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.
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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.
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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-

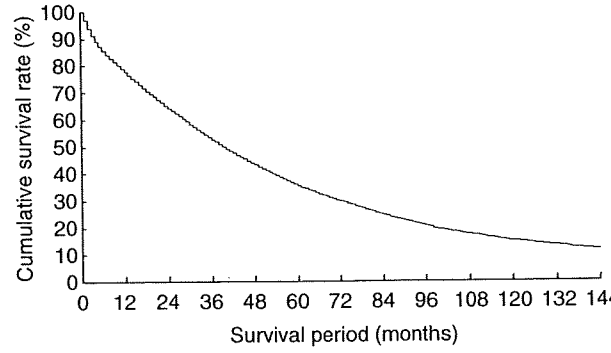

Figure 1 Cumulative survival rates of newly registered patients with hepatocellular carcinoma from 1992 to 2003. The 3-, 5- and 10-year cumulative survival rates were 52.5%, 35.4% and 14.7%, respectively ($n = 96\,404$).
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Table 10 Microscopic pathological 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.
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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.
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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.
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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.
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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.
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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.
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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.

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Staging of Hepatocellular Carcinoma

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

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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.

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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:

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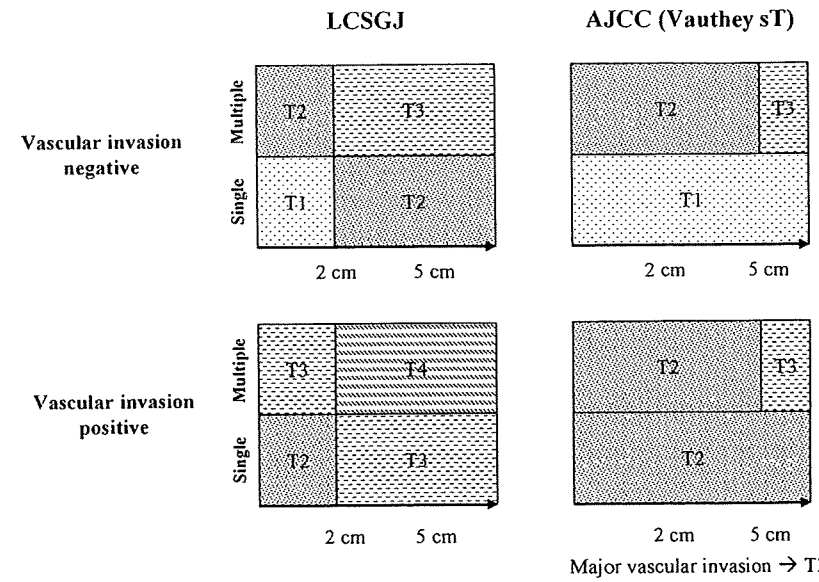

FIGURE 1. Comparison of the T classification in LCSGJ and AJCC/UICC.

