5 (1.9%)	1 (2.3%)
Other causes	276 (10.2%)	19 (7.0%)	2 (4.5%)
Unknown	402	20	3

Combined, combined hepatocellular and cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma. After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

Table 3 Clinical profile of patients with primary liver cancer

	HCC	ICC	Combined
Diagnosis	*n* = 33 731	*n* = 1505	*n* = 216
Computed tomography	13 160 (39.0%)	581 (38.6%)	89 (41.2%)
Magnetic resonance imaging	2 767 (8.2%)	181 (12.0%)	14 (6.5%)
Ultrasonography	9 257 (27.4%)	366 (24.3%)	59 (27.3%)
Selective angiography	6 495 (19.3%)	200 (13.3%)	34 (15.7%)
Histopathological finding	1 746 (5.2%)	115 (7.6%)	17 (7.9%)
Others	306 (0.9%)	62 (4.1%)	3 (1.4%)
Encephalopathy	*n* = 16 004	*n* = 699	*n* = 115
None	15 439 (96.5%)	696 (99.6%)	113 (98.3%)
Mild	425 (2.7%)	1 (0.1%)	0 (0.0%)
Coma occasionally	140 (0.9%)	2 (0.3%)	2 (1.7%)
Ascites	*n* = 16 321	*n* = 709	*n* = 116
Absent	14 230 (87.2%)	662 (93.4%)	105 (90.5%)
Slight	1 259 (7.7%)	18 (2.5%)	5 (4.3%)
Moderate	832 (5.1%)	29 (4.1%)	6 (5.2%)
Serum bilirubin (mg/mL)	*n* = 16 506	*n* = 685	*n* = 113
0.0–0.9	9 353 (56.7%)	427 (62.3%)	78 (69.0%)
1.0–1.9	5 535 (33.5%)	135 (19.7%)	26 (23.0%)
2.0–3.0	974 (5.9%)	23 (3.4%)	6 (5.3%)
≥3.1	644 (3.9%)	100 (14.6%)	3 (2.7%)
Serum albumin (g/dL)	*n* = 16 326	*n* = 668	*n* = 108
<2.8	1 252 (7.7%)	42 (6.3%)	3 (2.8%)
2.8–2.9	884 (5.4%)	35 (5.2%)	4 (3.7%)
3.0–3.5	4 886 (29.9%)	130 (19.5%)	24 (22.2%)
>3.5	9 304 (57.0%)	461 (69.0%)	77 (71.3%)
ICG R_{15} (%)	*n* = 11 003	*n* = 438	*n* = 89
≤14	3 736 (34.0%)	295 (67.4%)	51 (57.3%)
15–24	3 372 (30.6%)	100 (22.8%)	17 (19.1%)
25–40	2 558 (23.2%)	38 (8.7%)	17 (19.1%)
>40	1 337 (12.2%)	5 (1.1%)	4 (4.5%)
Prothrombin activity (%)	*n* = 15 256	*n* = 630	*n* = 107
<40	217 (1.4%)	8 (1.3%)	1 (0.9%)
40–49	348 (2.3%)	7 (1.1%)	3 (2.8%)
50–70	3 375 (22.1%)	62 (9.8%)	15 (14.0%)
71–80	3 546 (23.2%)	74 (11.7%)	21 (19.6%)
>80	7 770 (50.9%)	479 (76.0%)	67 (62.6%)
Platelet count ($\times 10^4/mm^3$)	*n* = 16 476	*n* = 673	*n* = 112
<3.0	130 (0.8%)	2 (0.3%)	0 (0.0%)
3.0–4.9	880 (5.3%)	3 (0.4%)	1 (0.9%)
5.0–9.9	5 437 (33.0%)	45 (6.7%)	20 (17.9%)
10.0–14.9	4 907 (29.8%)	75 (11.1%)	27 (24.1%)
15.0–19.9	2 839 (17.2%)	141 (21.0%)	31 (27.7%)
20.0–99.9	2 226 (13.5%)	398 (59.1%)	33 (29.5%)
>100	57 (0.3%)	9 (1.3%)	0 (0.0%)
Liver damage classification by LCSGJ	*n* = 14 295	*n* = 594	*n* = 105
A	8 478 (59.3%)	483 (81.3%)	75 (71.4%)
B	4 700 (32.9%)	81 (13.6%)	27 (25.7%)
C	1 117 (7.8%)	30 (5.1%)	3 (2.9%)

Table 3 *Continued*

	HCC	ICC	Combined
Child–Pugh classification	*n* = 15 651	*n* = 654	*n* = 112
A	11 119 (71.0%)	541 (82.7%)	87 (77.7%)
B	3 603 (23.0%)	94 (14.4%)	23 (20.5%)
C	929 (5.9%)	19 (2.9%)	2 (1.8%)
AFP (ng/mL)	*n* = 15 831	*n* = 496	*n* = 110
<15	5 756 (36.4%)	415 (83.7%)	37 (33.6%)
≤199	5 786 (36.5%)	58 (11.7%)	32 (29.1%)
≤399	902 (5.7%)	8 (1.6%)	8 (7.3%)
≤999	907 (5.7%)	7 (1.4%)	8 (7.3%)
≤9999	1 450 (9.2%)	7 (1.4%)	15 (13.6%)
≤99 999	704 (4.4%)	1 (0.2%)	8 (7.3%)
≥100 000	326 (2.1%)	0 (0.0%)	2 (1.8%)
AFP-L3 (%)	*n* = 6321	*n* = 76	*n* = 44
ND	2 234 (35.3%)	53 (69.7%)	10 (22.7%)
<5.0	1 349 (21.3%)	7 (9.2%)	1 (2.3%)
≤9.9	491 (7.8%)	3 (3.9%)	2 (4.5%)
≤14.9	309 (4.9%)	0 (0.0%)	2 (4.5%)
≤19.9	189 (3.0%)	1 (1.3%)	2 (4.5%)
≥20.0	1 749 (27.7%)	12 (15.8%)	27 (61.4%)
PIVKA-II (mAU/mL)	*n* = 14 209	*n* = 341	*n* = 96
<40	5 833 (41.1%)	289 (84.8%)	46 (47.9%)
≤99	2 004 (14.1%)	19 (5.6%)	8 (8.3%)
≤299	1 795 (12.6%)	12 (3.5%)	13 (13.5%)
≤499	641 (4.5%)	0 (0.0%)	3 (3.1%)
≤999	778 (5.5%)	7 (2.1%)	6 (6.3%)
≤2999	985 (6.9%)	7 (2.1%)	4 (4.2%)
≤9999	892 (6.3%)	3 (0.9%)	7 (7.3%)
≥10 000	1 281 (9.0%)	4 (1.2%)	9 (9.4%)
CEA (ng/mL)	*n* = 5716	*n* = 637	*n* = 79
<2.5	2 280 (39.9%)	219 (34.4%)	31 (39.2%)
≤4.9	2 078 (36.4%)	163 (25.6%)	19 (24.1%)
≤9.9	1 067 (18.7%)	100 (15.7%)	18 (22.8%)
≤19.9	211 (3.7%)	50 (7.8%)	6 (7.6%)
≤49.9	40 (0.7%)	48 (7.5%)	2 (2.5%)
≤99.9	14 (0.2%)	22 (3.5%)	1 (1.3%)
≥100	26 (0.5%)	35 (5.5%)	2 (2.5%)
CA 19-9 (U/mL)	*n* = 4533	*n* = 635	*n* = 67
<37	2 896 (63.9%)	206 (32.4%)	27 (40.3%)
≤99	1 134 (25.0%)	76 (12.0%)	16 (23.9%)
≤299	384 (8.5%)	84 (13.2%)	13 (19.4%)
≤999	70 (1.5%)	79 (12.4%)	6 (9.0%)
≤2999	26 (0.6%)	71 (11.2%)	3 (4.5%)
≤9999	13 (0.3%)	61 (9.6%)	1 (1.5%)
≥10 000	10 (0.2%)	58 (9.1%)	1 (1.5%)

AFP, alpha-fetoprotein; AFP-L3, lectin-reactive alpha-fetoprotein; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembrionic antigen; Combined, combined hepatocellular and cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; ICG R_{15}, indocyanine green retention rate at 15 min; LCSGJ, Liver Cancer Study Group of Japan; ND, not determined; PIVKA-II, protein induced by Vitamin K absence-II.

