Table 5 Tumor characteristics by imaging studies

	HCC		ICC		Combined	
Tumor size by imaging studies (cm)	*n* = 17 804		*n* = 746		*n* = 137	
Image ≤1	855	(4.8%)	11	(1.5%)	0	(0.0%)
Image ≤2	5 106	(28.7%)	58	(7.8%)	17	(12.4%)
Image ≤3	4 272	(24.0%)	133	(17.8%)	29	(21.2%)
Image ≤5	3 833	(21.5%)	231	(31.0%)	43	(31.4%)
Image ≤10	2 743	(15.4%)	269	(36.1%)	33	(24.1%)
Image ≤15	723	(4.1%)	40	(5.4%)	13	(9.5%)
Image ≤20	176	(1.0%)	4	(0.5%)	2	(1.5%)
Image ≤25	67	(0.4%)	0	(0.0%)	0	(0.0%)
Image >25	29	(0.2%)	0	(0.0%)	0	(0.0%)
No. tumors by imaging studies	*n* = 18 255		*n* = 792		*n* = 145	
Image 1	10 539	(57.7%)	584	(73.7%)	79	(54.5%)
Image 2	3 157	(17.3%)	55	(6.9%)	23	(15.9%)
Image 3	1 437	(7.9%)	25	(3.2%)	7	(4.8%)
Image 4	577	(3.2%)	11	(1.4%)	6	(4.1%)
Image 5	281	(1.5%)	4	(0.5%)	2	(1.4%)
Image ≥6	2 264	(12.4%)	113	(14.3%)	28	(19.3%)
Portal vein invasion by imaging studies	*n* = 17 455		*n* = 727		*n* = 139	
Image Vp0	15 170	(86.9%)	477	(65.6%)	98	(70.5%)
Image Vp1	532	(3.0%)	58	(8.0%)	11	(7.9%)
Image Vp2	485	(2.8%)	49	(6.7%)	8	(5.8%)
Image Vp3	689	(3.9%)	110	(15.1%)	19	(13.7%)
Image Vp4	579	(3.3%)	33	(4.5%)	3	(2.2%)
Hepatic vein invasion by imaging studies	*n* = 16 688		*n* = 694		*n* = 130	
Image Vv0	15 961	(95.6%)	600	(86.5%)	121	(93.1%)
Image Vv1	269	(1.6%)	31	(4.5%)	4	(3.1%)
Image Vv2	229	(1.4%)	42	(6.1%)	4	(3.1%)
Image Vv3	229	(1.4%)	21	(3.0%)	1	(0.8%)
Bile duct invasion by imaging studies	*n* = 16 536		*n* = 691		*n* = 126	
Image B0	16 134	(97.6%)	403	(58.3%)	108	(85.7%)
Image B1	181	(1.1%)	81	(11.7%)	5	(4.0%)
Image B2	96	(0.6%)	66	(9.6%)	8	(6.3%)
Image B3	74	(0.4%)	101	(14.6%)	0	(0.0%)
Image B4	51	(0.3%)	40	(5.8%)	5	(4.0%)
Distant metastases by imaging studies						
Lung	302		44		8	
Bone	207		15		6	
Adrenal gland	66		5		0	
Lymph node	228		152		21	
Brain	19		2		0	
Peritoneum	30		20		3	
Others	52		8		0	
Esophageal or gastric varices	*n* = 5 251		*n* = 33		*n* = 22	
F1, RC⁻	2 766	(52.7%)	22	(66.7%)	12	(54.5%)
F2 or RC⁻	2 123	(40.4%)	10	(30.3%)	10	(45.5%)
Rupture	362	(6.9%)	1	(3.0%)	0	(0.0%)

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 of (or tumor thrombus in) distal to the second order branches of the portal vein, but not of the second order branches; Vp2, invasion of (or tumor thrombus in) second order branches of the portal vein; Vp3, invasion of (or tumor thrombus in) first order branches of the portal vein; Vp4, invasion of (or tumor thrombus in) the main trunk of the portal vein and/or contralateral portal vein branch to the primarily involved lobe; Vv0, absence of invasion of (or tumor thrombus in) the 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.

Table 6 Major treatment of patients with primary liver cancer

	HCC		ICC		Combined	
Treatment for tumor	$n = 17\,986$		$n = 732$		$n = 141$	
Surgery	5 698	(31.7%)	491	(67.1%)	90	(63.8%)
Local ablation therapy	5 500	(30.6%)	18	(2.5%)	12	(8.5%)
Transcatheter arterial chemoembolization	5 693	(31.7%)	13	(1.8%)	19	(13.5%)
Chemotherapy	997	(5.5%)	194	(26.5%)	20	(14.2%)
Others	98	(0.5%)	16	(2.2%)	0	(0.0%)
Best supportive care	$n = 1\,388$		$n = 158$		$n = 16$	

Combined, combined hepatocellular and cholangiocarcinoma; HCC: hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

alone, gelatin sponge alone, and lipiodol plus gelatin sponge were used in 20.6%, 2.6% and 75.6% of cases, respectively (Table 9), with concomitant administration of anticancer agents in 93.2% of these patients. Regarding the extent of embolization, less than one segment, one segment to one lobe, more than one lobe and the whole liver were treated in 36.0%, 40.5%, 17.5% and 6.0% of patients, respectively. Treatment outcomes of CR and PR at 6 months occurred in 40.5% and 27.6% of patients, respectively.

Chemotherapy

Chemotherapy was given to 1862 patients with HCC, and of these patient 85.8%, 4.6% and 7.9% received chemotherapy intra-arterially, i.v. and p.o., respectively; treatment outcomes of CR and PR at 6 months occurred in 13.5% and 25.5% of patients, respectively. Of the patients with ICC, 232 underwent chemotherapy, and of these patients 22.4%, 55.2% and 15.9% received chemotherapy intra-arterially, i.v. and p.o., respectively; treatment outcomes of CR and PR at 6 months occurred in 4.0% and 11.9% of patients, respectively.

Pathological diagnosis

Pathological diagnosis was conducted in 40.4% of patients with HCC, whereas 59.6% of patients were not diagnosed pathologically. The percentage of diagnoses by biopsy alone, resected specimens alone, and both biopsy and resected specimens was 25.8%, 71.5% and 2.7%, respectively. Microscopic pathological results from biopsy and resected specimens are shown in Table 10. Well, moderately and poorly differentiated tumor types were found in 27.3% ($n = 1842$), 60.3% ($n = 4063$) and 11.6% ($n = 784$) of patients with HCC, respectively, whereas well, moderately and poorly differentiated tumor types were found in 23.3% ($n = 115$), 54.1% ($n = 268$) and 19.8% ($n = 98$) 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 6.5%, 48.0% and 45.6% of patients with HCC, respectively, and in 65.0%, 24.4% and 10.6% of patients with ICC, respectively.

Recurrence

During the period of this survey (<2 years after diagnosis), 28.8% of patients with HCC experienced recurrence of the disease. Transcatheter arterial embolization and local therapy were given to 58.3% and 27.2% of these patients, respectively, as treatment for recurrence in the liver. The most frequent organ of distant metastasis was the lung, followed by bone and lymph nodes. Radiation therapy, systemic chemotherapy and resection were chosen as treatment for distant organ metastasis.

Autopsy

Autopsy in 280 patients of primary liver cancer were registered, 238 of whom were patients with HCC. Liver cirrhosis was found in 81.5% of the autopsied patients with HCC, invasion of the portal vein, hepatic vein or bile duct was found in 72.4%, 42.7% and 25.8%, 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.

