



Figure 4. Low-magnification view of the tumor (A, hematoxylin and eosin stain) and immunohistochemical expression of hepatocyte antigen (B), vimentin (C and D) and Ki-67 (E and F). Hepatocellular carcinoma component (*), sarcoma component (**) and area of sarcoma invasive to the hepatocellular carcinoma component (black arrow) are shown (A). The hepatocellular carcinoma and sarcoma component form a clear 'mirror image' immunohistochemically. That is, hepatocyte antigen is positive in the hepatocellular carcinoma component and negative in the sarcoma component (B), whereas vimentin is positive in the sarcoma component around the area of neoplastic osteoid formation (D). The immunohistochemical expression of Ki-67 is very low (labeling index; 5%) in the hepatocellular carcinoma component (E). Immunohistochemical expression of Ki-67 in the transitional component (F, the same part of Fig. 3B). Ki-67 expression increases gradually from transitional component (*) to the sarcoma component (**).

outcome, our patient has remained free of recurrence for a prolonged period. We can speculate two probable reasons for the good outcome in this case. First, considering that the present tumor was smaller than in previously reported cases, we thought that it represented an early stage of hepatic carcinosarcoma manifested during follow-up abdominal ultrasonography for type C viral hepatitis. Second, since 93% of the metastatic lesions in previously reported patients with hepatic carcinosarcoma contained mainly sarcoma components, we thought that portal vein tumor thrombi in many of them might have contained sarcoma components. In contrast, in the present patient,

since the tumor had a concentric growth pattern, portal vein tumor thrombi were composed of only the HCC component without a sarcoma component. Moreover, although we conducted a detailed study of the tumor vessels using immunohistochemical staining for CD31 and CD34 in the region of high tumor vascularity, we were unable to detect tumor cell invasion or tumor thrombi in the tumor vessels. Therefore, the biological grade of malignancy of the tumor was probably similar to that of conventional HCC with a portal vein tumor thrombus. However, it should be noted that hepatic carcinosarcoma can metastasize and, at the site of metastasis undergo dedifferentiation into sarcoma

Table 2. Characteristics of reported cases of carcinosarcoma of the liver that met the WHO criteria on the basis of immunohistochemical staining

No.	Author	Age/ sex	HBsAg/ anti-HCV	Liver cirrhosis	Size (cm)	Carcinomatous element	Sarcomatous element	Treatment	Metastasis	Metastatic element	Outcome
1	Ooi et al. (2)	63/F	-/UN	-	15.0	HCC	Ch	CTX	Liver, Lung, LN	HCC	Dead (4mo)
2	Kubosawa et al. (3)	70/M	-/UN	+	4.0	HCC	Rh	CTX	Liver, LN, Ad	Sa	Dead (2mo)
3	Nakajima et al. (4)	74/M	-/UN	-	21.0	HCC, CCC	Lei	TAI	Liver, lung, LN	Ca + Sa	Dead (17mo)
4	Leger-Ravet et al. (5)	61/M	-/UN	+	10.0	HCC	Ch, Os	Resection, TAE	LN	Sa	Dead (9mo)
5	Fayyazi et al. (6)	46/M	UN/UN	+	10.0	HCC	Os	-	Peritoneum, Lung	Ca + Sa	Dead (7mo)
6	Ikebe et al. (7)	72/M	-/+	+	14.0	HCC	Ch	Resection	-	-	Alive (10mo)
7	Akasofu et al. (8)	52/M	+/-	+	19.0	HCC	Rh	CTX	Lung, LN, GB	Sa	Dead (3mo)
8	Aiko et al. (9)	48/M	-/-	-	16.0	HCC	Os	Resection	Liver, Peritoneum	Sa	Dead (4mo)
9	Nomura et al. (10)	84/M	-/-	-	9.0	CCC	Ch	-	Liver, LN	Ca + Sa	Dead (3mo)
10	Morise et al. (11)	54/M	-/-	+	6.0	HCC	Os	Resection	-	-	Alive (12mo)
11	Wang et al. (12)	52/F	-/-	-	15.0	CCC	Ch	Resection, CTX	-	-	Alive (UN)
12	Freeman et al. (13)	74/F	-/-	-	14.5	CCC	Lei	Resection	-	-	Alive (12mo)
13	She and Szakaes (14)	51/M	-/-	-	8.0	HCC, CCC, Endocrine	Rh, Lei, Os	-	Liver, Lung, Pancreas, Bone, LN	Ca + Sa	Dead (12days)
14	Lao et al. (15)	50/F	+/-	UN	14.0	HCC	Rh	Resection	-	-	Dead (3mo)
15	Lao et al. (15)	56/M	+/-	UN	13.0	HCC	MFH	Resection, CTX	Liver	Ca + Sa	Dead (5mo)
16	Lao et al. (15)	68/M	+/-	UN	9.0	HCC	MFH	Resection	Liver, Lung	Ca + Sa	Dead (6mo)
17	Lao et al. (15)	55/M	+/-	UN	6.0	HCC	Rh	Resection	LN	Ca + Sa	Dead (6mo)
18	Lao et al. (15)	40/M	+/-	UN	9.0	HCC	Fi	Resection, CTX, PEI	Liver	Ca + Sa	Alive (21mo)
19	Kwon et al. (16)	46/F	-/-	-	8.0	HCC	Ch, Os	Resection	Peritoneum	UN	Dead (22mo)
20	Sumiyoshi et al. (17)	74/F	-/-	-	15.0	CCC	Lei	-	Liver	Ca + Sa	Dead (2mo)
21	Present case	72/M	-/+	-	4.5	HCC	Os	Resection	-	-	Alive (30mo)