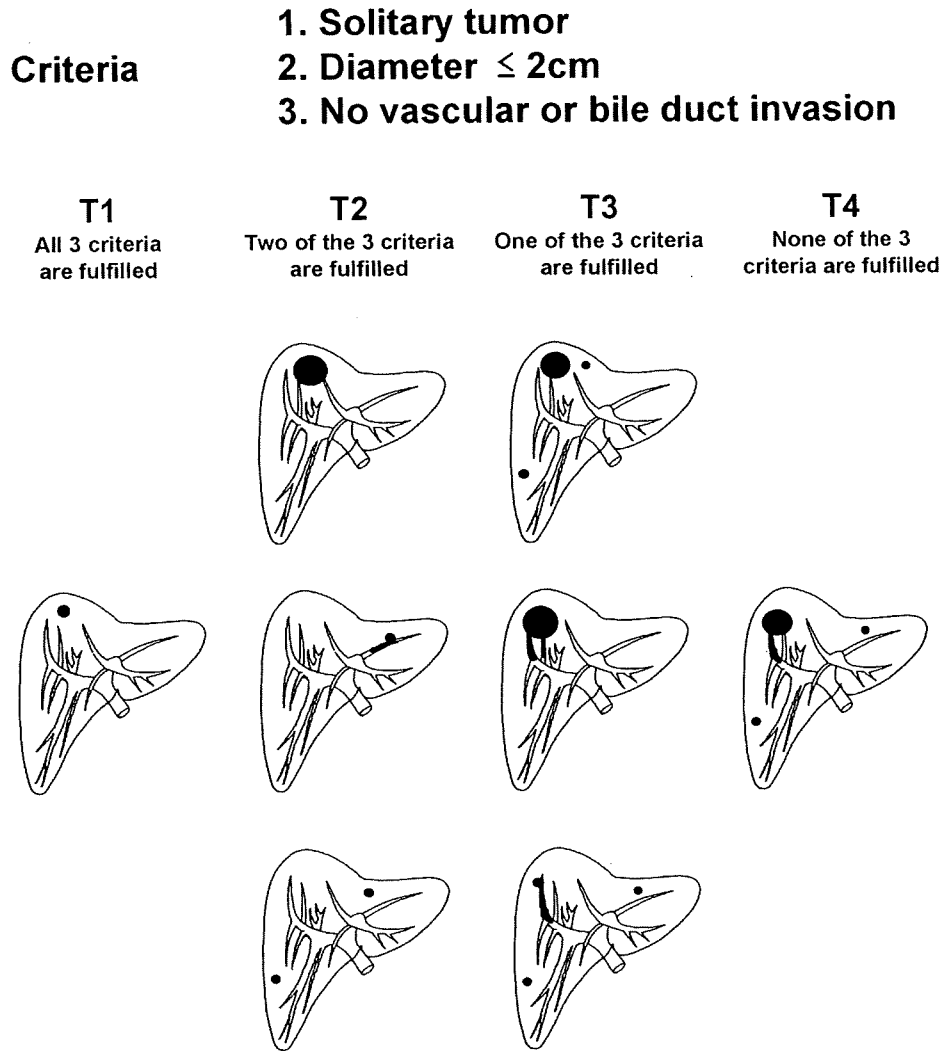

FIGURE 2. The T category of LCSGJ is determined on the basis of the "number," "size," and "vascular or bile duct invasion." All multiple tumors, including multicentric tumors and intrahepatic metastatic tumors, are equally counted.

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.

TABLE 4. Pathologic Factors of Curative-Hepatectomy-N0M0-Cohort

Variable	No. Patients	Median Survival Time (Year)	95% CI for Median	5-Year Survival Rate (%)	*P*
No. HCC					<0.0001
1	10176	6.05	5.87–6.26	58	
2	1968	4.47	4.16–4.85	46	
3	618	3.68	3.12–4.14	37	
4	611	2.75	2.30–3.35	27	
Diameter					<0.0001
2 cm	2767	6.87	6.30–7.25	67	
2–5 cm	7259	5.58	5.22–5.86	54	
5–10 cm	2313	3.96	3.62–4.21	43	
>10 cm	843	2.77	2.42–3.65	38	
Portal invasion					<0.0001
None	11740	5.91	5.66–6.02	57	
3rd branch	886	3.19	2.84–3.59	37	
2nd branch	333	1.48	1.10–2.01	30	
1st branch or trunk	298	1.07	0.89–1.41	18	
Hepatic venous invasion					<0.0001
None	12461	5.67	5.47–5.91	55	
Branch of HV	359	2.61	2.19–3.16	35	
Trunk of HV or IVC	200	1.31	1.05–1.92	21	
Bile duct invasion					<0.0001
None	12928	5.61	5.43–5.86	55	
Intrahepatic bile duct	200	2.36	1.64–4.42	38	
Extrahepatic bile duct	79	1.57	0.99–2.19	30	
Grade of differentiation					<0.0001
Well	3003	6.32	6.01–6.72	62	
Moderately	7589	5.23	5.04–5.55	52	
Poorly	1340	3.65	3.08–4.21	43	
Undifferentiated	65	2.8	1.41–5.53	37	
Background liver					<0.0001
Normal	1243	7.2	6.27*	63	
Hepatitis	4401	6.89	6.32*	62	
Cirrhosis	9242	4.82	4.60–5.02	48	
Gross classification†					<0.0001
Type 1	8753	6.02	5.87–6.26	59	
Type 2	2018	4.38	3.84–4.82	46	
Type 3	1130	5.04	4.37–5.94	51	
Multinodular type	641	3.98	3.55–4.52	42	
Massive type of Eggel	368	2.16	1.56–2.84	28	
Diffuse type of Eggel	33	1.41	0.40–2.58	22	
Hepatic involvement					<0.0001
1 segment of Couinaud	6769	6.12	5.98–6.42	60	
1 sector	3232	5.04	4.75–5.42	50	
2 sectors	2648	4.15	3.90–4.57	46	
3 sectors or more	530	2.84	2.39–3.40	32	
Fibrous capsule (pathologic)					0.12
None	2531	6.02	5.62–6.33	58	
Positive	9513	5.47	5.19–5.79	53	
Macroscopic intrahepatic metastasis					<0.0001
None	10642	6.02	5.86–6.19	58	
Within 1 sector	1574	3.61	3.31–4.07	40	
Within 2 sectors	951	3.22	2.89–3.67	36	
3 sectors or more	244	2.95	2.25–4.02	28	