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

	HCC	ICC	Combined
HBsAg	*n* = 16 340	*n* = 696	*n* = 115
Negative	13 803 (84.5%)	653 (93.8%)	93 (80.9%)
Positive	2 531 (15.5%)	43 (6.2%)	22 (19.1%)
Undetermined	6 (0.0%)	0 (0.0%)	0 (0.0%)
HBsAb	*n* = 5281	*n* = 179	*n* = 54
Negative	4 248 (80.4%)	147 (82.1%)	40 (74.1%)
Positive	1 004 (19.0%)	30 (16.8%)	14 (25.9%)
Undetermined	29 (0.5%)	2 (1.1%)	0 (0.0%)
HBcAb	*n* = 4149	*n* = 134	*n* = 40
Negative	1 983 (47.8%)	78 (58.2%)	13 (32.5%)
Positive	2 138 (51.5%)	56 (41.8%)	27 (67.5%)
Undetermined	28 (0.7%)	0 (0.0%)	0 (0.0%)
HBeAg	*n* = 3320	*n* = 93	*n* = 28
Negative	2 801 (84.4%)	89 (95.7%)	25 (89.3%)
Positive	506 (15.2%)	4 (4.3%)	3 (10.7%)
Undetermined	13 (0.4%)	0 (0.0%)	0 (0.0%)
HBeAb	*n* = 3195	*n* = 91	*n* = 27
Negative	1 689 (52.9%)	51 (56.0%)	17 (63.0%)
Positive	1 455 (45.5%)	40 (44.0%)	10 (37.0%)
Undetermined	51 (1.6%)	0 (0.0%)	0 (0.0%)
HCVAb	*n* = 16 504	*n* = 700	*n* = 115
Negative	5 004 (30.3%)	564 (80.6%)	64 (55.7%)
Positive	11 488 (69.6%)	134 (19.1%)	51 (44.3%)
Undetermined	12 (0.1%)	2 (0.3%)	0 (0.0%)

Combined, combined hepatocellular and cholangiocarcinoma; HBcAb, antibody to hepatitis B core antigen; HBeAb, antibody to hepatitis B e antigen; HBeAg, hepatitis B e antigen; HBsAb, antibody to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCVAb, hepatitis C virus antibody; ICC, intrahepatic cholangiocarcinoma.
After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

ICC, the mortality of newly registered patients during the study period was 36.3% and death rates due to cancer and hepatic failure were 80.0% and 10.4%, respectively (Table 2).

Past history

Of patients with HCC, 78.2% and 59.9% had a past history of chronic hepatitis and liver cirrhosis, respectively, whereas only 18.2% and 6.4% of ICC patients had this history, respectively. Interferon therapy had been given to 16.1% of HCC patients due to concomitant chronic hepatitis, and 28.8% and 22.3% of HCC patients and 9.1% and 12.1% of ICC patients had a past history of blood transfusion and habitual alcohol intake, respectively.

Clinical diagnosis

Clinical diagnosis of primary liver cancer in patients with HCC was made at a mean age of 65.5 years in males and 69.4 years in females. For patients with ICC, the corresponding mean ages were 66.5 years in males and 68.3 years in females. The mean ages were higher than those in the 16th survey. The male to female ratios for HCC and ICC patients were 2.55 and 1.64, 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 59.3%, 32.9% and 7.8% of patients, respectively, whereas 71.0%, 23.0% and 5.9% of HCC patients were in the Child–Pugh Class A, B and C categories, respectively (Table 3). Of the HCC patients, 36.4%, 36.5% and 27.1% had serum alpha-fetoprotein (AFP) levels of <15 ng/mL, 15–199 ng/mL and ≥200 ng/mL, respectively, and 64.4%, 4.9% and 30.7% of patients with HCC had serum levels of lectin-reactive AFP (AFP-L3) of <10%, 10.0–14.9% and ≥15%, respectively. Of the HCC patients, 41.1%, 14.1% and 44.8% had a protein induced by vitamin K absence or antagonist-II (PIVKA-II) level of <40 mAU/mL, 40–99 mAU/mL and

Table 5 Tumor characteristics by imaging studies

	HCC	ICC	Combined
Tumor size by imaging studies (cm)	*n* = 15 788	*n* = 604	*n* = 106
≤1	687 (4.4%)	2 (0.3%)	3 (2.8%)
≤2	4 436 (28.1%)	58 (9.6%)	11 (10.4%)
≤3	3 939 (24.9%)	106 (17.5%)	17 (16.0%)
≤5	3 495 (22.1%)	181 (30.0%)	30 (28.3%)
≤10	2 336 (14.8%)	200 (33.1%)	35 (33.0%)
≤15	598 (3.8%)	48 (7.9%)	10 (9.4%)
≤20	175 (1.1%)	8 (1.3%)	0 (0.0%)
≤25	50 (0.3%)	0 (0.0%)	0 (0.0%)
>25	72 (0.5%)	1 (0.2%)	0 (0.0%)
No. tumors by imaging studies	*n* = 16 187	*n* = 655	*n* = 110
1	9 365 (57.9%)	509 (77.7%)	65 (59.1%)
2	2 850 (17.6%)	42 (6.4%)	16 (14.5%)
3	1 265 (7.8%)	21 (3.2%)	7 (6.4%)
4	505 (3.1%)	9 (1.4%)	2 (1.8%)
5	254 (1.6%)	4 (0.6%)	4 (3.6%)
≥6	1 948 (12.0%)	70 (10.7%)	16 (14.5%)
Portal vein invasion by imaging studies	*n* = 15 169	*n* = 562	*n* = 110
Image-Vp0	13 184 (86.9%)	366 (65.1%)	76 (69.1%)
Image-Vp1	463 (3.1%)	39 (6.9%)	9 (8.2%)
Image-Vp2	449 (3.0%)	57 (10.1%)	6 (5.5%)
Image-Vp3	616 (4.1%)	85 (15.1%)	12 (10.9%)
Image-Vp4	457 (3.0%)	15 (2.7%)	7 (6.4%)
Hepatic vein invasion by imaging studies	*n* = 14 387	*n* = 544	*n* = 104
Image-Vv0	13 775 (95.7%)	469 (86.2%)	93 (89.4%)
Image-Vv1	215 (1.5%)	19 (3.5%)	5 (4.8%)
Image-Vv2	180 (1.3%)	32 (5.9%)	2 (1.9%)
Image-Vv3	217 (1.5%)	24 (4.4%)	4 (3.8%)
Bile duct invasion by imaging studies	*n* = 14 219	*n* = 527	*n* = 104
Image-B0	13 859 (97.5%)	291 (55.2%)	95 (91.3%)
Image-B1	141 (1.0%)	46 (8.7%)	4 (3.8%)
Image-B2	100 (0.7%)	69 (13.1%)	4 (3.8%)
Image-B3	82 (0.6%)	81 (15.4%)	0 (0.0%)
Image-B4	37 (0.3%)	40 (7.6%)	1 (1.0%)
Distant metastases by imaging studies			
Lung	259	25	3
Bone	207	17	1
Adrenal gland	57	4	2
Lymph node	199	113	9
Brain	12	1	0
Peritoneum	43	15	2
Others	30	10	0
Esophageal or gastric varices	*n* = 4894	*n* = 34	*n* = 18
F1, RC (−)	2 604 (53.2%)	24 (70.6%)	9 (50.0%)
F2 or RC (+)	1 990 (40.7%)	8 (23.5%)	7 (38.9%)
Rupture	300 (6.1%)	2 (5.9%)	2 (11.1%)

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; Combined, combined hepatocellular and cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; Vp0, absence of invasion of (or tumor thrombus in) the portal vein; Vp1, invasion (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 contra-lateral portal vein branch to the primarily involved lobe; Vv0, absence of invasion of (or tumor thrombus in) the hepatic 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. After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

Table 6 Main treatment of patients with primary liver cancer

	HCC	ICC	Combined
Treatment for tumor	*n* = 15 681	*n* = 597	*n* = 106
Surgery	5268 (33.6%)	408 (68.3%)	73 (68.9%)
Local ablation therapy	4890 (31.2%)	14 (2.3%)	5 (4.7%)
Transcatheter arterial chemoembolization	4636 (29.6%)	27 (4.5%)	12 (11.3%)
Chemotherapy	765 (4.9%)	117 (19.6%)	15 (14.2%)
Others	122 (0.8%)	31 (5.2%)	1 (0.9%)
Best supportive care	*n* = 1324	*n* = 133	*n* = 13

Combined, combined hepatocellular and cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma. After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

≥100 mAU/mL, respectively. In patients with ICC, 60.0%, 15.7% and 24.3% had a carcinoembryonic antigen level of <5.0 ng/mL, 5.0–9.9 ng/mL and ≥10 ng/mL, respectively, and 32.4%, 12.0% and 55.6% had a carbohydrate antigen (CA) 19-9 level of <37 U/mL, 37–99 U/mL and ≥100 U/mL, respectively (Table 3).

Of the patients with HCC, ICC, and combined HCC and ICC, those who were positive for hepatitis B surface antigen (HBsAg) comprised 15.5%, 6.2% and 19.1%, respectively. The percentages of antihepatitis C virus antibody-positive patients were 69.6%, 19.1% and 44.3%, respectively (Table 4).

Tumor size was determined using diagnostic imaging. Of patients with HCC, 32.5% and 47.0% had tumors of ≤2 cm and 2.1–5.0 cm, respectively. The corresponding numbers for patients with ICC were 9.9% and 47.5%, respectively (Table 5). Of the tumors, 57.9% and 77.7% were solitary in patients with HCC and ICC, respectively. In patients with HCC, 92.0% had a tumor stain, 2.3% exhibited tumor rupture, and 40.7% had esophagogastric varices of F2 or RC(+) or higher.

Major treatment

Of patients with HCC, 33.6%, 31.2% and 29.6% had undergone surgery (hepatectomy and liver transplantation), local ablation therapy and transcatheter arterial embolization, respectively. In patients with ICC, 68.3% and 19.6% had undergone surgery (hepatectomy) and chemotherapy, respectively, and in patients with combined HCC and ICC, 68.9% and 11.3% had undergone surgery (hepatectomy) and transcatheter arterial chemoembolization, respectively (Table 6). Among the HCC patients, 75.1%, 23.7% and 1.2% who underwent surgery, 55.9%, 38.8% and 5.3% of those treated with local ablation therapy, and 54.1%, 38.2% and 7.8% of those treated with transcatheter arterial embolization were in liver damage classes A, B and C, respectively.