Cumulative survival rates

The cumulative survival rates of newly-registered patients in the 13th to 18th follow-up surveys (1994–2005) whose final prognosis was defined as survival

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

	HCC		ICC		Combined	
Tumor size (cm)	*n* = 5277		*n* = 451		*n* = 85	
≤1	91	(1.7%)	8	(1.8%)	0	(0.0%)
≤2	846	(16.0%)	34	(7.5%)	10	(11.8%)
≤3	1360	(25.8%)	79	(17.5%)	16	(18.8%)
≤5	1534	(29.1%)	156	(34.6%)	31	(36.5%)
≤10	1066	(20.2%)	153	(33.9%)	18	(21.2%)
≤15	304	(5.8%)	15	(3.3%)	8	(9.4%)
≤20	57	(1.1%)	4	(0.9%)	1	(1.2%)
≤25	16	(0.3%)	2	(0.4%)	1	(1.2%)
>25	3	(0.1%)	0	(0.0%)	0	(0.0%)
No. of tumors	*n* = 5336		*n* = 458		*n* = 85	
1	3966	(74.3%)	384	(83.8%)	50	(58.8%)
2	792	(14.8%)	28	(6.1%)	16	(18.8%)
3	258	(4.8%)	9	(2.0%)	4	(4.7%)
4	96	(1.8%)	7	(1.5%)	3	(3.5%)
5	36	(0.7%)	6	(1.3%)	1	(1.2%)
≥6	188	(3.5%)	24	(5.2%)	11	(12.9%)
Tumor extent	*n* = 5189		*n* = 465		*n* = 85	
Hs	2099	(40.5%)	70	(15.1%)	25	(29.4%)
H1	1458	(28.1%)	138	(29.7%)	17	(20.0%)
H2	1284	(24.7%)	210	(45.2%)	32	(37.6%)
H3	259	(5.0%)	39	(8.4%)	9	(10.6%)
H4	89	(1.7%)	8	(1.7%)	2	(2.4%)
Growth type	*n* = 5105		*n* = 424		*n* = 83	
Eg	4731	(92.7%)	196	(46.2%)	60	(72.3%)
Ig	374	(7.3%)	228	(53.8%)	23	(27.7%)
Capsule formation	*n* = 5047		*n* = 416		*n* = 80	
Fc^-	1147	(22.7%)	379	(91.1%)	54	(67.5%)
Fc^+	3900	(77.3%)	37	(8.9%)	26	(32.5%)
Capsule infiltration	*n* = 4702		*n* = 288		*n* = 65	
$Fc\text{-}Inf^-$	2768	(58.9%)	265	(92.0%)	52	(80.0%)
$Fc\text{-}Inf^+$	1934	(41.1%)	23	(8.0%)	13	(20.0%)
Septum formation	*n* = 4968		*n* = 398		*n* = 79	
Sf^-	2313	(46.6%)	374	(94.0%)	51	(64.6%)
Sf^+	2655	(53.4%)	24	(6.0%)	28	(35.4%)
Serosal invasion	*n* = 5016		*n* = 429		*n* = 81	
S0	4022	(80.2%)	254	(59.2%)	52	(64.2%)
S1	755	(15.1%)	130	(30.3%)	21	(25.9%)
S2	161	(3.2%)	45	(10.5%)	7	(8.6%)
S3	78	(1.6%)	0	(0.0%)	1	(1.2%)
Lymph node metastasis	*n* = 4910		*n* = 449		*n* = 83	
Absent	4858	(98.9%)	312	(69.5%)	70	(84.3%)
Present	52	(1.1%)	137	(30.5%)	13	(15.7%)
Portal vein invasion	*n* = 5228		*n* = 445		*n* = 86	
Vp0	4384	(83.9%)	286	(64.3%)	52	(60.5%)
Vp1	481	(9.2%)	66	(14.8%)	20	(23.3%)
Vp2	166	(3.2%)	37	(8.3%)	7	(8.1%)
Vp3	126	(2.4%)	48	(10.8%)	6	(7.0%)
Vp4	71	(1.4%)	8	(1.8%)	1	(1.2%)
Hepatic vein invasion	*n* = 5088		*n* = 434		*n* = 82	
Vv0	4719	(92.7%)	354	(81.6%)	72	(87.8%)
Vv1	253	(5.0%)	36	(8.3%)	10	(12.2%)
Vv2	84	(1.7%)	30	(6.9%)	0	(0.0%)
Vv3	32	(0.6%)	14	(3.2%)	0	(0.0%)
Hepatic arterial invasion	*n* = 5057		*n* = 429		*n* = 82	
Va0	5020	(99.3%)	382	(89.0%)	81	(98.8%)
Va1	36	(0.7%)	26	(6.1%)	1	(1.2%)
Va2	1	(0.0%)	13	(3.0%)	0	(0.0%)
Va3	0	(0.0%)	8	(1.9%)	0	(0.0%)

Table 7 *Continued*

	HCC		ICC		Combined	
Bile duct invasion	*n* = 5184		*n* = 436		*n* = 84	
B0	5049	(97.4%)	214	(49.1%)	73	(86.9%)
B1	70	(1.4%)	72	(16.5%)	4	(4.8%)
B2	21	(0.4%)	60	(13.8%)	4	(4.8%)
B3	29	(0.6%)	70	(16.1%)	1	(1.2%)
B4	15	(0.3%)	20	(4.6%)	2	(2.4%)
Intrahepatic metastasis	*n* = 5187		*n* = 450		*n* = 85	
Im0	4076	(78.6%)	346	(76.9%)	55	(64.7%)
Ims	215	(4.1%)	14	(3.1%)	5	(5.9%)
Im1	353	(6.8%)	38	(8.4%)	8	(9.4%)
Im2	362	(7.0%)	37	(8.2%)	9	(10.6%)
Im3	181	(3.5%)	15	(3.3%)	8	(9.4%)
Peritoneal dissemination	*n* = 5164		*n* = 449		*n* = 84	
Absent	5132	(99.4%)	432	(96.2%)	83	(98.8%)
Present	32	(0.6%)	17	(3.8%)	1	(1.2%)
Surgical margin	*n* = 5174		*n* = 447		*n* = 85	
Presence of cancer invasion	320	(6.2%)	56	(12.5%)	10	(11.8%)
Absence of cancer invasion	4854	(93.8%)	391	(87.5%)	75	(88.2%)
Non-cancerous portion	*n* = 5146		*n* = 436		*n* = 84	
Normal liver	461	(9.0%)	309	(70.9%)	15	(17.9%)
Chronic hepatitis / liver fibrosis	2519	(49.0%)	90	(20.6%)	41	(48.8%)
Liver cirrhosis	2166	(42.1%)	37	(8.5%)	28	(33.3%)
Extent of hepatic resection	*n* = 5148		*n* = 467		*n* = 86	
Hr0	1579	(30.7%)	32	(6.9%)	13	(15.1%)
HrS	1203	(23.4%)	35	(7.5%)	23	(26.7%)
Hr1	1163	(22.6%)	61	(13.1%)	12	(14.0%)
Hr2	1072	(20.8%)	294	(63.0%)	32	(37.2%)
Hr3	131	(2.5%)	45	(9.6%)	6	(7.0%)
Lymph node dissection	*n* = 4925		*n* = 457		*n* = 84	
Not performed	4807	(97.6%)	185	(40.5%)	67	(79.8%)
Performed	118	(2.4%)	272	(59.5%)	17	(20.2%)
Residual cancer	*n* = 5078		*n* = 442		*n* = 79	
Absent	4800	(94.5%)	397	(89.8%)	69	(87.3%)
Present	278	(5.5%)	45	(10.2%)	10	(12.7%)
Distant metastases	*n* = 5214		*n* = 452		*n* = 86	
Absent	5175	(99.3%)	440	(97.3%)	84	(97.7%)
Present	39	(0.7%)	12	(2.7%)	2	(2.3%)
TNM stage by LCSGJ	*n* = 5268		*n* = 452		*n* = 84	
I	689	(13.1%)	24	(5.3%)	3	(3.6%)
II	2647	(50.2%)	121	(26.8%)	21	(25.0%)
III	1342	(25.5%)	149	(33.0%)	34	(40.5%)
IV A	534	(10.1%)	43	(9.5%)	20	(23.8%)
IV B	56	(1.1%)	115	(25.4%)	6	(7.1%)

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.