*References 10, 11, and 33.
†Type 1, simple nodular type; Type 2, simple nodular type with extranodular growth; Type 3, confluent multinodular type.
CI indicates confidence interval.

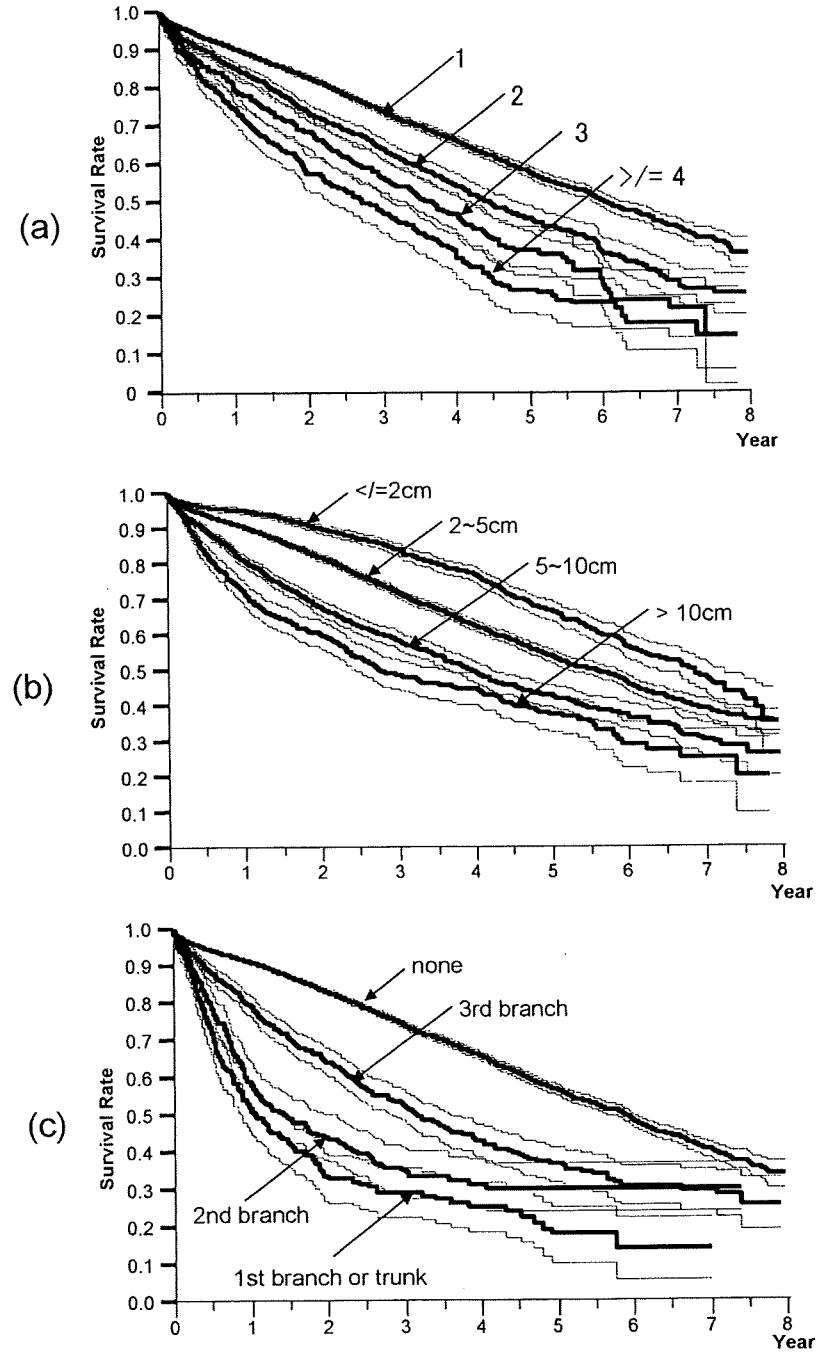

FIGURE 3. Kaplan-Meier survival analysis (solid line) with 95% confidence interval (dotted line) for patients in the curative-hepatectomy-N0M0 cohort stratified according to the number of liver nodules (a), the maximum diameter of liver nodules (b), and the location of portal invasion (c). The number, median survival time (95% CI), and 5-year survival rate of patients are described in Table 4.

hepatitis C antibody was considered to be positive for hepatitis C serology. A history of alcohol consumption of 86 g of ethanol per day over a 10-year period was defined as positive.[24]

Statistical Analysis

Survival was measured from the time of hepatic resection, and death was the endpoint. Survival curves were constructed using the Kaplan-Meier product-limit method and compared using a log-rank test. Significant prognostic factors in a univariate analysis were entered into a Cox proportional hazards model using stepwise selection to identify independent predictors of death. Statistical significance was defined as a P value <0.05. Statistical Analysis System, version 8 (SAS Institute Inc., Cary, NC) was used for statistical analyses. Based on these survival analyses, the LCSGJ T classification was developed and the effects of liver cirrhosis and degree of liver damage as defined by LCSGJ were evaluated because these variables were components of other tumor classification scheme, such as CLIP or JIS.

The abilities of the LCSGJ T classification and the AJCC T classification to accurately predict survival were verified and compared by the cross-validation method. Patients