Surgery

Of patients with HCC, 5282 underwent hepatectomy and 45 received a liver transplantation. Macroscopic analysis of the resected specimens showed that 58.2% of cases were of the single nodular type. Of patients with ICC, 408 underwent hepatectomy and one received a liver transplant, and 65.8% of these cases were of the mass-forming type. Macroscopic results from the resected specimens are shown in Table 7. In the HCC patients who underwent hepatectomy, tumors of size ≤ 2 cm, 2–5 cm, and 5–10 cm were found in 17.6%, 53.7% and 20.1% of patients, respectively, and 74% of the tumors were solitary. Vascular invasion in the portal vein, hepatic vein and bile duct was found in 15.1%, 7.5% and 2.7% of the patients, respectively. Regarding findings in non-cancerous parts of the liver, normal liver, chronic hepatitis/liver fibrosis and liver cirrhosis were found in 9.0%, 46.9% and 44.0% of the patients, respectively. The extent of surgical resection was Hr0, HrS, Hr1, Hr2 and Hr3 in 31.4%, 24.5%, 21.1%, 20.5% and 2.5% of the patients, respectively (Table 7).

In patients with ICC, tumors of size ≤ 2 cm, 2–5 cm, and 5–10 cm were found in 8.7%, 46.7% and 34.0% of patients, respectively, and 80.8% of the tumors were solitary.

Local ablation therapy

Of patients with HCC, 5986 underwent local ablation therapy. Ethanol injection therapy, microwave

Table 7 Operative findings or macroscopic pathological characteristics of surgical specimen (hepatic resection)

	HCC	ICC	Combined
Tumor size (cm)	*n* = 4763	*n* = 353	*n* = 69
≤1	71 (1.5%)	3 (0.8%)	2 (2.9%)
≤2	769 (16.1%)	28 (7.9%)	5 (7.2%)
≤3	1195 (25.1%)	53 (15.0%)	15 (21.7%)
≤5	1361 (28.6%)	112 (31.7%)	23 (33.3%)
≤10	957 (20.1%)	120 (34.0%)	18 (26.1%)
≤15	283 (5.9%)	31 (8.8%)	6 (8.7%)
≤20	86 (1.8%)	5 (1.4%)	0 (0.0%)
≤25	19 (0.4%)	0 (0.0%)	0 (0.0%)
>25	22 (0.5%)	1 (0.3%)	0 (0.0%)
No. tumors	*n* = 4741	*n* = 359	*n* = 67
1	3509 (74.0%)	290 (80.8%)	46 (68.7%)
2	676 (14.3%)	22 (6.1%)	11 (16.4%)
3	224 (4.7%)	12 (3.3%)	2 (3.0%)
4	86 (1.8%)	9 (2.5%)	1 (1.5%)
5	44 (0.9%)	1 (0.3%)	2 (3.0%)
≥6	202 (4.3%)	25 (7.0%)	5 (7.5%)
Tumor extent	*n* = 4802	*n* = 370	*n* = 70
Hs	1992 (41.5%)	44 (11.9%)	22 (31.4%)
H1	1285 (26.8%)	115 (31.1%)	17 (24.3%)
H2	1186 (24.7%)	173 (46.8%)	24 (34.3%)
H3	245 (5.1%)	35 (9.5%)	4 (5.7%)
H4	94 (2.0%)	3 (0.8%)	3 (4.3%)
Growth type	*n* = 4757	*n* = 348	*n* = 67
Eg	4429 (93.1%)	161 (46.3%)	46 (68.7%)
Ig	328 (6.9%)	187 (53.7%)	21 (31.3%)
Capsule formation	*n* = 4770	*n* = 354	*n* = 67
Fc (−)	1073 (22.5%)	316 (89.3%)	48 (71.6%)
Fc (+)	3697 (77.5%)	38 (10.7%)	19 (28.4%)
Capsule infiltration	*n* = 3610	*n* = 33	*n* = 19
Fc-inf (−)	1976 (54.7%)	12 (36.4%)	8 (42.1%)
Fc-inf (+)	1634 (45.3%)	21 (63.6%)	11 (57.9%)
Septum formation	*n* = 4497	*n* = 344	*n* = 62
Sf (−)	2053 (45.7%)	332 (96.5%)	41 (66.1%)
Sf (+)	2444 (54.3%)	12 (3.5%)	21 (33.9%)
Serosal invasion	*n* = 4745	*n* = 354	*n* = 67
S0	3822 (80.5%)	175 (49.4%)	48 (71.6%)
S1	673 (14.2%)	133 (37.6%)	15 (22.4%)
S2	151 (3.2%)	44 (12.4%)	3 (4.5%)
S3	99 (2.1%)	2 (0.6%)	1 (1.5%)
Lymph node metastasis	*n* = 4546	*n* = 360	*n* = 66
Absent	4500 (99.0%)	243 (67.5%)	57 (86.4%)
Present	46 (1.0%)	117 (32.5%)	9 (13.6%)
Portal vein invasion	*n* = 4795	*n* = 364	*n* = 68
Vp0	4073 (84.9%)	214 (58.8%)	47 (69.1%)
Vp1	378 (7.9%)	49 (13.5%)	9 (13.2%)
Vv2	158 (3.3%)	45 (12.4%)	5 (7.4%)
Vp3	122 (2.5%)	48 (13.2%)	5 (7.4%)
Vp4	64 (1.3%)	8 (2.2%)	2 (2.9%)
Hepatic vein invasion	*n* = 4768	*n* = 360	*n* = 69
Vv0	4410 (92.5%)	275 (76.4%)	63 (91.3%)
Vv1	208 (4.4%)	42 (11.7%)	4 (5.8%)
Vv2	100 (2.1%)	26 (7.2%)	2 (2.9%)
Vv3	50 (1.0%)	17 (4.7%)	0 (0.0%)
Hepatic arterial invasion	*n* = 4574	*n* = 335	*n* = 68
Va0	4530 (99.0%)	281 (83.9%)	66 (97.1%)
Va1	32 (0.7%)	21 (6.3%)	1 (1.5%)
Va2	9 (0.2%)	17 (5.1%)	1 (1.5%)
Va3	3 (0.1%)	16 (4.8%)	0 (0.0%)

Table 7 *Continued*

	HCC	ICC	Combined
Bile duct invasion	*n* = 4771	*n* = 354	*n* = 69
B0	4642 (97.3%)	165 (46.6%)	63 (91.3%)
B1	53 (1.1%)	53 (15.0%)	4 (5.8%)
B2	34 (0.7%)	50 (14.1%)	2 (2.9%)
B3	25 (0.5%)	56 (15.8%)	0 (0.0%)
B4	17 (0.4%)	30 (8.5%)	0 (0.0%)
Intrahepatic metastasis	*n* = 4765	*n* = 365	*n* = 69
Im0	3666 (76.9%)	262 (71.8%)	51 (73.9%)
Ims	180 (3.8%)	12 (3.3%)	4 (5.8%)
Im1	356 (7.5%)	30 (8.2%)	4 (5.8%)
Im2	387 (8.1%)	48 (13.2%)	7 (10.1%)
Im3	176 (3.7%)	13 (3.6%)	3 (4.3%)
Peritoneal dissemination	*n* = 4775	*n* = 368	*n* = 66
Absent	4745 (99.4%)	354 (96.2%)	66 (100.0%)
Present	30 (0.6%)	14 (3.8%)	0 (0.0%)
Surgical margin	*n* = 4626	*n* = 352	*n* = 65
Presence of cancer invasion	271 (5.9%)	47 (13.4%)	7 (10.8%)
Absence of cancer invasion	4355 (94.1%)	305 (86.6%)	58 (89.2%)
Non-cancerous portion	*n* = 4665	*n* = 345	*n* = 66
Normal liver	422 (9.0%)	259 (75.1%)	9 (13.6%)
Chronic hepatitis/liver fibrosis	2190 (46.9%)	56 (16.2%)	39 (59.1%)
Liver cirrhosis	2053 (44.0%)	30 (8.7%)	18 (27.3%)
Extent of hepatic resection	*n* = 4818	*n* = 375	*n* = 70
Hr0	1511 (31.4%)	25 (6.7%)	16 (22.9%)
HrS	1182 (24.5%)	23 (6.1%)	17 (24.3%)
Hr1	1015 (21.1%)	55 (14.7%)	13 (18.6%)
Hr2	988 (20.5%)	223 (59.5%)	22 (31.4%)
Hr3	122 (2.5%)	49 (13.1%)	2 (2.9%)
Lymph node dissection	*n* = 4610	*n* = 365	*n* = 68
Not performed	4493 (97.5%)	127 (34.8%)	59 (86.8%)
Performed	117 (2.5%)	238 (65.2%)	9 (13.2%)
Residual cancer	*n* = 4752	*n* = 366	*n* = 67
Absent	4482 (94.3%)	325 (88.8%)	63 (94.0%)
Present	270 (5.7%)	41 (11.2%)	4 (6.0%)
Distant metastases	*n* = 4806	*n* = 369	*n* = 69
Absent	4751 (98.9%)	361 (97.8%)	68 (98.6%)
Present	55 (1.1%)	8 (2.2%)	1 (1.4%)
TNM stage by LCSGJ	*n* = 4827	*n* = 364	*n* = 70
I	664 (13.8%)	20 (5.5%)	5 (7.1%)
II	2355 (48.8%)	80 (22.0%)	24 (34.3%)
III	1249 (25.9%)	118 (32.4%)	22 (31.4%)
IV A	494 (10.2%)	45 (12.4%)	15 (21.4%)
IV B	65 (1.3%)	101 (27.7%)	4 (5.7%)