Table 8 Local ablation therapy

	HCC		ICC		Combined	
	n = 17 794		*n* = 734		*n* = 147	
Not performed	11 121	(62.5%)	704	(95.9%)	132	(89.8%)
Performed	6 673	(37.5%)	30	(4.1%)	15	(10.2%)
EIT	1 241	(18.6%)	6	(20.0%)	3	(20.0%)
MCT	565	(8.5%)	2	(6.7%)	0	(0.0%)
RFA	4 812	(72.1%)	21	(70.0%)	12	(80.0%)
Others	55	(0.8%)	1	(3.3%)	0	(0.0%)
Percutaneous or not	*n* = 6 488		*n* = 29		*n* = 14	
Percutaneous	5 597	(86.3%)	21	(72.4%)	13	(92.9%)
Others	891	(13.7%)	8	(27.6%)	1	(7.1%)
No. tumors	*n* = 6 518		*n* = 29		*n* = 15	
1	4 643	(71.2%)	21	(72.4%)	11	(73.3%)
2	1 219	(18.7%)	6	(20.7%)	3	(20.0%)
3	412	(6.3%)	0	(0.0%)	1	(6.7%)
4	123	(1.9%)	2	(6.9%)	0	(0.0%)
5	56	(0.9%)	0	(0.0%)	0	(0.0%)
≥6	65	(1.0%)	0	(0.0%)	0	(0.0%)
Tumor size (cm)	*n* = 6 326		*n* = 27		*n* = 14	
≤1	560	(8.9%)	2	(7.4%)	0	(0.0%)
≤2	3 189	(50.4%)	10	(37.0%)	7	(50.0%)
≤3	1 800	(28.5%)	11	(40.7%)	4	(28.6%)
≤5	688	(10.9%)	4	(14.8%)	3	(21.4%)
≤10	89	(1.4%)	0	(0.0%)	0	(0.0%)
≤15	0	(0.0%)	0	(0.0%)	0	(0.0%)
≤20	0	(0.0%)	0	(0.0%)	0	(0.0%)
≤25	0	(0.0%)	0	(0.0%)	0	(0.0%)
>25	0	(0.0%)	0	(0.0%)	0	(0.0%)
Modalities combined with local ablation therapy	*n* = 6 500		*n* = 28		*n* = 14	
None	4 096	(63.0%)	20	(71.4%)	10	(71.4%)
Transcatheter arterial embolization	2 182	(33.6%)	5	(17.9%)	4	(28.6%)
others	222	(3.4%)	3	(10.7%)	0	(0.0%)
Efficacy evaluation at 6 months	*n* = 5 378		*n* = 23		*n* = 11	
CR	4 318	(80.3%)	9	(39.1%)	10	(90.9%)
PR	530	(9.9%)	4	(17.4%)	1	(9.1%)
SD	160	(3.0%)	5	(21.7%)	0	(0.0%)
PD	370	(6.9%)	5	(21.7%)	0	(0.0%)

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.

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 55.0%, 37.9% and 16.5%, respectively. 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 liver damage classification by

Table 9 Transcatheter arterial embolization

	HCC		ICC		Combined	
	n = 17 898		*n* = 736		*n* = 149	
Not performed	9 710	(54.3%)	707	(96.1%)	113	(75.8%)
Performed	8 188	(45.7%)	29	(3.9%)	36	(24.2%)
Embolic materials	*n* = 7 850		*n* = 28		*n* = 37	
Lipiodol	1 621	(20.6%)	8	(28.6%)	16	(43.2%)
Gelatin sponge	205	(2.6%)	1	(3.6%)	0	(0.0%)
Lipiodol + gelatin sponge	5 936	(75.6%)	18	(64.3%)	21	(56.8%)
Others	88	(1.1%)	1	(3.6%)	0	(0.0%)
Extent of embolization	*n* = 7 157		*n* = 26		*n* = 34	
Less than one segment	2 578	(36.0%)	8	(30.8%)	6	(17.6%)
One segment to one lobe	2 896	(40.5%)	8	(30.8%)	16	(47.1%)
More than one lobe	1 252	(17.5%)	4	(15.4%)	7	(20.6%)
Whole liver	431	(6.0%)	6	(23.1%)	5	(14.7%)
Efficacy evaluation at 6 months	*n* = 5 448		*n* = 13		*n* = 24	
CR	2 208	(40.5%)	4	(30.8%)	3	(12.5%)
PR	1 502	(27.6%)	1	(7.7%)	5	(20.8%)
SD	632	(11.6%)	3	(23.1%)	6	(25.0%)
PD	1 106	(20.3%)	5	(38.5%)	10	(41.7%)

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.

LCSGJ 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).

Changes in the cumulative survival rates of HCC patients

The cumulative survival rates of newly-registered HCC patients in the 5th to 18th follow-up surveys (1978–2005) whose final prognosis was defined as survival or death (excluding cases of unknown outcome) divided into three groups (1978–1985, 1986–1995 and 1996–2005) were also calculated (Fig. 1). The 3- and 5-year cumulative survival rates were 15.7% and 9.5% in patients between 1978 and 1985 ($n = 7852$), 42.1% and 26.8% between 1986 and 1995 ($n = 51\,719$), and 56.6% and 39.3% between 1996 and 2005 ($n = 88\,590$), respectively.

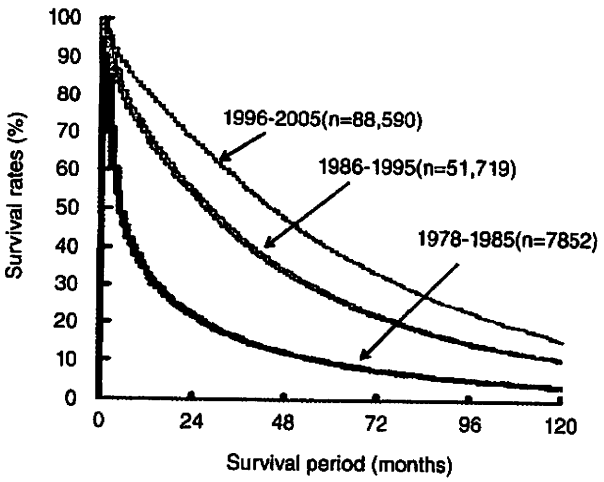

Figure 1 Cumulative survival rates of newly-registered patients in the 5th to 18th follow-up surveys (1978–2005) divided into three groups (1978–1985, 1986–1995 and 1996–2005) are shown. The 3- and 5-year cumulative survival rates were 15.7%, 9.5% in patients between 1978 and 1985 ($n = 7852$), 42.1% and 26.8% between 1986 and 1995 ($n = 51\,719$), and 56.6% and 39.3% between 1996 and 2005 ($n = 88\,590$), respectively.