were randomly divided into 2 groups: a training sample and a validation sample. In the training sample, 2 predictive models were constructed using the Cox proportional hazards model, which included either the LCSGJ T classification or the AJCC T classification as a covariate. In the validation sample, each estimated model from the test sample was used to predict the survival for each patient. The predicted survival curves, plotted based on each model, were compared with the observed survival curves in the validation sample plotted by the Kaplan-Meier method. The predictive accuracies were compared in terms of the residual, which was the difference between the observed survival time and the predicted survival time in the validation sample. An analysis of variance using the Generalized Estimating Equation method was used to compare the absolute values of the residuals between the 2 T classifications.[25]

RESULTS

Of the 14,922 patients who underwent hepatic resection for HCC, 10,259 were alive and 4663 had died. The direct cause of death was HCC in 2886 patients, liver failure in 844, gastrointestinal bleeding in 81, rupture of esophageal varices in 112, rupture of HCC in 38, operative death in 186, and other in 516.

The demographic and clinicopathologic characteristics of the 13,566 patients in the curative-hepatectomy-N0M0 cohort are shown in Tables 3and 4. The survival curves according to the number of HCCs are shown in Figure 3a. Single HCC showed the best prognosis, and the survival time gradually decreased with an increase in the number of HCCs. The diameter of the largest nodule significantly influenced survival (Fig. 3b). Patients with HCC ≤2 cm had a significantly longer duration of survival than those with HCC of 2 to 5 cm ($P < 0.0001$). The survival curves according to the location of portal invasion are shown in Figure 3c. The significant factors identified by a multivariate analysis are shown in Table 5. Vascular or bile duct invasion (portal vein, hepatic vein, or bile duct invasion) had the greatest impact on survival, followed by the presence of liver cirrhosis in the background liver, diameter of HCC, alpha-fetoprotein, number of HCCs, degree of liver damage, hepatic involvement,