B0–B4, described in Table 5; Combined, combined hepatocellular and cholangiocarcinoma; Eg, expansive growth, well-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; HCC, hepatocellular carcinoma; 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; 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 segmentectomy); Hr2, resection of two segments (right or left lobectomy or central bisegmentectomy); Hr3, resection of three segments (right or left trisegmentectomy); Ig, infiltrative growth, poorly demarcated border; Im0, absence of intrahepatic metastasis; Ims, intrahepatic metastasis within the subsegment in which the principal tumor is located; Im1, intrahepatic metastasis within the subsegment in which the principal tumor is located; Im2, intrahepatic metastasis in two segments; Im3, intrahepatic metastasis to three or more segments; LCSGJ, Liver Cancer Study Group of Japan; Sf (–), absence of formation of a fibrous septum within the tumor; Sf (+), presence of fibrous septum within the tumor; S0, absence of invasion of the serosa; S1, tumor invasion of the serosa; S2, tumor invasion of adjacent organs; S3, tumor rupture with intraperitoneal bleeding; 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 to the second order branches of the hepatic artery; Va3, invasion to the left or right hepatic artery, or the proper hepatic artery; Vp0–Vp4, described in Table 5; Vv0–Vv3, described in Table 5.
After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

Table 8 Local ablation therapy

	HCC	ICC	Combined
	$n = 13\,703$	$n = 521$	$n = 87$
Not performed	7717 (56.3%)	492 (94.4%)	75 (86.2%)
Performed	5986 (43.7%)	29 (5.6%)	12 (13.8%)
EIT	1283 (21.4%)	6 (20.7%)	0 (0.0%)
MCT	697 (11.6%)	9 (31.0%)	7 (58.3%)
RFA	3937 (65.8%)	12 (41.4%)	5 (41.7%)
Others	69 (1.2%)	2 (6.9%)	0 (0.0%)
	$n = 5917$	$n = 29$	$n = 12$
Percutaneous	4956 (83.8%)	16 (55.2%)	4 (33.3%)
Others	961 (16.2%)	13 (44.8%)	8 (66.7%)
No. tumors	$n = 5695$	$n = 26$	$n = 10$
1	4063 (71.3%)	22 (84.6%)	4 (40.0%)
2	1084 (19.0%)	3 (11.5%)	2 (20.0%)
3	337 (5.9%)	0 (0.0%)	3 (30.0%)
4	100 (1.8%)	0 (0.0%)	0 (0.0%)
5	43 (0.8%)	0 (0.0%)	0 (0.0%)
≥6	68 (1.2%)	1 (3.8%)	1 (10.0%)
Tumor size (cm)	$n = 5644$	$n = 25$	$n = 10$
≤1	478 (8.5%)	4 (16.0%)	4 (40.0%)
≤2	2610 (46.2%)	12 (48.0%)	2 (20.0%)
≤3	1667 (29.5%)	6 (24.0%)	2 (20.0%)
≤5	716 (12.7%)	2 (8.0%)	2 (20.0%)
≤10	101 (1.8%)	1 (4.0%)	0 (0.0%)
≤15	17 (0.3%)	0 (0.0%)	0 (0.0%)
≤20	26 (0.5%)	0 (0.0%)	0 (0.0%)
≤25	14 (0.2%)	0 (0.0%)	0 (0.0%)
>25	15 (0.3%)	0 (0.0%)	0 (0.0%)
Efficacy evaluation	$n = 5272$	$n = 25$	$n = 10$
CR	4332 (82.2%)	16 (64.0%)	9 (90.0%)
PR	696 (13.2%)	5 (20.0%)	0 (0.0%)
MR	88 (1.7%)	0 (0.0%)	0 (0.0%)
NC	76 (1.4%)	3 (12.0%)	0 (0.0%)
PD	80 (1.5%)	1 (4.0%)	1 (10.0%)

Combined, combined hepatocellular and cholangiocarcinoma; CR, complete response; EIT, ethanol injection therapy; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; MCT, microwave coagulation therapy; MR, minor response; NC, no change; PD, progressive disease; PR, partial response; RFA, radiofrequency ablation therapy.
After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

coagulation therapy, and radiofrequency ablation therapy were given to 21.4%, 11.6% and 65.8% of these patients, respectively, suggesting a marked increase in the use of radiofrequency ablation therapy (Table 8). Percutaneous treatment was given in 83.8% of these cases and, of these patients, 71.3% had one tumor, 54.7% had a tumor of size ≤ 2 cm, and 29.5% had a tumor of 2–3 cm. Treatment outcomes of complete response (CR) and partial response (PR) occurred in 82.2% and 13.2% of patients, respectively.

Transcatheter arterial embolization

Transcatheter arterial embolization was conducted in 6881 patients with HCC. Of these patients, lipiodol alone, embolic material alone, and lipiodol + embolic material were used in 22.0%, 2.3% and 73.9% of cases, respectively (Table 9), with concomitant administration of anticancer agents in 90.7% of these patients. Regarding the extent of embolization, less than one segment, one segment to one lobe, more than one lobe, and the

Table 9 Transcatheter arterial embolization

	HCC	ICC	Combined
	$n = 13\,510$	$n = 518$	$n = 89$
Not performed	6629 (49.1%)	483 (93.2%)	66 (74.2%)
Performed	6881 (50.9%)	35 (6.8%)	23 (25.8%)
Lipiodol	1513 (22.0%)	7 (20.0%)	9 (39.1%)
Embolic material	157 (2.3%)	4 (11.4%)	0 (0.0%)
Lipiodol + embolic material	5083 (73.9%)	23 (65.7%)	13 (56.5%)
Others	128 (1.9%)	1 (2.9%)	1 (4.3%)
	$n = 6724$	$n = 35$	$n = 23$
Without anticancer agents	628 (9.3%)	6 (17.1%)	5 (21.7%)
With anticancer agents	6096 (90.7%)	29 (82.9%)	18 (78.3%)
Extent of embolization	$n = 6317$	$n = 33$	$n = 21$
Less than one segment	1947 (30.8%)	7 (21.2%)	3 (14.3%)
One segment to one lobe	2557 (40.5%)	12 (36.4%)	8 (38.1%)
More than one lobe	1153 (18.3%)	10 (30.3%)	5 (23.8%)
Whole liver	660 (10.4%)	4 (12.1%)	5 (23.8%)
Efficacy evaluation	$n = 5636$	$n = 30$	$n = 20$
CR	1569 (27.8%)	1 (3.3%)	1 (5.0%)
PR	2452 (43.5%)	9 (30.0%)	9 (45.0%)
MR	582 (10.3%)	6 (20.0%)	1 (5.0%)
NC	614 (10.9%)	7 (23.3%)	5 (25.0%)
PD	419 (7.4%)	7 (23.3%)	4 (20.0%)

Combined, combined hepatocellular and cholangiocarcinoma; CR, complete response; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; MR, minor response; NC, no change; PD, progressive disease; PR, partial response.
After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

entire liver were treated in 30.8%, 40.5%, 18.3% and 10.4% of patients, respectively. Treatment outcomes of CR and PR occurred in 27.8% and 43.5% of patients, respectively.

Chemotherapy

Chemotherapy was given to 2236 patients with HCC, and 90.0% of these patients received chemotherapy via the hepatic artery; treatment outcomes of CR and PR occurred in 15.9% and 30.0% of patients, respectively. Of the patients with ICC, 151 underwent chemotherapy and, of these patients, 38.4%, 47.7% and 13.2% received chemotherapy intra-arterially, intravenously and orally, respectively; treatment outcomes of CR and PR occurred in 1.7% and 15.7% of patients, respectively.