HBsAg, hepatitis B surface antigen; anti-HCV, antibody to hepatitis C virus; UN, unknown; Ch, chondrosarcoma; CTX, chemotherapy; LN, lymph node; mo, month; Rh, rhabdomyosarcoma; Ad, adrenal gland; Sa, sarcoma; CCC, cholangiocellular carcinoma; Lei, leiomyosarcoma; TAI, transarterial injection; Ca, carcinoma; Ca + Sa, carcinoma and sarcoma; Os, osteosarcoma; TAE, transarterial embolization; GB, gallbladder; endocrine, endocrine carcinoma; MFH, malignant fibrous histiocytoma; Fi, fibrosarcoma; PEI, percutaneous ethanol injection.

elements. Therefore, intensive follow-up is considered to be mandatory.

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Conflict of interest statement

None declared.

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An analysis of risk factors for pancreatic fistula after pancreaticoduodenectomy: clinical impact of bile juice infection on day 1

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Abstract

Background Postoperative pancreatic fistula (POPF) is a most striking complication after pancreatic resection. The objective of this study is to reveal the risk factors for POPF defined by the international study group after pancreaticoduodenectomy in a Japanese high-volume center.

Methods During the recent 4 years, 220 patients underwent pancreaticoduodenectomies. In patients of obstructive jaundice, preoperative biliary drainage was performed by percutaneous ($n=71$) and/or retrograde ($n=38$) approach. Pancreaticojejunostomy was performed using either duct-to-mucosa anastomosis ($n=180$) or dunking method ($n=40$). Risk factors for POPF (grade B or grade C POPF by international definition) were evaluated using univariate and multivariate analyses.

Results POPF was found in 109 (50%) patients; grade A in 45 (21%), grade B in 54 (25%), and grade C in 10 patients (5%). One patient died of intra-abdominal hemorrhage caused by POPF. Univariate and multivariate analyses revealed that independent risk factors for grade B or grade C POPF were the size of the main pancreatic duct (<3 mm; relative risk (RR), 3.3; $p=0.002$), body mass index (≥ 20 , RR 2.5, $p=0.03$), and bile juice infection on day 1 (RR, 2.2; $p=0.04$). The performance of biliary drainage or method of pancreaticojejunostomy was not a significant risk factor for POPF. Bile juice infection on day 1 was significantly associated with retrograde biliary drainage ($p<0.001$).

Conclusions Bile juice infection on day 1 was a significant risk factor for grade B or grade C POPF after pancreaticoduodenectomy. Although the performance or the status of biliary drainage itself was not a risk factor for POPF, percutaneous biliary drainage might be advantageous against retrograde drainage to reduce the risk of biliary infection.