TABLE 5. Multivariate Analysis by Cox Proportional Hazard Model

Variable	Relative Risk	95% Confidence Interval		*P*
		Lower	Upper	
Vascular or bile duct invasion				<0.0001
Negative	1			
Positive	1.36	1.29	1.43	
Liver cirrhosis				<0.0001
Negative	1			
Positive	1.26	1.20	1.32	
Diameter				<0.0001
≤2 cm	1			
>2 cm	1.21	1.14	1.28	
Alpha-fetoprotein				<0.0001
≤20 ng/mL	1			
>20 ng/mL	1.20	1.15	1.25	
No. nodules				<0.0001
Single	1			
Multiple	1.18	1.12	1.23	
Degree of liver damage				<0.0001
A	1			
B or C	1.15	1.10	1.20	
Hepatic involvement				<0.0001
≤1 segment*	1			
>1 segment*	1.14	1.09	1.19	
Differentiation				<0.0001
Well-differentiated HCC	1			
Except for well-differentiated HCC	1.14	1.08	1.20	
Gross classification				<0.0001
Simple nodular type	1			
Except for simple nodular type	1.13	1.08	1.18	
Esophageal varices				0.0058
Negative	1			
Positive	1.07	1.02	1.13	

*Segment of Couinaud.

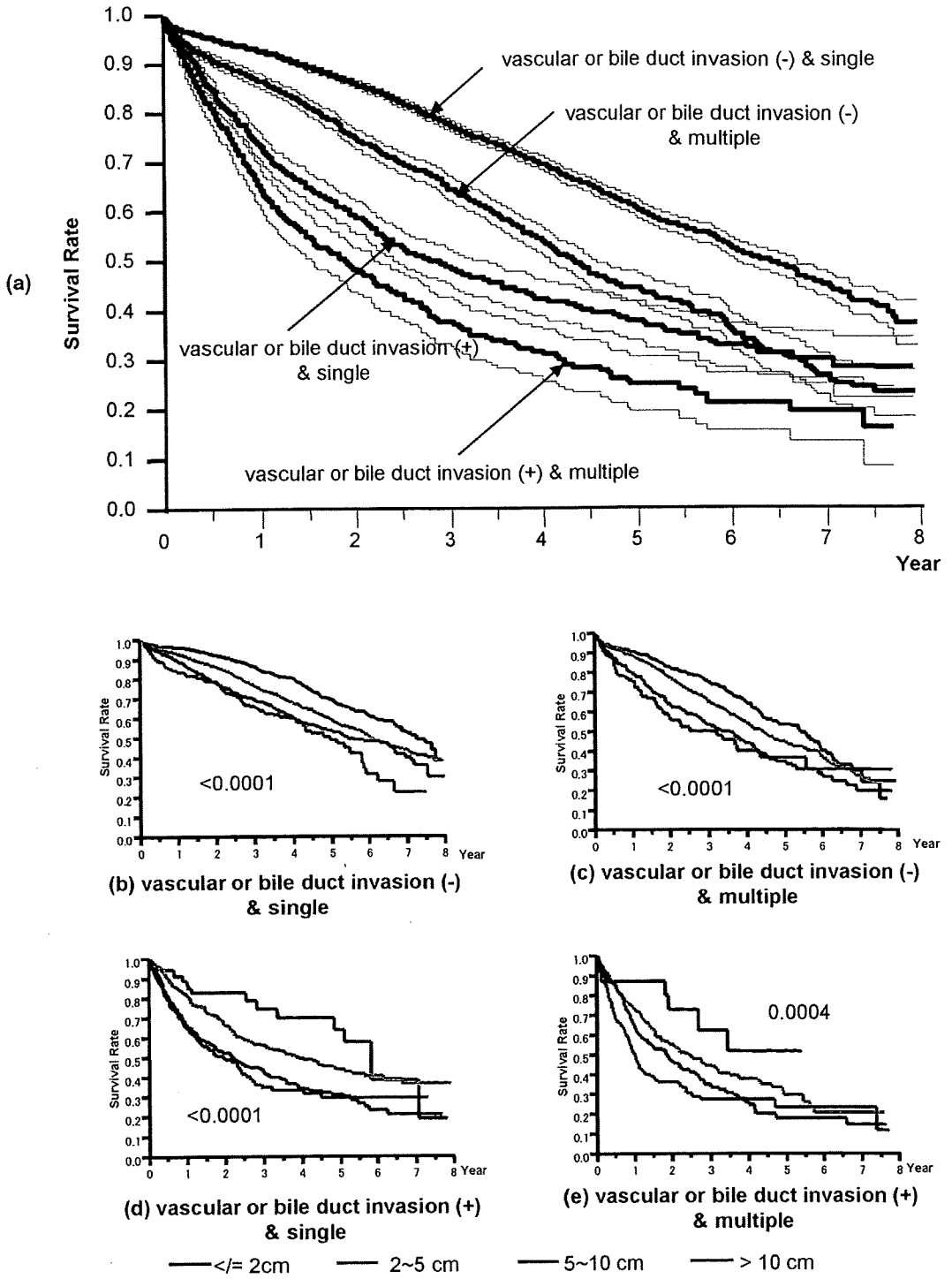

FIGURE 4. Kaplan-Meier survival analysis (solid line) with 95% confidence interval (dotted line) for patients in the curative-hepatectomy-N0M0 cohort stratified according to vascular or bile duct invasion, and growth pattern (single or multiple). The number, median survival time (95% CI), and 5-year survival rate of patients with vascular or bile duct invasion (−) and single, vascular or bile duct invasion (−) and multiple, vascular or bile duct invasion (+) and single, and vascular or bile duct invasion (+) and multiple were 8565, 6.41 years (6.08–6.71), 61%; 2461, 4.37 years (4.12–4.61), 45%; 1163, 2.90 years (2.48–3.23), 38%; and 615, 1.92 years (1.56–2.28), 25% ($P < 0.0001$) (a). Influence of tumor size in the 4 groups (b, c, d, e). Tumor size significantly influenced survival in all of the groups.

grade of differentiation, gross classification, and presence of esophageal varices.

Development of T Classification