Pathological diagnosis

Pathological diagnosis was conducted in 49.1% of patients with HCC, whereas 50.9% of patients were not diagnosed pathologically. The percentage of diagnoses by biopsy alone, resected specimens alone, and both biopsy and resected specimens was 29.9%, 66.6% and 3.4%, respectively. Microscopic pathological results from biopsy and resected specimens are shown in Table 10. Well-, moderately and poorly differentiated tumor types were found in 29.5%, 58.5% and 10.7% of patients with HCC, respectively, whereas well-, moder-

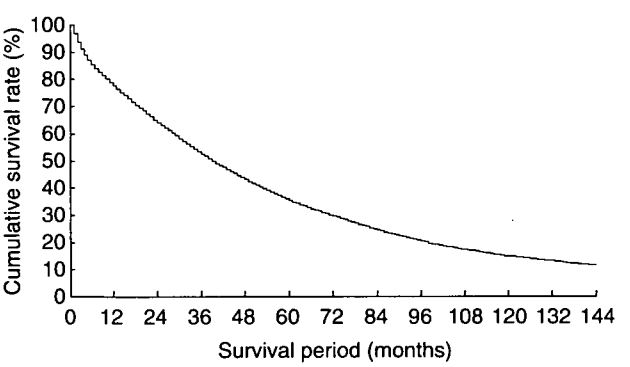

Figure 1 Cumulative survival rates of newly registered patients with hepatocellular carcinoma from 1992 to 2003. The 3-, 5- and 10-year cumulative survival rates were 52.5%, 35.4% and 14.7%, respectively ($n = 96\,404$).
After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

Table 10 Microscopic pathological findings of surgical or biopsy specimens

	HCC	ICC	Combined
Capsule formation	*n* = 4860	*n* = 340	*n* = 68
fc (−)	1152 (23.7%)	324 (95.3%)	51 (75.0%)
fc (+)	3708 (76.3%)	16 (4.7%)	17 (25.0%)
Capsule infiltration	*n* = 3620	*n* = 15	*n* = 17
fc-inf (−)	1125 (31.1%)	7 (46.7%)	3 (17.6%)
fc-inf (+)	2495 (68.9%)	8 (53.3%)	14 (82.4%)
Septum formation	*n* = 4558	*n* = 323	*n* = 63
sf (−)	1602 (35.1%)	309 (95.7%)	37 (58.7%)
sf (+)	2956 (64.9%)	14 (4.3%)	26 (41.3%)
Serosal invasion	*n* = 4657	*n* = 335	*n* = 67
s0	3985 (85.6%)	199 (59.4%)	50 (74.6%)
s1	486 (10.4%)	95 (28.4%)	14 (20.9%)
s2	107 (2.3%)	40 (11.9%)	2 (3.0%)
s3	79 (1.7%)	1 (0.3%)	1 (1.5%)
Lymph node metastasis	*n* = 3472	*n* = 328	*n* = 53
Absent	3423 (98.6%)	195 (59.5%)	46 (86.8%)
Present	49 (1.4%)	133 (40.5%)	7 (13.2%)
Portal vein invasion	*n* = 4877	*n* = 352	*n* = 70
vp0	3445 (70.6%)	171 (48.6%)	37 (52.9%)
vp1	1046 (21.4%)	104 (29.5%)	20 (28.6%)
vp2	186 (3.8%)	41 (11.6%)	4 (5.7%)
vp3	136 (2.8%)	33 (9.4%)	8 (11.4%)
vp4	64 (1.3%)	3 (0.9%)	1 (1.4%)
Hepatic vein invasion	*n* = 4758	*n* = 350	*n* = 68
vv0	4142 (87.1%)	243 (69.4%)	57 (83.8%)
vv1	496 (10.4%)	72 (20.6%)	9 (13.2%)
vv2	78 (1.6%)	19 (5.4%)	2 (2.9%)
vv3	42 (0.9%)	16 (4.6%)	0 (0.0%)
Hepatic arterial invasion	*n* = 4488	*n* = 320	*n* = 69
va0	4436 (98.8%)	295 (92.2%)	67 (97.1%)
va1	47 (1.0%)	16 (5.0%)	1 (1.4%)
va2	3 (0.1%)	3 (0.9%)	1 (1.4%)
va3	2 (0.0%)	6 (1.9%)	0 (0.0%)
Bile duct invasion	*n* = 4773	*n* = 335	*n* = 68
b0	4609 (96.6%)	151 (45.1%)	56 (82.4%)
b1	97 (2.0%)	69 (20.6%)	10 (14.7%)
b2	24 (0.5%)	42 (12.5%)	1 (1.5%)
b3	29 (0.6%)	45 (13.4%)	1 (1.5%)
b4	14 (0.3%)	28 (8.4%)	0 (0.0%)
Intrahepatic metastasis	*n* = 4648	*n* = 354	*n* = 69
im0	3626 (78.0%)	252 (71.2%)	45 (65.2%)
ims	177 (3.8%)	13 (3.7%)	6 (8.7%)
im1	387 (8.3%)	31 (8.8%)	8 (11.6%)
im2	300 (6.5%)	40 (11.3%)	4 (5.8%)
im3	158 (3.4%)	18 (5.1%)	6 (8.7%)
Surgical margin	*n* = 4588	*n* = 353	*n* = 65
Presence of cancer invasion	388 (8.5%)	77 (21.8%)	14 (21.5%)
Absence of cancer invasion	4200 (91.5%)	276 (78.2%)	51 (78.5%)
Non-cancerous portion	*n* = 4941	*n* = 348	*n* = 71
Normal liver	313 (6.3%)	238 (68.4%)	11 (15.5%)
Chronic hepatitis or liver fibrosis	2378 (48.1%)	72 (20.7%)	38 (53.5%)
Liver cirrhosis	2250 (45.5%)	38 (10.9%)	22 (31.0%)

Table 10 *Continued*

	HCC	ICC	Combined
Liver fibrosis	*n* = 2718	*n* = 155	*n* = 34
F0 (normal)	174 (6.4%)	107 (69.0%)	4 (11.8%)
F1	417 (15.3%)	16 (10.3%)	5 (14.7%)
F2	502 (18.5%)	13 (8.4%)	8 (23.5%)
F3	499 (18.4%)	4 (2.6%)	8 (23.5%)
F4 (liver cirrhosis)	1126 (41.4%)	15 (9.7%)	9 (26.5%)

b0–b4, described in Tables 5 and 7; Combined, combined hepatocellular and cholangiocarcinoma; fc, fc-inf, described in Table 7; F1, fibrosis expansion of portal tract; F2, bridging fibrosis formation; F3, bridging fibrosis formation accompanying lobular distortion; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; im0–im3, described in Table 7; sf, s0–s3, described in Table 7; va0–va3, described in Table 7; vp0–vp4, vv0–vv3, described in Tables 5 and 7.
After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

Table 11 Cumulative survival rates (%) of HCC patients treated with hepatic resection (1992–2003)

	N	Year									
		1	2	3	4	5	6	7	8	9	10
All cases	27 062	87.8	78.3	69.2	61.1	53.4	47.5	41.1	35.9	31.2	27.7
Tumor size (cm)											
≤2	5 017	95.1	90.1	83.8	76.8	68.0	60.3	53.1	46.9	41.1	36.6
2–5	13 896	91.4	82.7	72.7	63.9	55.6	49.1	42.0	36.5	31.7	27.8
5–10	4 972	80.6	66.5	56.3	48.1	42.0	38.0	33.1	28.3	23.8	21.6
>10	2 127	66.6	51.8	42.7	36.8	32.1	29.1	25.4	22.8	20.8	20.8
Tumor number											
1	19 046	90.8	82.9	74.4	66.8	59.2	53.2	46.5	41.2	36.2	32.0
2	4 011	86.1	74.6	64.1	55.0	46.4	39.4	33.6	26.9	22.3	19.9
≥3	3 174	75.1	59.1	47.5	37.6	30.0	25.8	20.5	17.5	14.3	12.6
Portal vein invasion											
Vp0	22 079	91.6	83.3	74.2	65.9	57.6	51.0	43.9	38.3	33.4	29.6
Vp1	1 987	78.6	63.1	52.6	44.3	38.7	34.9	32.9	29.5	24.7	20.9
Vp2	822	59.2	42.3	31.8	26.2	23.8	23.4	21.5	18.9	17.7	17.7
Vp3 or Vp4	976	50.4	32.8	25.8	21.9	18.4	16.6	14.9	13.0	8.5	–
Non-cancerous portion											
Normal liver	2 173	86.8	77.0	69.4	63.7	59.0	55.9	50.0	46.8	40.9	39.0
Chronic hepatitis/liver fibrosis	9 374	90.3	81.9	73.7	66.7	60.4	55.9	50.2	44.6	40.4	36.9
Liver cirrhosis	11 631	86.7	76.6	66.5	57.5	48.1	41.2	34.1	29.5	24.8	21.5
Liver damage classification by LCSGJ											
A	17 433	89.9	81.5	73.4	65.6	58.4	52.3	45.8	40.9	35.8	31.9
B	7 260	85.2	74.0	63.0	54.3	45.3	39.4	33.2	28.0	23.9	20.8
C	631	74.1	59.1	48.3	42.1	35.5	33.7	29.8	22.0	20.3	15.2
TNM stage by LCSGJ											
I	3 342	96.3	92.4	86.9	80.1	71.3	64.5	56.6	51.7	46.0	40.5
II	11 772	93.1	85.6	76.7	68.3	60.1	53.4	45.8	39.3	34.4	30.3
III	5 817	83.4	70.2	58.5	49.5	41.9	36.5	31.4	27.4	23.6	21.1
IV A	1 687	62.0	44.0	34.0	27.5	22.9	21.0	19.6	15.4	11.5	10.7
IV B	319	52.7	36.0	25.2	22.6	15.5	14.3	14.3	14.3	14.3	14.3

HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan; Vp0–Vp4, described in Tables 5 and 7.
After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

Table 12 Cumulative survival rates (%) of HCC patients treated with local ablation therapy (1992–2003)