Table 10 Microscopic pathological findings of surgical or biopsy specimens

	HCC		ICC		Combined	
Capsule formation	*n* = 5221		*n* = 406		*n* = 84	
Fc⁻	1293	(24.8%)	386	(95.1%)	54	(64.3%)
Fc⁺	3928	(75.2%)	20	(4.9%)	30	(35.7%)
Capsule infiltration	*n* = 3850		*n* = 16		*n* = 30	
Fc-inf⁻	1264	(32.8%)	8	(50.0%)	8	(26.7%)
Fc-inf⁺	2586	(67.2%)	8	(50.0%)	22	(73.3%)
Septum formation	*n* = 4983		*n* = 372		*n* = 83	
Sf⁻	1930	(38.7%)	348	(93.5%)	41	(49.4%)
Sf⁺	3053	(61.3%)	24	(6.5%)	42	(50.6%)
Serosal invasion	*n* = 4959		*n* = 409		*n* = 82	
S0	4267	(86.0%)	267	(65.3%)	61	(74.4%)
S1	537	(10.8%)	96	(23.5%)	15	(18.3%)
S2	84	(1.7%)	44	(10.8%)	5	(6.1%)
S3	71	(1.4%)	2	(0.5%)	1	(1.2%)
Lymph node metastasis	*n* = 3984		*n* = 427		*n* = 70	
Absent	3938	(98.8%)	257	(60.2%)	57	(81.4%)
Present	46	(1.2%)	170	(39.8%)	13	(18.6%)
Portal vein invasion	*n* = 5368		*n* = 430		*n* = 87	
vp0	3971	(74.0%)	223	(51.9%)	41	(47.1%)
Vp1	1019	(19.0%)	137	(31.9%)	33	(37.9%)
Vp2	167	(3.1%)	37	(8.6%)	6	(6.9%)
Vp3	138	(2.6%)	31	(7.2%)	7	(8.0%)
Vp4	73	(1.4%)	2	(0.5%)	0	(0.0%)
Hepatic vein invasion	*n* = 5320		*n* = 423		*n* = 84	
Vv0	4714	(88.6%)	304	(71.9%)	61	(72.6%)
Vv1	499	(9.4%)	85	(20.1%)	23	(27.4%)
Vv2	77	(1.4%)	24	(5.7%)	0	(0.0%)
Vv3	30	(0.6%)	10	(2.4%)	0	(0.0%)
Hepatic arterial invasion	*n* = 5160		*n* = 402		*n* = 82	
Va0	5103	(98.9%)	377	(93.8%)	79	(96.3%)
Va1	54	(1.0%)	18	(4.5%)	2	(2.4%)
Va2	2	(0.0%)	3	(0.7%)	1	(1.2%)
Va3	1	(0.0%)	4	(1.0%)	0	(0.0%)
Bile duct invasion	*n* = 5279		*n* = 403		*n* = 87	
B0	5095	(96.5%)	184	(45.7%)	66	(75.9%)
B1	108	(2.0%)	91	(22.6%)	15	(17.2%)
B2	37	(0.7%)	50	(12.4%)	3	(3.4%)
B3	21	(0.4%)	61	(15.1%)	1	(1.1%)
B4	18	(0.3%)	17	(4.2%)	2	(2.3%)
Intrahepatic metastasis	*n* = 5206		*n* = 430		*n* = 86	
Im0	4147	(79.7%)	322	(74.9%)	52	(60.5%)
Ims	238	(4.6%)	17	(4.0%)	5	(5.8%)
Im1	384	(7.4%)	39	(9.1%)	11	(12.8%)
Im2	299	(5.7%)	34	(7.9%)	10	(11.6%)
Im3	138	(2.7%)	18	(4.2%)	8	(9.3%)
Surgical margin	*n* = 5104		*n* = 434		*n* = 84	
Presence of cancer invasion	408	(8.1%)	80	(18.4%)	13	(15.5%)
Absence of cancer invasion	4696	(91.9%)	354	(81.6%)	71	(84.5%)
Non-cancerous portion	*n* = 5395		*n* = 414		*n* = 84	
Normal liver	349	(6.5%)	269	(65.0%)	9	(10.7%)
Chronic hepatitis or liver fibrosis	2587	(48.0%)	101	(24.4%)	46	(54.8%)
Liver cirrhosis	2459	(45.6%)	44	(10.6%)	29	(34.5%)
Liver fibrosis	*n* = 3153		*n* = 169		*n* = 49	
F0 (normal)	184	(5.8%)	82	(48.5%)	5	(10.2%)
F1	429	(13.6%)	39	(23.1%)	3	(6.1%)
F2	532	(16.9%)	14	(8.3%)	12	(24.5%)
F3	578	(18.3%)	13	(7.7%)	12	(24.5%)
F4 (liver cirrhosis)	1430	(45.4%)	21	(12.4%)	17	(34.7%)

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.

Table 11 Cumulative survival rates (%) of HCC patients treated with hepatic resection (1994–2005)

		n	Year									
			1	2	3	4	5	6	7	8	9	10
All cases		25 066	88.2%	78.4%	69.5%	61.7%	54.2%	48.1%	42.0%	36.9%	32.5%	29.0%
Tumor size (cm)	≤2	4 363	95.8%	91.1%	85.4%	78.2%	69.4%	61.7%	53.4%	46.5%	40.5%	35.5%
	2–5	12 801	91.9%	82.9%	73.2%	65.0%	56.8%	50.2%	43.9%	38.8%	34.2%	30.6%
	5–10	4 802	82.3%	68.7%	58.5%	50.2%	44.0%	39.1%	34.0%	29.8%	26.0%	23.6%
	>10	2 044	66.5%	50.6%	42.5%	36.7%	32.1%	29.5%	25.9%	22.6%	20.3%	18.5%
Tumor number	1	17 531	91.0%	82.9%	74.8%	67.7%	60.2%	54.0%	47.5%	42.1%	37.5%	33.2%
	2	3 692	87.3%	75.3%	64.8%	55.9%	48.0%	40.3%	34.8%	28.5%	24.6%	22.7%
	≥3	3 010	75.7%	59.6%	48.1%	38.4%	30.6%	26.3%	22.0%	19.3%	15.3%	13.7%
Portal vein invasion	Vp0	20 195	92.2%	83.7%	74.9%	67.0%	59.0%	52.4%	45.5%	40.1%	35.3%	31.3%
	Vp1	1 978	79.3%	64.9%	54.2%	45.7%	39.1%	34.3%	31.9%	28.1%	24.2%	22.9%
	Vp2	820	61.0%	45.4%	33.6%	27.6%	23.3%	22.8%	20.6%	17.0%	16.0%	16.0%
	Vp3 or Vp4	1 021	52.1%	33.6%	26.4%	22.4%	18.3%	16.6%	14.8%	13.1%	10.5%	8.4%
Non-cancerous portion	Normal liver	1 801	86.2%	76.2%	68.9%	63.6%	59.1%	55.7%	51.1%	46.9%	43.4%	37.6%
	Chronic hepatitis/ liver fibrosis	9 581	90.4%	81.5%	73.4%	67.0%	60.8%	55.8%	50.2%	45.6%	41.7%	39.0%
	Liver cirrhosis	10 401	87.3%	77.0%	67.3%	58.3%	49.1%	42.1%	35.1%	30.2%	25.4%	22.1%
Liver damage classification by LCSGJ	A	16 963	90.0%	81.5%	73.3%	66.0%	59.0%	52.9%	46.3%	41.5%	36.7%	33.2%
	B	6 478	85.6%	73.8%	63.6%	54.8%	45.3%	39.2%	33.8%	28.6%	25.1%	21.3%
	C	454	73.4%	56.0%	44.9%	39.8%	35.0%	32.1%	30.9%	22.9%	21.7%	21.7%
TNM Stage by LCSGJ	I	2 846	96.9%	93.6%	88.7%	81.8%	73.0%	66.1%	57.6%	51.3%	45.4%	38.1%
	II	12 458	92.7%	84.1%	75.3%	67.4%	59.7%	53.4%	46.1%	40.4%	35.9%	32.5%
	III	4 223	82.2%	68.1%	56.1%	47.2%	39.5%	34.1%	30.6%	26.9%	23.6%	21.4%
	IV A	1 398	60.3%	42.4%	31.9%	25.9%	21.4%	19.7%	17.8%	15.3%	12.5%	11.9%
	IV B	253	53.1%	33.6%	24.2%	21.7%	16.5%	14.1%	14.1%	14.1%	14.1%	14.1%

HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan; TNM, Tumor–Node–Metastasis; Vp0–V94, described in Tables 5 and 7.

Table 12 Cumulative survival rates (%) of HCC patients treated with local ablation therapy (1994–2005)

		n	Year									
			1	2	3	4	5	6	7	8	9	10
All cases		27 150	92.8%	81.4%	68.6%	56.5%	45.6%	37.1%	29.8%	23.9%	19.5%	15.7%
Liver damage classification by LCSGJ	A	14 370	95.5%	87.2%	76.3%	65.5%	54.2%	44.4%	36.6%	30.3%	25.0%	19.9%
	B	9 751	92.4%	78.5%	63.4%	50.0%	38.7%	31.0%	24.2%	18.0%	14.7%	12.4%
	C	1 757	77.2%	56.2%	41.2%	28.1%	21.6%	16.9%	12.3%	9.4%	7.1%	5.4%
Tumor number	1	16 883	94.2%	84.5%	73.2%	62.3%	51.9%	42.8%	35.1%	28.8%	23.8%	19.4%
	2	5 638	92.4%	79.8%	65.9%	51.8%	39.6%	32.8%	24.4%	18.7%	15.5%	11.7%
	3	2 307	91.6%	76.8%	60.9%	46.3%	35.0%	25.8%	20.6%	15.7%	11.5%	10.9%
	4	812	88.5%	72.6%	55.3%	41.1%	30.8%	21.4%	17.7%	13.1%	6.9%	3.4%
	≥5	1 079	82.9%	62.1%	44.0%	33.0%	23.4%	20.4%	13.9%	12.2%	9.1%	7.2%
Tumor size (cm)	≤1	1 792	96.6%	90.6%	81.6%	72.1%	60.1%	49.8%	44.6%	38.4%	31.1%	25.7%
	1–2	12 253	95.2%	86.4%	75.1%	63.7%	52.7%	43.0%	34.0%	27.3%	22.0%	18.1%
	2–3	7 714	93.0%	79.7%	64.8%	51.9%	40.0%	32.1%	25.5%	20.1%	16.4%	13.4%
	3–5	3 257	88.2%	71.0%	55.7%	41.8%	32.4%	26.1%	20.8%	17.6%	15.3%	8.7%
	>5	809	76.9%	58.9%	43.6%	33.7%	25.5%	21.0%	15.6%	10.6%	9.1%	-

HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan.