Based on the results of the multivariate analysis, we stratified patients into 4 groups according to the presence of vascular or bile duct invasion, and the number of HCCs (single or multiple). Because these factors had the first and fifth highest relative risk for death in stepwise Cox proportional model (Table 5), and were used in the previous LCSGJ-TNM scheme, third edition. The survival curves of these 4 groups were clearly separate, and the differences in survival between any 2 of these groups were significant; the P values of all combinations were less than 0.0001 (Fig. 4a). The impact of tumor size on survival was analyzed within each group because it had third highest relative risk for death in stepwise Cox proportional model, and were used in the previous LCSGJ-TNM scheme, third edition. In all of the groups, tumor size significantly affected survival (Fig. 4b–e). In particular, patients with tumors that were 2 cm or smaller in diameter had a more favorable prognosis in all of the groups. The median survival time (95% CI) and the 5-year survival rate of patients with HCCs of 2 cm or smaller were as follows: 7.3 years (6.9-*) and 70% in patients with single tumor without vascular or bile duct invasion (Fig. 4b), 5.4 years (4.5–6.0) and 54% in patients with multiple tumors without vascular or bile duct invasion (Fig. 4c), 5.8 years (4.9-*) and 64% in patients with single tumor with vascular or bile duct invasion (Fig. 4d), and years (1.9-*) and 52% in patients with multiple tumors with vascular or bile duct invasion (Fig. 4e). (*Not calculated because survival curve remains above a survival rate of 50%.) Patients with tumors 2 cm or smaller in diameter had a more favorable prognosis regardless of vascular or bile duct invasion or growth pattern (single or multiple). Therefore, these criteria [growth pattern (single or multiple), vascular or bile duct invasion, and size ($\leq$2 cm or >2 cm)] were used to determine T classification. Patients who had none of these 3 factors were assigned to T1, and those with 1, 2, and 3 factor(s) were considered T2, T3, and T4. The survival of patients according to this T classification is shown in Figure 5a. The median survival time (95% CI) and 5-year survival rate of patients with T4 HCC in the curative-N0M0-cohort was 1.85 years (1.49–2.33 years) and 24%, which was similar to the