	N	Year									
		1	2	3	4	5	6	7	8	9	10
All cases	23 836	92.3	79.7	66.0	53.2	42.0	33.3	26.3	20.8	16.7	13.2
Liver damage classification by LCSGJ											
A	12 038	95.3	86.0	74.5	62.8	51.2	41.5	33.8	27.4	22.2	17.3
B	8 723	91.8	77.1	60.9	46.9	35.2	26.7	20.9	16.1	12.2	10.3
C	1 741	77.6	56.3	39.5	26.5	20.2	16.2	10.7	7.0	7.0	5.6
Tumor number											
1	14 439	93.7	83.1	70.9	59.3	48.4	39.1	31.7	25.6	21.2	17.7
2	5 056	92.0	78.1	63.8	49.4	37.3	29.8	21.7	16.6	13.1	10.1
3	2 112	90.6	76.2	59.0	43.6	31.7	21.6	17.7	12.0	9.0	7.0
4	785	87.9	69.6	51.7	37.6	27.3	19.7	14.5	11.3	9.0	4.8
≥5	1 055	82.9	60.9	42.3	29.4	21.1	17.0	12.3	11.5	6.5	5.2
Tumor size (cm)											
≤1	1 480	96.8	90.4	80.8	71.8	58.6	48.4	42.5	35.6	30.3	27.2
1–2	10 418	95.0	85.6	73.4	61.4	50.1	40.5	32.0	25.6	20.1	16.3
2–3	6 823	92.1	77.7	62.0	47.8	35.9	27.3	21.5	16.4	12.8	10.0
3–5	3 027	87.6	68.6	52.0	37.9	27.8	21.5	15.6	11.6	11.1	5.7
>5	830	76.0	56.5	38.8	28.6	21.1	16.0	8.9	6.0	3.0	-

HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan.
After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

ately and poorly differentiated tumor types were found in 16.7%, 59.2% and 19.5% of patients with ICC, respectively. Regarding microscopic pathological findings in non-cancerous parts of the liver, normal liver, chronic hepatitis/liver fibrosis, and liver cirrhosis were found in 6.3%, 48.1% and 45.5% of patients with HCC, respectively, and in 68.4%, 20.7% and 10.9% of patients with ICC, respectively.

Recurrence

During the period of this survey (less than 2 years after diagnosis), 29.4% of patients with HCC experienced recurrence of the disease. Transcatheter arterial embolization and local therapy were given to 53.3% and 24.5% of these patients, respectively, as treatment for recurrence in the liver. The most frequent organ of

Table 13 Cumulative survival rates (%) of HCC patients treated with transcatheter arterial embolization (1992–2003)

	N	Year									
		1	2	3	4	5	6	7	8	9	10
All cases	23 368	77.2	57.9	42.4	30.6	22.6	16.7	12.7	9.2	6.5	4.4
Liver damage classification by LCSGJ											
A	11 094	83.7	66.4	51.4	38.6	29.8	22.7	18.3	13.3	8.7	5.7
B	8 365	75.4	54.6	37.5	25.8	18.2	12.6	8.5	6.3	4.9	2.9
C	2 303	56.8	32.7	19.8	11.9	7.0	5.2	3.9	2.8	2.8	2.8
Tumor number											
1	9 444	82.9	67.1	52.7	39.4	29.7	22.6	18.0	13.3	9.4	6.9
2	4 535	81.6	62.4	44.9	32.3	23.0	16.9	11.0	8.8	6.5	3.7
3	2 592	79.3	56.5	37.6	25.3	19.0	12.7	9.1	6.7	4.5	2.2
4	1 201	81.1	53.9	36.8	26.9	19.0	13.6	9.3	7.4	4.6	4.6
≥5	4 827	62.3	39.5	25.0	16.8	11.9	8.4	6.3	4.2	2.8	1.5

HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan.
After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

Table 14 Cumulative survival rates (%) of ICC patients (1992–2003)

	N	Year									
		1	2	3	4	5	6	7	8	9	10
All cases	3499	49.2	33.3	26.9	22.3	19.6	17.3	15.8	14.6	13.1	12.5
Hepatic resection											
Performed	1626	70.5	52.2	43.8	37.2	32.7	28.8	26.5	24.8	22.1	22.1
Not performed	331	59.5	39.4	26.9	18.5	17.4	14.9	10.0	5.0	5.0	0.0
Cases of hepatic resection											
Tumor size (cm)											
≤2	134	83.6	77.3	72.9	65.5	62.6	62.6	56.9	56.9	56.9	56.9
2–5	699	77.0	58.7	50.9	41.8	34.6	29.5	28.4	25.3	19.9	19.9
5–10	558	62.4	41.9	32.0	28.2	26.5	23.4	21.4	20.2	20.2	20.2
>10	148	55.6	33.2	27.4	25.4	21.8	16.3	16.3	16.3	10.9	–
Tumor number											
1	1201	75.5	57.8	49.9	42.6	38.6	34.0	32.0	30.3	27.7	27.7
2	123	67.1	48.5	37.0	31.5	25.0	25.0	21.5	17.9	11.9	11.9
≥3	212	44.6	22.1	15.7	13.1	7.7	7.7	5.1	5.1	5.1	5.1
Residual tumor											
Absent	759	80.2	63.5	53.5	47.4	42.7	39.4	37.7	34.3	30.5	30.5
Present	609	58.3	35.0	29.4	22.0	19.4	15.9	13.4	13.4	10.7	10.7
Lymph node metastasis											
Absent	1028	80.1	63.3	54.1	45.9	41.1	36.5	33.3	30.9	27.2	27.2
Present	495	52.4	29.4	23.1	19.3	15.6	11.7	11.7	11.7	11.7	11.7

ICC, intrahepatic cholangiocarcinoma.
After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

distant metastasis was the lung (34.5%), followed by bone (33.1%), and lymph nodes. Radiation therapy, systemic chemotherapy and resection were chosen as treatment for distant organ metastasis.

Autopsy

Autopsy was performed in 306 patients, 261 of whom were patients with HCC. Liver cirrhosis was found in 74.7% of the autopsied patients with HCC, invasion of the portal vein, hepatic vein or bile duct was found in 62.8%, 33.8% and 15.0%, respectively, and distant metastasis was found most frequently in the lung. In patients with ICC, the most frequent distant metastasis site was also the lung.

Additional statistics

The cumulative survival rates of newly registered patients in the 12th to 17th follow-up surveys (1992–2003) whose final prognosis was defined as survival or death (excluding cases of unknown outcome) were calculated for cases of HCC, ICC, and combined HCC and ICC.

HCC

The 3-, 5- and 10-year cumulative survival rates in all patients with HCC were 52.5%, 35.4% and 14.7%, respectively (Fig. 1). Cumulative survival rates for patients with HCC were also stratified by initial treatment, which included hepatectomy (Table 11), local ablation therapy (ethanol injection therapy, microwave coagulation therapy, and radiofrequency ablation therapy) (Table 12), and transcatheter arterial embolization (Table 13). In newly registered patients in the 16th and 17th surveys, the level of liver injury was estimated from data collected in the surveys.

ICC and combined HCC and ICC

For ICC, cumulative survival rates were calculated for all patients and based on various background factors. For combined HCC and ICC, cumulative survival rates were calculated for all patients (Tables 14,15).

CONCLUSION

PRIMARY LIVER CANCER is the third leading cause of cancer death in Japanese people, following tracheal-bronchial-lung and gastric cancers; more than

Table 15 Cumulative survival rates (%) of combined HCC and ICC (1992–2003)

	N	Year									
		1	2	3	4	5	6	7	8	9	10
All cases	557	57.3	38.0	27.2	22.0	18.5	15.4	13.4	11.9	11.9	9.9
Hepatic resection											
Performed	328	68.5	46.8	38.2	31.3	29.7	26.5	22.9	20.0	20.0	16.7
Not performed	110	55.7	34.1	14.5	11.0	3.7	1.8	1.8	1.8	–	–

HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.
After Ikai *et al.* (2007), with permission from the Japan Society of Hepatology.

34 000 individuals die annually due to liver cancer. In the 17th Nationwide Follow-up Survey of Primary Liver Cancer, approximately 27% of patients with primary liver cancer were newly registered. We hope that the results of this follow-up survey will contribute to research and improved medical practice for primary liver cancer.

ACKNOWLEDGMENTS

WE WOULD LIKE to express our sincere gratitude to the doctors of the 645 medical institutions that participated in this follow-up survey, to Mrs M. Uose, M. Ogawa and T. Idutsu for data compilation, and to Mrs Y. Hiraishi for data analysis.