Newly-registered patients were increasing and their survival rates were improving.

DISCUSSION

PRIMARY LIVER CANCER is the fourth leading cause of cancer death in Japanese people, following tracheal-bronchial-lung, gastric and colorectal cancers; more than 34 000 people die annually due to liver cancer. In the 18th Nationwide Follow-Up Survey of Primary Liver Cancer, approximately 30% of patients with primary liver cancer were newly registered. Compared with the 17th follow-up survey,[11] this follow-up survey in HCC indicated an increase in elder patients and women, a decrease in patients positive for hepatitis B surface antigen and hepatitis C virus antibody, and a decrease in tumor size at the clinical diagnosis. In the local ablation therapy, ratio of radio frequency ablation therapy was increasing. Advance in diagnostic and therapeutic modalities were considered to have contributed to an improvement in survival of patients with HCC between 1978 and 2005.

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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Table 13 Cumulative survival rates (%) of HCC patients treated with transcatheter arterial embolization (1994–2005)

		n	Year									
			1	2	3	4	5	6	7	8	9	10
All cases		3955	51.7%	35.1%	28.5%	23.7%	20.3%	18.1%	16.7%	14.5%	12.5%	12.5%
Liver damage	A	1658	72.0%	53.1%	43.9%	36.2%	31.3%	27.6%	26.1%	23.7%	21.2%	21.2%
classification	B	2294	36.3%	21.6%	17.1%	14.4%	12.2%	11.0%	9.6%	5.8%	0.0%	-
by LCSGJ	C	137	88.3%	81.3%	75.2%	67.9%	62.8%	59.8%	59.8%	54.8%	54.8%	54.8%
Tumor number	1	738	77.8%	58.9%	49.4%	40.1%	32.3%	26.5%	25.3%	23.6%	18.2%	18.2%
	2	547	63.7%	43.4%	33.4%	29.0%	26.7%	24.9%	23.6%	20.4%	18.1%	18.1%
	3	129	55.3%	32.8%	28.6%	22.2%	19.0%	14.2%	14.2%	14.2%	14.2%	14.2%
	4	1272	76.3%	58.8%	49.4%	41.2%	36.3%	32.2%	30.8%	28.4%	24.8%	24.8%
	≥5	102	75.7%	49.4%	36.5%	31.3%	27.8%	27.8%	22.2%	22.2%	22.2%	22.2%

HCC, hepatocellular carcinoma; LCSGJ, Liver Cancer Study Group of Japan.

Table 14 Cumulative survival rates (%) of ICC patients (1994–2005)

			n	Year									
				1	2	3	4	5	6	7	8	9	10
All cases			3955	51.7%	35.1%	28.5%	23.7%	20.3%	18.1%	16.7%	14.5%	12.5%	12.5%
Hepatic resection		Performed	1658	72.0%	53.1%	43.9%	36.2%	31.3%	27.6%	26.1%	23.7%	21.2%	21.2%
		Not performed	2294	36.3%	21.6%	17.1%	14.4%	12.2%	11.0%	9.6%	5.8%	0.0%	-
Cases of hepatic resection	Tumor size (cm)	≤2	137	88.3%	81.3%	75.2%	67.9%	62.8%	59.8%	59.8%	54.8%	54.8%	54.8%
		2–5	738	77.8%	58.9%	49.4%	40.1%	32.3%	26.5%	25.3%	23.6%	18.2%	18.2%
		5–10	547	63.7%	43.4%	33.4%	29.0%	26.7%	24.9%	23.6%	20.4%	18.1%	18.1%
		>10	129	55.3%	32.8%	28.6%	22.2%	19.0%	14.2%	14.2%	14.2%	14.2%	14.2%
	Tumor number	1	1272	76.3%	58.8%	49.4%	41.2%	36.3%	32.2%	30.8%	28.4%	24.8%	24.8%
		2	102	75.7%	49.4%	36.5%	31.3%	27.8%	27.8%	22.2%	22.2%	22.2%	22.2%
		≥3	186	42.2%	19.5%	16.6%	12.3%	6.3%	4.2%	4.2%	2.1%	2.1%	2.1%
	Residual tumor	Absent	784	77.7%	59.3%	50.6%	43.1%	37.6%	35.6%	33.6%	30.2%	26.5%	26.5%
		Present	608	64.4%	41.4%	31.3%	22.1%	20.6%	20.6%	10.3%	10.3%	10.3%	-
	Lymph node metastasis	Absent	1046	80.6%	64.6%	54.5%	45.3%	39.9%	36.2%	33.8%	30.2%	28.8%	28.8%
		Present	497	55.9%	29.8%	22.8%	17.9%	15.3%	10.7%	10.7%	10.7%	8.0%	8.0%

ICC, intrahepatic cholangiocarcinoma.

Table 15 Cumulative survival rates (%) of combined HCC and ICC (1994–2005)

		n	Year									
			1	2	3	4	5	6	7	8	9	10
All cases		653	58.6%	40.5%	29.7%	23.4%	19.8%	17.8%	15.7%	14.5%	12.7%	12.7%
Hepatic resection	Performed	354	70.7%	50.5%	40.7%	31.0%	28.2%	26.1%	21.9%	20.0%	20.0%	20.0%
	Not performed	299	44.2%	28.8%	16.9%	14.2%	10.6%	8.9%	8.9%	8.9%	0.0%	-

HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma.

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EDITORIAL

Radiofrequency ablation of hepatocellular carcinoma: Current status

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Abstract

Ablation therapy is one of the best curative treatment options for malignant liver tumors, and can be an alternative to resection. Radiofrequency ablation (RFA) of primary and secondary liver cancers can be performed safely using percutaneous, laparoscopic, or open surgical techniques, and RFA has markedly changed the treatment strategy for small hepatocellular carcinoma (HCC). Percutaneous RFA can achieve the same overall and disease-free survival as surgical resection for patients with small HCC. The use of a laparoscopic or open approach allows repeated placements of RFA electrodes at multiple sites to ablate larger tumors. RFA combined with transcatheter arterial chemoembolization will make the treatment of larger tumors a clinically viable treatment alternative. However, an accurate evaluation of treatment response is very important to secure successful RFA therapy. Since a sufficient safety margin (at least 0.5 cm) can prevent local tumor recurrences, an accurate evaluation of treatment response is very important to secure successful RFA therapy. To minimize complications of RFA, clinicians should be familiar with the imaging features of each type of complication. Appropriate management of complications is essential for successful RFA treatment.

INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most common solid cancers worldwide, with an estimated annual incidence of at least one million new patients[1-4]. Furthermore, the liver is second only to lymph nodes as a common site of metastasis from other solid cancers[5-8]. Surgery is the only curative option for HCC; however, the majority of primary liver cancers are not suitable for curative resection at the time of diagnosis. Difficulties in surgical resection may be related to size, site, and number of tumors, vascular and extrahepatic involvement as well as the general condition and liver function of the patient[9-12]. There is, therefore, a need to develop a simple and effective technique for the treatment of unresectable tumors within the liver. In recent years, local ablative techniques [percutaneous ethanol injection (PEI), microwave coagulation therapy (MCT) and radiofrequency ablation (RFA)] have emerged in clinical practice to expand the pool of patients considered for liver-directed therapies[13-16].

Localized application of thermal energy induces tumor cell destruction. When tumor cells are heated above

45-50℃, intracellular proteins are denatured and cell membranes are destroyed through the dissolution and melting of lipid bilayers[17]. RFA is a localized thermal treatment technique designed to produce tumor destruction by heating tumor tissue to temperatures that exceed 60℃[17]. The alternating current of radiofrequency waves passing down from an uninsulated electrode tip into the surrounding tissues generates changes in the direction of ions and creates ionic agitation and frictional heating. This tissue heating then drives extracellular and intracellular water out of the tissue, resulting in tissue destruction by coagulative necrosis[18,19]. Currently, RFA has gained popularity based on the ease of use, safety, reasonable cost and applicability to minimally invasive techniques. This paper reviews the current status of RFA for HCC.