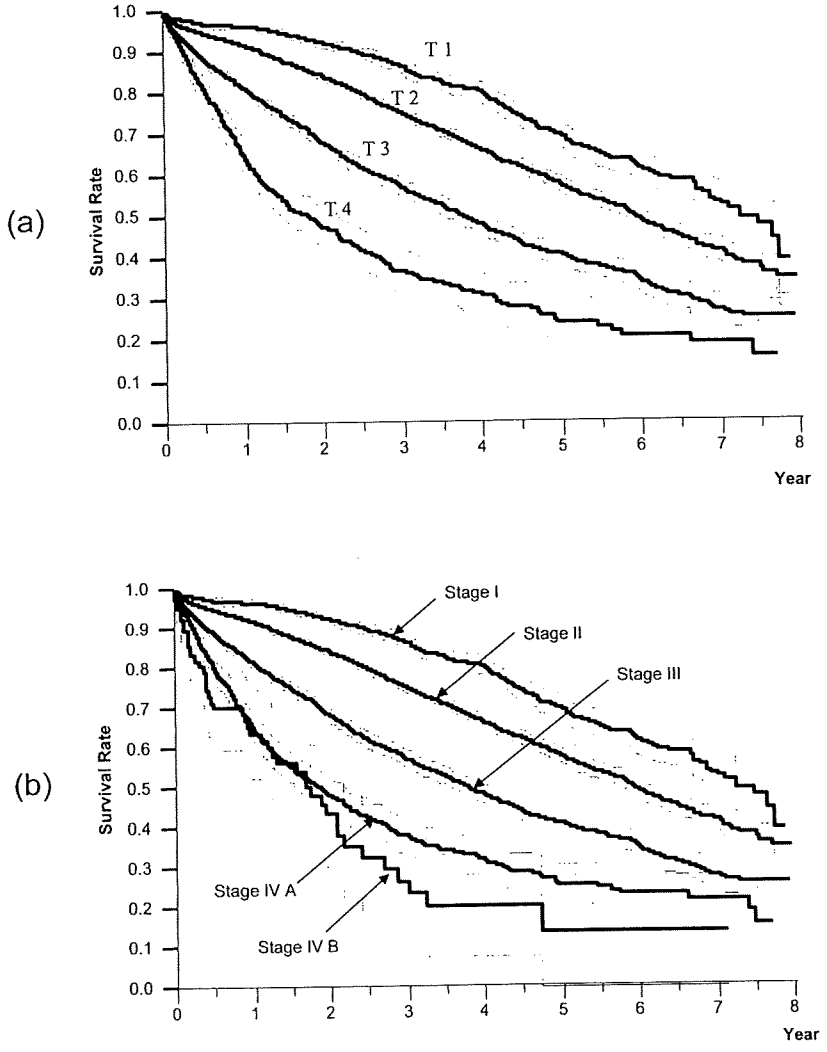

FIGURE 5. Kaplan-Meier survival analysis (solid line) with 95% confidence interval (dotted line) for patients in the curative-hepatectomy-N0M0 cohort stratified according to the T classification (a) and the stage (b) of LCSGJ.