REFERENCES

1 Okuda K, The Liver Cancer Study Group of Japan. Primary liver cancers in Japan. *Cancer* 1980; 45: 2663–9.
2 The Liver Cancer Study Group of Japan. Primary liver cancer in Japan. *Cancer* 1984; 54: 1747–55.
3 The Liver Cancer Study Group of Japan. Primary liver cancer in Japan – Sixth report. *Cancer* 1987; 60: 1400–11.
4 The Liver Cancer Study Group of Japan. Primary liver cancer in Japan. *Ann Surg* 1990; 211: 277–87.
5 Tobe T, Kameda H, Okudaira M, Ohto M, eds. *Primary Liver Cancer In Japan*. New York: Springer-Verlag, 1992.
6 The Liver Cancer Study Group of Japan. Predictive factors for long term prognosis after partial hepatectomy for patients with hepatocellular carcinoma in Japan. *Cancer* 1994; 74: 2772–80.
7 Arii S, Yamaoka Y, Futagawa S *et al.* Results of surgical and nonsurgical treatment for small-sized hepatocellular carcinomas: a retrospective and nationwide survey in Japan. The Liver Cancer Study Group of Japan. *Hepatology* 2000; 32: 1224–9.
8 Ikai I, Itai Y, Okita K *et al.* Report of the 15th follow-up survey of primary liver cancer. *Hepatol Res* 2004; 28: 21–9.
9 Ikai I, Arii S, Ichida T *et al.* Report of the 16th follow-up survey of primary liver cancer. *Hepatol Res* 2005; 32: 163–72.
10 Takayasu K, Arii S, Ikai I *et al.* For Liver Cancer Study Group of Japan. Long term outcome of transcatheter arterial lipiodol chemoembolization for unresectable hepatocellular carcinoma; nationwide prospective cohort study of 8 510 patients. *Gastroenterology* 2006; 131: 461–9.
11 Ikai I, Takayasu K, Omata M *et al.* A modified Japan integrated stage score for prognostic assessment in patients with hepatocellular carcinoma. *J Gastroenterol* 2006; 41: 884–92.
12 Liver Cancer Study Group of Japan. *General Rules for the Clinical and Pathological Study of Primary Liver Cancer, Second English Edition*. Tokyo: Kanehara, 2003.

Staging of Hepatocellular Carcinoma

Assessment of the Japanese TNM and AJCC/UICC TNM Systems in a Cohort of 13,772 Patients in Japan

Masami Minagawa, MD, PhD,† Iwao Ikai, MD, PhD,*‡ Yutaka Matsuyama, PhD,*§ Yoshio, Yamaoka, MD, PhD,*‡ and Masatoshi Makuuchi, MD, PhD*†*

Objective: The aims of this study were to present evidence to develop and validate the Japanese Tumor-Node-Metastasis (TNM) staging system for primary liver cancer and to compare its discriminatory ability and predictive power with those of Vauthey's simplified staging, which was adopted as the TNM staging system of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC).

Summary Background Data: Among many staging systems for hepatocellular carcinoma, the Japanese TNM staging system and the AJCC/UICC staging system were developed based on a survival analysis of surgical patients. These 2 staging systems have not been compared in large series.

Methods: The Liver Cancer Study Group of Japan (LCSGJ) prospectively collected clinicopathologic data of 63,736 patients with primary liver cancer from 1995 to 2001. Among them, 13,772 patients received curative hepatic resection. Based on univariate and multivariate survival analyses, the Japanese TNM staging system was developed. The accuracy of the Japanese TNM staging system for predicting patient survival was compared with that of the AJCC/UICC staging system using the cross-validation method.

Results: The independent prognostic factors (relative risk; 95% confidence interval) were vascular or bile duct invasion (1.36;1.29–1.43), liver cirrhosis (1.26;1.20–1.32), diameter (≤2 cm or >2 cm) (1.21;1.14–1.28), alpha-fetoprotein (1.20;1.15–1.25), single/multiple (1.18;1.12–1.23), liver damage (1.15;1.10–1.20), hepatic involvement (1.14;1.09–1.19), histologic differentiation (1.14;1.08–1.20), gross classification (1.13;1.08–1.18), and esophageal varices (1.07;1.02–1.13). Based on these results, 3 criteria (vascular or bile duct invasion, diameter, and single/multiple) were selected. Patients with none of these 3 factors were considered T1, and those with 1, 2, and 3 factors were T2, T3, and T4, respectively. The number of patients and 5-year survival rates for T1, T2, T3, and T4 were 2078, 70%; 6853, 58%; 3021, 41%; and 582, 24% ($P < 0.0001$), respectively, while those for the AJCC-T were 8457, 61% in T1, 2888, 46% in T2, and 1189, 30% in T3 ($P < 0.0001$). While both the LCSGJ-T and the AJCC-T had good discriminating ability, the former was significantly superior ($P = 0.0007$).

Conclusions: Our findings support the development of LCSG stage. While both staging systems allow for the clear stratification of patients into prognostic groups, the LCSGJ staging may be more appropriate for stratifying patients with early-stage HCC.

(*Ann Surg* 2007;245: 909–922)

Over the past 20 years, great progress has been made in the diagnosis of hepatocellular carcinoma (HCC); high-risk groups for this disease can be established, and the number of patients with resectable HCC and small-sized HCC is increasing. Under these circumstances, liver transplantation, hepatic resection, radiofrequency ablation, and transarterial chemoembolization have all been used in these patients according to their clinicopathologic characteristics and hepatic functional reserve, but the optimal management for these patients remains controversial.[1,2] As a result, there is an increasing need for a staging system that can reflect the prognosis and permit the stratification of these patients for clinical trials. Several staging systems have been proposed: Okuda staging, the Cancer of the Liver Italian Program (CLIP), the Barcelona Clinic Liver Cancer staging, the Japan Integrated Staging Score (JIS), the Chinese University Prognostic Index, and the French Score.[3–8] All of these staging systems include liver function parameters, and the percentages of patients who received hepatic resection among all of the patients used to develop the stages were 18.5% (Okuda), 10.4% (Chinese University Prognostic Index), 6% (CLIP), and 7% (French). In an attempt to standardize the staging of HCC, the American Hepatico-Pancreatico-Biliary Association organized a consensus conference that was cosponsored by the American Joint Committee on Cancer (AJCC) in 2002. The consensus panel made important observations regarding the purposes of various staging systems and noted that 2 types of staging systems were required to adequately stage the spectrum of HCC:

From the *Liver Cancer Study Group of Japan; †the Department of Hepato-Biliary-Pancreatic Surgery, Department of Artificial Organ and Transplantation, Graduate School of Medicine, University of Tokyo, Tokyo, Japan; ‡Department of Gastroenterological Surgery, Kyoto University Graduate School of Medicine, Kyoto, Japan; §Department of Biostatistics, School of Health Sciences and Nursing, University of Tokyo, Tokyo, Japan.

Reprints: Masami Minagawa, MD, PhD, Department of Hepato-Biliary-Pancreatic Surgery, Department of Artificial Organ and Transplantation, Graduate School of Medicine, University of Tokyo, 7-3-1, Hongo, Bunkyo-ku, Tokyo, 113-8655, Japan. E-mail: minagawa-tky@umin.ac.jp.

ISSN: 0003-4932/07/24506-0909
DOI: 10.1097/01.sla.0000254368.65878.da

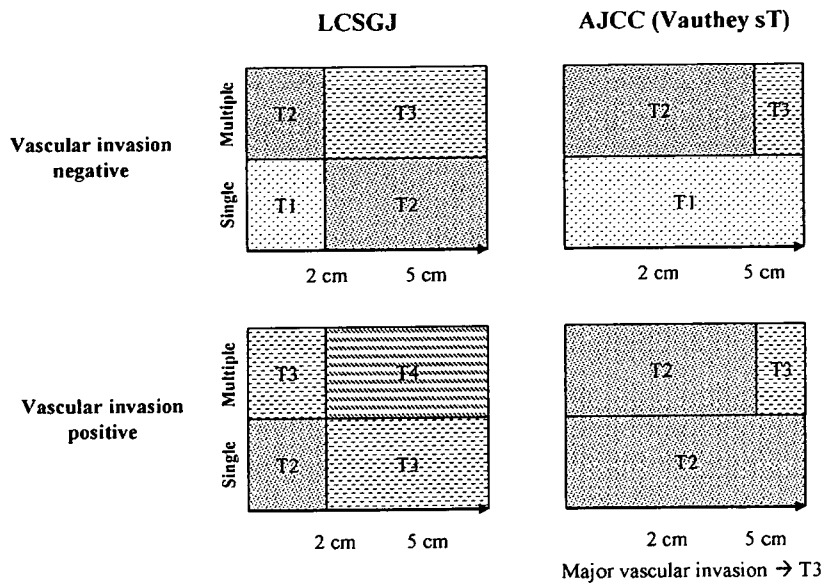

FIGURE 1. Comparison of the T classification in LCSGJ and AJCC/UICC.