Keywords Pancreaticoduodenectomy · Postoperative pancreatic fistula (POPF) · Biliary drainage · Bile juice infection

Introduction

With the advancement of imaging studies, surgical techniques, and perioperative management, the mortality rate of pancreaticoduodenectomy has decreased to 0–9% in high-volume centers. However, the morbidity rate still remains in the range of 30–50% [1–3], and postoperative pancreatic fistula (POPF) is the most common complication of pancreaticoduodenectomy, which would lead to not only prolongation of the hospital stay but also lethal morbidity or surgical mortality. The incidence of POPF is reported to be 0–17% based on a variety of definition of pancreatic fistula [4–6]. Recently, an international study group of pancreatic fistula (ISGPF) defined POPF by reviewing numerous reported series [7]. ISGPF classified POPF into three categories, grade A as a transient or minor fistula, grade B as a major fistula with prolongation of hospital stay, and grade C necessitating surgical intervention. This classification is useful to evaluate the incidence of POPF objectively throughout the age and institution [8]. In the present study, we focused on grade B

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and grade C POPF after pancreaticoduodenectomy and analyzed the risk factors for POPF in a Japanese high-volume center hospital.

Patients and methods

Between August 2003 and December 2006, 220 patients underwent pancreaticoduodenectomies in our institute. The diseases included invasive pancreatic cancer in 108 patients, bile duct cancer in 26 patients, ampullary or duodenal cancer in 33 patients, intraductal papillary mucinous tumor in 22 patients, neuroendocrine tumor in 9 patients, gallbladder cancer in 2 patients, metastatic cancers in 2 patients, and other diseases in 18 patients. Five staff surgeons performed all of the operations. One chief resident and one resident assisted each attending surgeon perioperatively.

Surgical procedures of pancreaticoduodenectomy

The details of our standard surgical procedure of pancreaticoduodenectomy have been described elsewhere [9]. All of the patients with obstructive jaundice ($n=101$) underwent only percutaneous biliary drainage (PTCD, $n=63$), only endoscopic retrograde biliary drainage ($n=30$) or both of PTCD and retrograde biliary drainage ($n=8$) in the previous hospital or in our institute. The remaining 119 patients underwent pancreaticoduodenectomy without biliary drainage. Pancreaticoduodenectomy was performed when the serum bilirubin concentration decreased less than 5 mg/dl. Patients received preoperative intravenous antibiotic prophylaxis using a second-generation cephalosporin. After removal of the pancreatic head, we routinely wrapped the stump of the gastroduodenal artery using the falciform ligament to prevent the bleeding caused by pancreatic leakage [10]. The surgical procedures consisted of standard Whipple procedure (SW) in 58 patients and pylorus-preserving pancreaticoduodenectomy (PPPD) in 162 patients. Combined portal vein resection was performed in 54 patients (24.5%) of all 220 patients; 48 patients with pancreatic invasive cancer, 3 patients with bile duct cancer, and 3 patients with other disease.

Pancreaticojejunostomy was performed in 217 out of 220 patients. In the remaining three patients, the remaining pancreatic parenchyma was left unreconstructed or external pancreatic tube was placed because the remaining pancreatic parenchyma was very small. A jejunal loop was lifted, and pancreaticojejunostomy was performed by duct-to-mucosa anastomosis ($n=180$) or dunking method ($n=40$) with external drainage ($n=215$), or with internal stent ($n=5$). The anterior and posterior pancreatic walls were tightly affixed to the jejunal serosa by interrupted sutures.

Hepaticojejunostomy was then made by interrupted sutures with external drainage ($n=209$), with internal stent ($n=7$), or without stenting ($n=4$).