EQUIPMENT

RFA electrodes and generators

Three types of RF electrodes are currently available commercially: two brands of retractable needle electrodes (model 70 and model 90 Starburst XL needles, RITA Medical Systems, Mountain View, CA, USA; LeVeen needle electrode, Boston Scientific, Boston, MA, USA) and an internally cooled electrode (Cool-Tip RF electrode; Radionics, Burlington, MA, USA)[15].

The needle electrodes of RITA consist of a 14-gauge insulated outer needle that houses nine retractable curved electrodes of various lengths. When the electrodes are extended, the device assumes the approximate configuration of a Christmas tree. Nine of the electrodes are hollow and contain thermocouples in their tips in order to measure the temperature of adjacent tissue. The alternating electric current generator comes in a 250-W model at 460 kHz (Model 1500X RF Generator, RITA Medical Systems). The ablation algorithm is based on temperature at the tips of the electrodes. After the ablation cycle is completed, a temperature reading from the extended electrodes in excess of 50℃ at 1 min is considered to indicate satisfactory ablation.

Another RFA device (LeVeen Needle Electrode; Radiotherapeutics) has retractable curved electrodes and an insulated 17-gauge outer needle that houses 10 solid retractable curved electrodes that, when deployed, assume the configuration of an umbrella. The electrodes are manufactured in different lengths (2- to 4.0-cm umbrella diameter). The alternating electric current generator is 200 W operated at 480 kHz (RF 3000; Boston Scientific). The ablation algorithm is based on tissue impedance, and ablation is considered successful if the device impedes out.

The third RFA device (Cool-Tip radiofrequency electrode; Radionics) has an insulated hollow 17-gauge needle with an exposed needle tip of variable length (2- or 3-cm). The tip of the needle contains a thermocouple to record the temperature of adjacent tissue. The shaft of the needle has two internal channels to allow the needle to be perfused with chilled water. In an attempt to further increase the size of the ablation area, the manufacturer placed three of the cooled needles in a parallel triangular cluster with a common hub. The generator has a peak power output of 200 W and is operated at 480 kHz (CC-1; Radionics). The ablation algorithm is based on tissue impedance, and ablation is considered successful if the device impedes out. As a result, successful ablations usually increase the temperature of the ablated tissue to above 60℃.

Selection criteria of patients with HCC

In patients with HCC, exclusion criteria should include evidence of extrahepatic metastases and/or lobar and local portal venous thrombosis or uncontrolled liver disease decompensation, patients with clotting impairment, renal failure, or Child-Pugh class C cirrhosis. In the EASL Consensus Conference criteria[20], all patients that had tumor nodules with a maximum diameter of 3 cm and not more than three in number with contraindications for surgery are included.

Assessment of technical effectiveness

The technical effectiveness of ablation is commonly assessed by findings on contrast-enhanced computed tomography (CT) or magnetic resonance imaging. A tumor was considered to have been successfully ablated when there were no longer any enhanced regions within the entire tumor during the arterial phase and at least a 0.5 cm margin of apparently normal hepatic tissue surrounding the tumor during the portal phase (Figure 1)[21-23]. This safety margin for RFA therapy is necessary from the perspective of partial volume effect. Failure to establish a sufficient ablative safety margin was shown to be an independently significant risk factor for local tumor progression on multivariate analysis[24]. Part of the tumor was diagnosed as remaining viable when images of the ablated area showed nodular peripheral enhancement[25].

CLINICAL OUTCOMES

Percutaneous approach

A randomized control trial (RCT) has shown that RFA achieved survival rates similar to those achieved following resection[26] (Table 1). Chen *et al*[26] conducted a RCT on 180 patients with a solitary HCC $\leq$ 5 cm indicated to receive either percutaneous RFA or surgical resection. This study showed percutaneous RFA achieved the same overall and disease-free survival rates as surgical resection for patients with small solitary HCC. The 1- and 4-year overall survival rates after percutaneous RFA and surgery were 95.8%, 67.9% and 93.3%, 64.0%, respectively. The corresponding disease-free survival rates were 85.9%, 46.4% and 86.6%, 51.6%, respectively. However, in cases of primary liver cancer in which local curative therapy was achieved by securing a safety margin, the 4-year survival rate was relatively high, at 66%-82% (results in Japan)[27,28]. Percutaneous RFA has an advantage over liver resection in providing a better short-term postoperative result because local ablative therapy is a less invasive procedure. Although

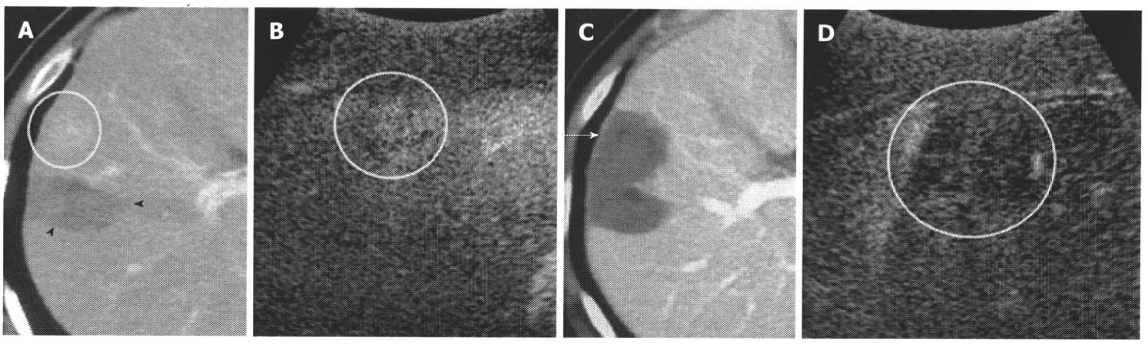

Figure 1 A 61-year-old man with 1.5-cm recurrent hepatocellular carcinoma after ablation therapy in segment 5 of the liver. A: Early-phase dynamic computed tomography (CT) scan shows recurrent tumor (circle). Non-enhanced area (arrowheads) was previously treated by radiofrequency ablation (RFA); B: Contrast harmonic ultrasound (US) using Levovist shows enhancement of viable focus of a hepatocellular carcinoma (HCC) nodule (circle); C: Portal-phase dynamic CT scan, which was obtained 3 d after RFA shows that the tumor was not enhanced, indicating complete necrosis of the lesion (arrow); D: Contrast harmonic US, which was obtained 3 d after ablation shows non-enhanced area (circle).

Table 1 Studies comparing radiofrequency ablation *vs* hepatic resection for hepatocellular carcinoma

Author, yr	Study type	RFA/resection	RFA/resection (mean tumor size, cm)	RFA *vs* resection (%) (overall survival)	*P*
Chen, 2006	RCT	90/90	-/-	65.9 *vs* 64.0 (4-yr)	NS
Takayama, 2009	Retrospective	1315/1235	1.6/1.8	95 *vs* 94 (2-yr)	0.28
Ueno, 2009	Retrospective	123/110	2.0/2.7	63 *vs* 80 (5-yr)	0.06
Hiraoka, 2008	Retrospective	105/59	-/-	59.3 *vs* 59.4 (5-yr)	NS
Abu-Hilal, 2008	Retrospective	34/34	3.0/3.8	57 *vs* 56 (5-yr)	0.3
Gnglielmi, 2008	Retrospective	23/33	-/-	45 *vs* 55 (5-yr)	0.7
Wakai, 2006	Retrospective	64/85	-/-	30 *vs* 53 (10-yr)	0.012
Ogihara, 2005	Retrospective	40/47	4.6/7.4	39 *vs* 31 (5-yr)	0.79
Montorsi, 2005	Prospective	58/40	-/-	30 *vs* 53 (4-yr)	0.018
Vivarelli, 2004	Retrospective	79/79	-/-	33 *vs* 65 (3-yr)	0.002

RFA: Radiofrequency ablation; RCT: Randomized control trial; NS: Not significant.

promising, these data need to be confirmed in larger RCTs before local ablative therapy can replace partial hepatectomy in the treatment of good surgical candidates.