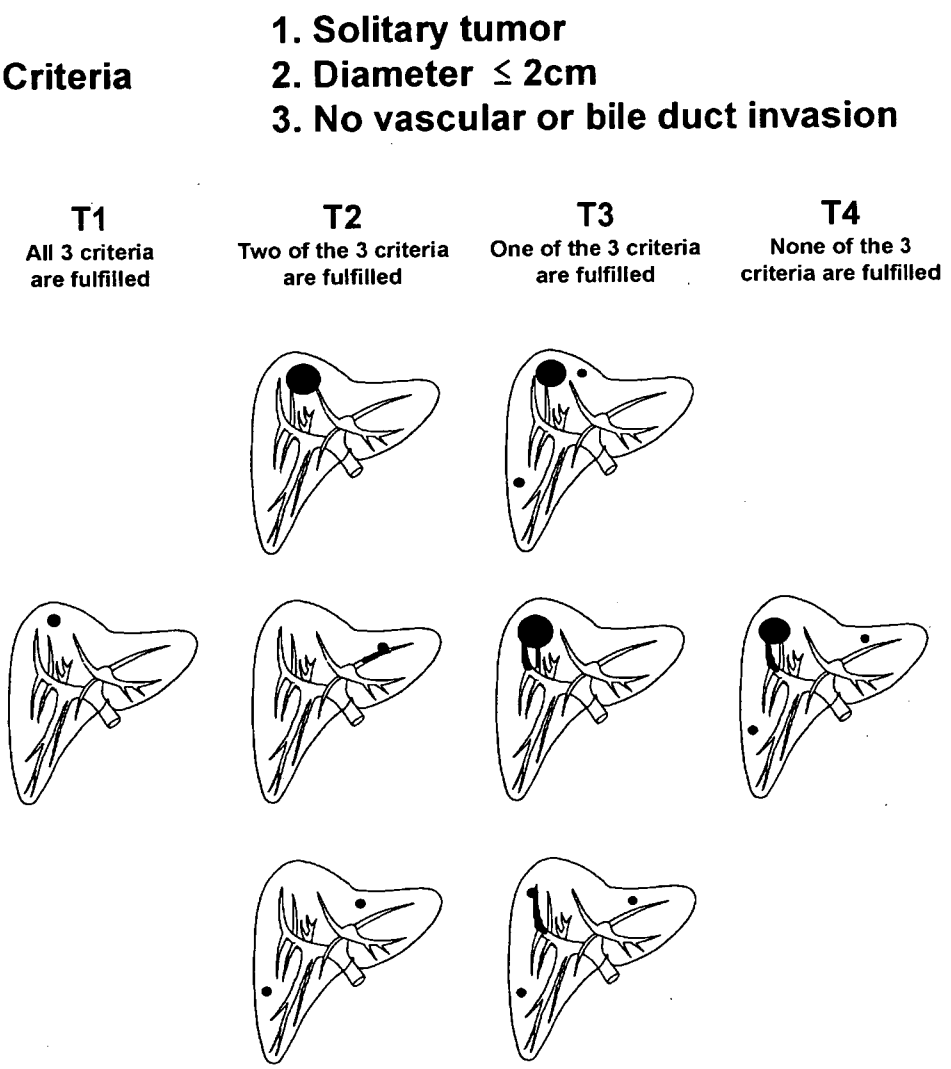

FIGURE 2. The T category of LCSGJ is determined on the basis of the "number," "size," and "vascular or bile duct invasion." All multiple tumors, including multicentric tumors and intrahepatic metastatic tumors, are equally counted.

a medical staging system that covered all patients with HCC and a surgical staging system that was designed for patients who were operable.[9] The staging systems described above are considered medical staging systems.

There are currently 2 surgical staging systems, which were developed based on the analysis of patients who received hepatic resection: one from the Liver Cancer Study Group of Japan (LCSGJ) and another from the AJCC/International Union Against Cancer (UICC). In 1983, the LCSGJ first introduced an HCC Tumor-Node-Metastasis (TNM) scheme, which has subsequently been revised, most recently from the third to 4th edition in 2000.[10,11] Vauthey et al developed a simplified staging system for HCC in 2002,[12] which was adopted as the TNM staging system of AJCC/UICC after minor changes.[13] The prognostic power and stratification ability of the Japanese TNM Staging System has been verified in Japanese and Chinese patients,[14–16] and it has been compared with the AJCC/UICC staging system.[16] These 2 staging systems have some similarities; for example, parameters of liver function are not included, patients with distant metastasis are assigned to the highest stage, and those with hepatic lymph node metastasis are assigned to the second highest stage. In contrast, they use different methods for determining the T classification (Figs. 1, 2). In this paper, we present evidence for the development of the Japanese TNM system, validate the system, and compare its discriminatory ability and predictive power to those of the AJCC/UICC staging system in 13,772 patients who received curative hepatic resection.

MATERIALS AND METHODS

Source of Data

LCSGJ determined the classification and handling methods of primary liver cancer in 1965 and started a nationwide registration of clinicopathologic and prognostic data of patients with primary liver cancer.[17–23] Questionnaires that included 178 items of clinicopathologic data were mailed to all of the LCSGJ-approved hospitals in Japan, and these data were entered into a computer, once every 3 years from 1970 (first) to 1979 (4th), and once every 2 years after 1981 (fifth). The status of the presence of recurrence, additional treatment, and final prognosis of the registered patients were also followed until confirmation of death at every survey. Micropathologic data of liver tumor were requested on the form from the 12th survey. Accordingly, the data from the 12th to 15th surveys were used in this study. The number of patients and hospitals in each survey are shown in Table 1. Of the total 66,007 patients with primary liver cancer, the clinical diagnosis of 63,736 patients (96.6%) was HCC, and 18,948 (29.7%) received hepatic resection. Of these, 1189 patients without pathologic data, 956 with incomplete survival data, and 1881 without data on operative curability, distant metastasis, or hepatic lymph node metastasis were excluded, which meant that eventually 14,922 patients were included in this study (hepatectomy-cohort). Of these 14,922 patients, the operations were not curative in 1150, and 13,772 received curative hepatic resection (curative-hepatectomy-cohort). Among these patients, 76 had distant metastasis, 147 had hepatic lymph node metastasis, and 17 had both. The 13,566 remaining patients were included in the curative-hepatectomy-N0M0 cohort.

TABLE 1. Number of Registered Patients and Clinical Diagnosis

No. Survey	Year of Survey	No. Hospitals	No. Newly Registered Patients	Clinical Diagnosis						
				Hepatocellular Carcinoma	Cholangiocellular Carcinoma	Bile Duct Cystadenocarcinoma	Combined Hepatocellular and Cholangiocarcinoma	Hepatoblastoma	Sarcoma	Others
12th	1995	649	15,782	13,381	432	22	56	18	11	71
13th	1997	825	16,539	15,804	517	32	78	26	10	72
14th	1999	829	17,534	16,666	627	32	93	18	13	85
15th	2001	791	18,843	17,885	626	30	101	24	12	165
Total		—	66,007	63,736	2,202	116	328	84	46	393

TABLE 2. Degree of Liver Damage by LCSGJ

Item	Degree of Liver Damage*		
	A	B	C
Ascites	None	Controllable	Uncontrollable
Serum bilirubin (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	3.0–3.5	<3.0
ICG R_{15} (%)	<15	15–40	>40
Prothrombin activity (%)	>80	50–80	<50

*The severity of each finding is evaluated separately. Degree of liver damage is recorded as A, B, or C, based on the highest grade that contained at least 2 findings.
ICG R_{15}, indocyanine green retention rate at 15 minutes.

The prognosis was examined in February 2001, and was categorized as alive, dead, or unknown. Death was subclassified according to the direct cause: death by HCC, liver failure, gastrointestinal bleeding, rupture of HCC, operative death, and other. All deaths were counted as events and living patients were censored to the date of the last follow-up. Curative resection was defined as that in which the entire tumor could be removed macroscopically. Lymph node involvement and distant metastasis were based on macroscopic inspection and palpation at the time of surgery. Tumor size was based on the largest dimension of the tumor specimen. Portal, hepatic venous, and bile duct invasion were defined by macroscopic examination of resected specimens. The number of HCCs was defined by the total number of nodules, including intrahepatic metastasis, in the resected specimen. Hepatic involvement means the number of segments in which liver tumors are present. The degree of liver damage as a guide to liver function was defined by LCSGJ based on ascites, serum bilirubin, serum albumin, indocyanine green retention rate at 15 minutes, and prothrombin activity (Table 2).[10,11,22] The serologic presence of hepatitis B surface antigen was considered to be positive evidence of hepatitis B serology, and

TABLE 3. Demographics of Curative-Hepatectomy-N0M0-Cohort

Variable	No. Patients	Median Survival Time (yr)	95% CI for Median	5-Year Survival Rate (%)	*P*
Gender					0.81
Male	10783	5.47	5.22–5.75	54	
Female	2776	5.76	5.45–6.05	56	
Age					0.02
<60 yr	4408	5.95	5.50–6.26	56	
60 yr	9095	5.33	5.10–5.61	53	
Hepatitis B surface antigen					0.5
None	10472	5.47	5.22–5.8	54	
Positive	2682	5.76	5.46–6.08	55	
Hepatitis C antibody					0.23
None	4193	6.02	5.76–6.56	57	
Positive	9025	5.32	5.12–5.58	53	
Esophageal varices					<0.0001
None	10083	5.86	5.59–5.99	56	
Positive	2188	4.42	4.13–4.71	46	
Alcohol					0.84
None	8873	5.62	5.37–5.89	55	
Positive	3063	5.52	5.07–5.95	54	
Smoking					0.07
None	5398	5.8	5.46–6.00	56	
Positive	5866	5.31	5.10–5.58	53	
Degree of liver damage*					<0.0001
A	8463	5.99	5.86–6.24	59	
B	3685	4.59	4.36–4.89	47	
C	377	3.24	2.70–4.12	35	
Alpha-fetoprotein					<0.0001
20 ng/mL	5744	6.4	6.13–6.72	64	
20–10,000 ng/mL	6587	4.71	4.53–4.95	48	
>10,000 ng/mL	622	2.74	2.23–3.65	37	
PIVKA-2†					<0.0001
<100 mU/mL	6371	6.01	5.8–6.24	59	
100–1000 mU/mL	2059	5.05	4.53–5.47	51	
1000 mU/mL	1899	3.85	3.56–4.40	42	

*By the Liver Cancer Study Group of Japan (Table 2).
CI indicates confidence interval; PIVKA-2, des-γ-carboxy prothrombin.