TABLE 6. T Classification and Stage of LCSGJ

Variable	No. Patients	Median Survival Time (yr)	95% CI for Median	5-Year Survival Rate (%)	*P*
T classification Curative-hepatectomy-N0M0-cohort					<0.0001
1	2078	7.25	6.88–*	70	
2	6853	5.93	5.75–6.11	58	
3	3021	3.79	3.56–4.05	41	
4	582	1.85	1.49–2.33	24	
Stage: Curative-hepatectomy-cohort					<0.0001
I	2078	7.25	6.88–*	70	
II	6853	5.93	5.75–6.11	58	
III	3021	3.79	3.56–4.05	41	
IVA	712	1.89	1.57–2.22	25	
IVB	76	1.70	1.12–2.42	15	

*Not calculated because survival curve remains above a survival rate of 50%.

values in patients with hepatic lymph node metastasis in the curative-hepatectomy-cohort (any T N1 M0); 1.9 years (1.3–2.5 years) and 32%. This prompted us to combine these patients into a single group; stage IVA. Patients with extrahepatic metastasis (any T any N M1) showed a median survival time (95% CI) of 1.7 years (1.1–2.4 years) and a 5-year survival rate of 15%, and these patients were assigned to stage IVB. Patients with T1N0M0, T2N0M0, and T3N0M0 HCC were assigned to stage I, stage II, and stage III, respectively (Table 6). The survival curves are shown in Figure 5b. The distribution of curative-hepatectomy-N0M0-cohort by LCSGJ-T and AJCC T is shown in Table 7.

The effects of liver cirrhosis and degree of liver damage as defined by LCSGJ on patients with T1, T2, T3, and T4 HCC are shown in Figure 6 because these variables are components of other tumor classification scheme, such as CLIP or JIS. The presence of liver cirrhosis in the background liver was a negative prognostic factor in patients with all of the T-classes of HCC. The degree of liver damage significantly influenced the prognosis of patients with T1, T2, or T3 tumor ($P < 0.0001$), but did not affect the prognosis of patients with T4 HCC ($P = 0.509$).

Although patients with T1 or T4 HCC are identical with regard to the presence of 3 factors [growth pattern (single or multiple), vascular or bile duct invasion, and size (≤2 cm or >2 cm)], patients with T2 or T3 tumor can be subclassified into 3 groups according to combinations of these 3 factors. While no survival difference was observed in patients with T2 tumor ($P = 0.220$), among patients with T3 tumor, those with vascular or bile duct invasion showed a significantly worse outcome than those without. When patients with T3 HCC were stratified according to negative factors, the number, median survival time (95% CI), and 5-year survival rate of those with HCCs of 2 cm or smaller, single HCCs, and HCCs without vascular or bile duct invasion were 25, *years (1.9-*), 52%; 1,086, 2.7 years (2.4–3.2), 37%; and 1,917, 4.1 year (3.8-4.5), 42% ($P < 0.0001$).

TABLE 7. Distribution of Curative-Hepatectomy-N0M0-Cohort by LCSGJ and AJCC-T Classifications

	LCSGJ-T					
	T1	T2	T3	T4	Total	%
AJCC-T						
T1	2078	6308	71	0	8457	67.5
T2	0	542	2151	195	2888	23.0
T3	0	3	799	387	1189	9.5
Total	2078	6853	3021	582	12,534	
%	16.6	54.7	24.1	4.6		

Validation of T Classification and Comparison With AJCC T

A total of 13,566 patients in the curative-hepatectomy-N0M0-cohort were randomly assigned to either a training sample (n = 6819 patients with 1964 deaths) or a test sample (n = 6747 patients with 1943 deaths) to validate its prognostic significance. Table 8 shows the prediction models constructed by a Cox proportional hazards model in the training sample based on the LCSGJ T classification and the AJCC T classification. In the training sample, both of these models had good discriminating ability. Figure 7 shows the results of the application of each predictive model to the validation sample. The results of an analysis of variance using the Generalized Estimating Equation method for 2 residual sum of squares of each patient are shown in Table 9. The negative estimate of LCSGJ T versus AJCC T (−0.0017) indicated that the difference between the estimated survival time and actual survival time with LCSGJ-T was significantly smaller than that with AJCC T after adjusting for stage ($P = 0.0007$).

DISCUSSION

LCSGJ published *The General Rules for the Clinical and Pathologic Study of Primary Liver Cancer*, 4th edition, which described the present staging system, in November 2000.[10] The previous AJCC/UICC TNM staging system, introduced in 1988, was derived from the TNM classification