RFA has also been investigated for treating patients with large or multifocal tumors. However, the size and number of tumors are important factors determining the local recurrence rate after RFA[29]. Apart from the larger tumor volume, large liver cancers more frequently have irregular borders and satellite lesions. Therefore, precise tailoring of the size and shape of the thermal lesion is important in RFA for large liver cancers. A number of precisely calculated overlapping coagulation zones are necessary to treat large liver cancers. To increase the size of the coagulation zone in RFA, investigators tried using vascular occlusion during RFA[30,31]. Temporary interruption of hepatic blood flow using vascular occlusion techniques (e.g. balloon catheter occlusion of the hepatic artery, transcatheter arterial embolization (TAE), or transcatheter arterial chemoembolization (TACE) has been shown to increase the efficacy of interstitial thermotherapy due to a significant increase in lesion volume. Vascular occlusion causes a reduction of heat dispersion, thus increasing the range of therapeutic thermal coagulation. Peng *et al*[32] reported a series of 120 patients with HCC, and the 1-, 2-, 3-, and 5-year overall survival rates for the TACE-RFA and RFA groups were 93%, 83%, 75%, 50%, and 89%, 76%, 64%, 42%, respectively ($P = 0.045$).

Ultrasound (US)-guided procedures are necessary but have limited use when the tumor is located under the diaphragm. However, saline solution injection into the pleural cavity can separate the lung and liver on B-mode US, i.e. artificial pleural effusion acts as an acoustic media. There are reports on the feasibility and safety of RFA with artificially induced pleural effusion for HCC located in the right subphrenic region[33-36]. In a series of 24 patients with HCC located in the hepatic dome, 200-1100 mL of 5% glucose solution was infused intrathoracically to separate the lung and liver, thus, complete tumor necrosis in a single session was achieved in 96.4% of patients[36].

Multiple RFA sessions for locally progressive HCCs were previously required because it is frequently difficult to distinguish viable tumors from necrotic tissue on B-mode US[37]. However, contrast-enhanced harmonic US imaging is able to evaluate small hypervascular HCCs even when B-mode US cannot adequately characterize the tumors[38-43]. In particular, contrast harmonic US has been improved by the development of second-generation contrast agents such as sulfur hexafluoride microbubbles (So-

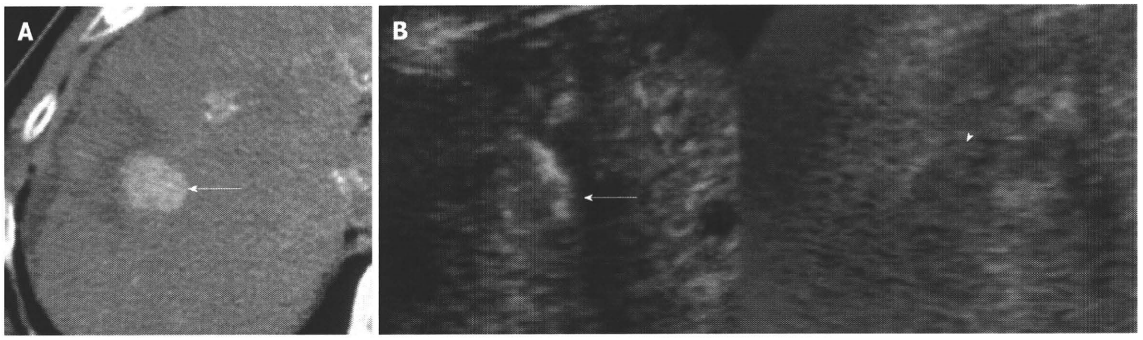

Figure 2 A 71-year-old man with 2.0 cm local tumor progression of hepatocellular carcinoma after radiofrequency ablation therapy in segment 8 of the liver. A: Early-phase dynamic computed tomography (CT) scan shows outgrowth pattern of locally progressive hepatocellular carcinoma (HCC) (arrow). The lesion borders an unenhanced area, which was previously treated; B: Left: Contrast harmonic Doppler ultrasound (US) using Levovist shows enhancement of local tumor progression of HCC (arrow). Therefore, an enhanced lesion can be identified as a target for the insertion of a single RF electrode; Right: B-mode US shows a HCC nodule demonstrated as a low echoic lesion with an unclear border (arrowhead).

noVue; Bracco SpA, Milan, Italy), perflutren lipid microbubbles (Definity; Bristol- Myers Squibb, North Billerica, MA, USA), perflutren protein microbubbles (Optison; GE Healthcare, Buckinghamshire, UK), and perfluorocarbon microbubbles (Sonazoid; Daiichi-Sankyo, Tokyo, Japan). These microbubbles provide stable nonlinear oscillation in a low power acoustic field due to the hard shell of these bubbles, producing great detail in the harmonic signals in real-time[44-49]. It has been reported that contrast harmonic sonography-guided RFA is an efficient approach for guiding further ablation of hepatic malignancies that are not clearly demarcated by B-mode US (Figure 2)[50-54].

Laparoscopic/open surgical approach

The use of a laparoscopic or open approach allows repeated placements of RFA electrodes at multiple sites to ablate larger tumors. The laparoscopic approach appears to be the safest and most effective method for small tumors on the liver surface, and offers the advantages of laparoscopic US, which provides better resolution of the number and location of liver tumors[55,56]. Moreover, a hand-assisted technique can be applied safely and effectively to laparoscopic liver surgery[57-59]. An intraoperative US probe is inserted into the peritoneal cavity together with the surgeon's hand through a hand-access device. An RF electrode can be subcostally or intercostally advanced into a liver tumor under direct guidance by intraoperative US. Therefore, a hand-assisted laparoscopic US-guided method has advantages for both laparoscopic and open surgical approaches. The postoperative recovery of patients was shorter compared with that after an open surgical approach. Ishiko *et al*[57] reported that the surgical procedures consisted of 5 RFA to tumors in the caudate lobe with hand-assisted laparoscopic surgery (HALS), and a postoperative CT scan demonstrated sufficient ablation in all patients and there was no surgical mortality. The HALS approach has several advantages; it facilitates and expedites the procedure, reduces the stress factor on the surgeon, greatly improves exposure, and facilitates immediate and efficient control of bleeding vessels with the internal hand. The hand-access device, which essentially consists of a cuff with a spiral inflatable valve, enables withdrawal and reinsertion of the hand without loss of pneumoperitoneum during the procedure. However, the local treatment failure rate of the laparoscopic approach was higher in patients with HCC nodules situated deep within the liver and measuring 4 cm or more in diameter[60]. Great difficulty can be encountered during treatment of lesions located close to the gallbladder or in contact with the diaphragm.

Although more invasive, open RFA can be performed more easily and the puncture course of the RF needle can be more widely selected than that during the laparoscopic approach. It has been reported that patients undergoing radical open RFA demonstrated few ablation site recurrences even though the nodules measured more than 4 cm in diameter and/or there were more than three nodules[61,62]. Open RFA can be indicated for patients who are considered suitable for open surgery with large, numerous, or deeply located tumors that cannot be accurately accessed by a laparoscopic approach. Furthermore, when patients have synchronous liver metastases, open surgical RFA can be performed in conjunction with resection of the primary cancer.

Local controllability (local tumor progression)

The local recurrence rate after RFA for HCC ranged from 1.7% to 41%[63-70] (Table 2). As reported by Kudo[28], in a series of 141 HCC patients who underwent curative RFA therapy, local tumor progression was observed in 9 cases (local tumor progression rate, 6.3%), whereas the cumulative local tumor progression rate, calculated by the Kaplan-Meier method, was 12% at 4 years. The rate may have depended on the size of nodules treated and the skill of the surgeons. There has not been any definitive report of local recurrence of nodules measuring 2-cm or smaller, and we ourselves have not encountered any case showing such recurrence, suggesting that recurrence in such cases is exceptional. The risk of local tumor progression increases with size, but the local tumor progression rate

Table 2 Studies comparing local tumor progression rates of radiofrequency ablation for hepatocellular carcinoma

Author	Yr	*n*	Tumor size (mean, cm)	Follow-up period (mean, mo)	Local tumor progression rate (%)
Rossi *et al*[63]	1996	41	2.3	22.6	5.0
Buscarini *et al*[64]	2001	60	-	26.8	14
Choi *et al*[65]	2004	53	2.1	23	21
Lu *et al*[66]	2005	87	2.5	12.7	5.8
Shiina *et al*[67]	2005	118	-	34.8	1.7
Solmi *et al*[68]	2006	63	2.8	32.3	41
Hänsler *et al*[69]	2007	21	4.2	-	21
Waki *et al*[70]	2010	88	-	36	4.8

differs markedly depending on whether or not a circumferential 5-mm safety margin is secured. In a meta-analysis of RFA *vs* PEI in HCC, the survival rate showed a significant benefit for RFA over PEI at 1, 2, 3 and 4 years[71]. The survival advantage increased over time with Relative Risk values of: 1.28 (95% CI: 1.12-1.45) and 1.24 (95% CI: 1.05-1.48) for RFA *vs* PEI at 3- and 4-years, respectively. Likewise, RFA achieved significantly lower rates of local recurrence (RR: 0.37, 95% CI: 0.23-0.59)[71].

Complications

Complications reported following percutaneous RFA of malignant liver tumors in 2320 patients treated at 41 different hospitals in Italy indicate that the mortality rate was 0.3% with an overall complication rate of 7.1%[72,73]. The authors described major complications (2.4% incidence) including death, hemorrhage, RFA needle-track seeding, RFA lesion abscess, perforation of gastrointestinal viscus, liver failure, biloma, biliary stricture, portal vein thrombosis, and hemothorax or pneumothorax requiring drainage, and minor complications (4.7% incidence) including pain, fever, and asymptomatic pleural effusion. Another recent review indicated that complication rates for percutaneous, laparoscopic, and open RFA of hepatic tumors in 3670 patients were 7.2%, 9.5%, and 9.9%, respectively[74]. Complications directly related to the liver included bleeding (1.6%), intrahepatic abscess (1.1%), biliary or hepatic vascular injury (1.7%), and liver failure (0.8%). Complications that arose in less than 1% of hepatic tumor RFA patients included pulmonary problems (pneumothorax, hydrothorax, pleural effusion), grounding pad skin burn, myoglobinemia or myoglobinuria, renal failure, coagulopathy, tumor seeding of the needle track, excessive hormone release from treated neuroendocrine tumors, cardiac problems (myocardial infarction, arrhythmia), and injury to the diaphragm or adjacent viscera. Although Llovet *et al*[75] reported that dissemination along the puncture route was observed in 12.5% of their patients, only a few such cases have been reported in Japan, and dissemination may not occur at such a high frequency. This complication was almost absent in many reports from Japan[28]. Overall, the frequency of major complications of percutaneous RFA was 0.6%-8.9%, which was higher than that of PEI, but generally lower than that of MCT[28].

Some investigators have suggested that tumor location is closely related to the risk of major complications. Central tumors close to the hepatic hilum were reported to be unsuitable for percutaneous RFA because of the risk of injuring adjacent bile ducts[15]. It was also suggested that RFA for nodules adjacent to large vessels might often result in incomplete necrosis because of a heat sink effect. In addition, peripheral tumors adjacent to extrahepatic organs were also suggested to be unsuitable because of the risk of heat injuries, such as intestinal perforation and pleural effusion[72,76]. Thus, there may be difficulty with RFA of nodules in such high-risk locations, possibly resulting in complications or preventing adequate treatment. However, Teratani *et al*[77] reported that there was no difference in early complication rates according to tumor location. The effort to achieve thorough ablation increased the total number of electrode insertions, and this may have led to an increase in complications.

To minimize complications of RFA for malignant liver tumors, knowledge of risk factors and prevention methods is required. In addition, because early and accurate diagnosis is necessary for the proper management of complications, not only radiologists but also hepatologists and surgeons should be familiar with the imaging features of each type of complication. Appropriate management of complications is essential for successful treatment with RFA.

CONCLUSION

RFA can be performed safely using percutaneous, laparoscopic, or open surgical techniques, and has markedly changed the treatment strategy for small HCC. RFA combined with TACE will likely make the treatment of larger tumors a clinically viable treatment alternative. Moreover, an accurate evaluation of treatment response is very important to secure successful RFA therapy. A sufficient safety margin can prevent local tumor recurrences. However, surgery is still the recommended treatment modality for patients with both primary hepatic malignancies. For inoperable lesions, RFA will likely play a significant role with a potential curative intent. Currently, the important clinical issue is that follow-up studies need to be performed for the early detection and treatment of recurrence, either locally or at different sites after RFA.

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REVIEW

Hepatic encephalopathy as a complication of liver cirrhosis: An Asian perspective

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Key words
Asian cohort, drug therapy, hepatic encephalopathy, incidence, liver cirrhosis, liver transplantation, pathophysiology, treatment, response rate, survival rate.

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Abstract

Hepatic encephalopathy is one of the most important clinical manifestations in decompensated liver cirrhosis. Accepted concepts regarding the pathophysiology of hepatic encephalopathy are that the endogenous neurotoxic substances, including ammonia: (i) escape from catabolism by the liver due both to the impaired function of the cirrhotic liver and also to the presence of portal systemic shunting; (ii) circulate at elevated concentrations in the systemic blood flow; (iii) reach the brain through the blood-brain barrier; and (iv) impair cerebral function leading to disturbances of consciousness. The majority of these toxic substances are produced in the intestine by the bacterial flora, and are absorbed into the portal venous flow. The epidemiology of liver cirrhosis depends particularly on its etiology, and shows a marked geographic difference worldwide between Western, and Asian countries. Hepatic encephalopathy developed at an annual rate of 8% in cirrhotics in Far Eastern studies. In Eastern and Far East countries, therapeutic options are similar to those in the western hemisphere, but pronounced application of dietary restriction, antimicrobial agents, disaccharides, shunt obliteration and branched chain amino acids is noted. In spite of improved therapeutic options for encephalopathy, the long-term survival is still low. Thus, hepatic encephalopathy remains a serious complication of liver cirrhosis. Establishment of truly effective prevention modalities and broader application of liver transplantation will help rescue patients suffering from this complication of liver cirrhosis in the near future.

Introduction

Hepatic encephalopathy is one of the most important clinical manifestations in decompensated liver cirrhosis and, on this entity, much description has already been made.[1] However, the majority of this literature comes from Western countries, where the ethnicities as well as etiologies of liver cirrhosis differ largely from Eastern and Far East countries. Particularly focusing on this point of view, we attempt in this review article to elucidate an Asian perspective on clinical characteristics of hepatic encephalopathy as a complication of liver cirrhosis.

Pathophysiology

Mechanisms of the development of hepatic encephalopathy should be understood precisely in order to establish recommendations for the diagnosis and treatment of this clinical manifestation in liver cirrhosis. Although complete agreement has not yet been reached, the currently accepted concepts to explain the pathophysiology of cirrhotic encephalopathy are that: (i) the endogenous neurotoxic substances, including ammonia, escape from catabolism by the liver, due both to the impaired function of the cirrhotic liver and also to the presence of portal systemic shunt; (ii) these then circulate at elevated concentrations in the systemic blood flow; (iii) reach the brain through the blood-brain barrier; and (iv) impair cerebral function leading to altered higher functions and consciousness (Fig. 1). The majority of these toxic substances are produced in the intestine by the bacterial flora, and are absorbed into the portal venous flow.[2,3] Candidate substances include ammonia,[2,3] glutamine,[4] methionine and related monoamines, serotonin,[5] benzodiazepines,[6] and gamma-amino-butyric acid (GABA).[7] Regarding the microorganisms in the intestinal flora, anerobes seem to be particularly responsible for synthesis of such nitrogenous compounds from food origins.[8,9]

Diagnosis

In cases that are already known to have liver cirrhosis, the diagnosis of hepatic encephalopathy is relatively straight forward since the neurologic and psychiatric symptoms appear with other signs of liver failure, such as ascites and jaundice (Table 1). Otherwise, differential diagnosis includes any disease that can lead to disturbance of consciousness, including cerebrovascular disorders, central nervous infections, cardiovascular diseases and syncope,