An antecolic gastrojejunostomy and duodenojejunostomy were performed in SW and PPPD, respectively. The anastomosis was made by the Albert-Lembert ($n=200$), layer-to-layer ($n=7$), Gambee method ($n=2$), or stapled mechanical anastomosis ($n=11$). A Braun jejunojejunostomy was made to prevent direct exposure of the anastomotic site to pancreatic and bile juice ($n=127$). Gastric tubes and jejunal feeding tubes were placed in 126 and 148 patients, respectively. In 11 patients, stapled Roux-en-Y reconstruction was performed using ILS (Proximate ILS™ 29 or 25 mm, Ethicon Endo-Surgery, Cincinnati, OH, USA) in PPPD ($n=6$) or ENDO-GIA (ENDO-GIA Reticulator™ 60, US Surgical, Norwalk, CT, USA) in SW ($n=5$) [11].

Two closed drains, sized 8 or 10 mm in diameter, were inserted beside the pancreatojejunostomy, and intermittent suction of the drainage fluid was performed in principle. When amylase-rich fluid was discharged from the drain on postoperative day 4–7, the drains were cut to let out the infectious fluid. Most of the patients underwent external drainage of bile juice via hepaticojejunostomy, and we routinely cultured bacteria in the bile juice on day 1. Drains were exchanged under fluoroscope on day 14; thereafter, they were exchanged as required until removal. Patients were allowed to be discharged from the hospital and to go home, when they could eat almost half of the regular diet and had one abdominal drain left with slight output.

Definition of outcome measures

POPF was defined according to the definition proposed by an international study group on pancreatic fistula [7], i.e., when the amylase concentration of the drain fluid obtained on or after postoperative day 3 was greater than three times the serum amylase concentration. Pancreatic fistulas were classified into grades A, B, and C according to severity; briefly, grade A was “transient fistula”, not associated with a delay in hospital discharge; grade B fistula led to a delay in discharge, with persistent drainage for more than 3 weeks; and a grade C fistula was usually associated with major complications. Because grade A POPF can be a “transient” fistula, we focused on the risk factors for grade B and grade C POPF, which are significant POPF associated with prolongation of hospital stay.

Delayed gastric emptying (DGE) were classified into grades A, B, and C according to the recent report [12], i.e., in grade A, patient was unable to tolerate solid oral intake by seven postoperative days, and vomiting is uncommon; whereas in grades B and C, there is usually vomiting. In grade B, patient was unable to tolerate solid oral intake by

14 postoperative days; in grade C, 21 postoperative days. Grades B and C DGE were considered to be significant complications.

Univariate and multivariate analysis of risk factors for POPF

Univariate analyses of risk factors for POPF (grade B or C) were performed in relation to the following clinicopathological variables, including age (≥ 65 , < 65), sex, body mass index (BMI, ≥ 20 , < 20), carcinoembryonic antigen (≥ 5 , < 5 ng/mL), CA19-9 (≥ 37 , < 37 IU/mL), the disease, dilatation of the main pancreatic duct (≥ 3 , < 3 mm), status of preoperative biliary drainage, duration of operation (≥ 540 , < 540 min), operative blood loss (≥ 800 , < 800 mL), surgical procedures (PPPD vs SW), method of pancreaticojejunostomy (duct-to-mucosa anastomosis or dunking method), placement of external pancreatic drainage, duration of hospital stay (days), and bile juice infection on day 1. The thresholds of age, BMI, duration of operation, and operative blood loss were determined on the median value of each parameter. Multivariate analyses were conducted using the significant factors in the univariate analyses.

Statistical analysis

Analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows statistical software (SPSS Inc., Chicago, IL, USA). Chi-square test or Fisher's exact test for univariate analysis and Mann–Whitney U test were used to compare the variables between the two groups. Data were expressed as median and range. A p value of less than 0.05 was considered statistically significant.

Results

The overall mortality rate was 0.9% ($n=2$). One patient developed massive intra-abdominal bleeding on day 7 and died of hypovolemic condition. Another patient was found to have Guillain–Barre syndrome on day 10 and died of respiratory failure. Postoperative surgical complication included POPF in 109 patients (50%), grade A in 45 (20%), grade B in 54 (25%), and grade C in 10 (5%); grade B or grade C DGE in 61 patients (28%), wound infection in 18 patients (8%), intra-abdominal collection in 18 patients (8%), bile leakage in 2 patients (0.9%), gastric leakage in 2 patients (0.9%), liver abscess in 3 patients (1.3%), pulmonary embolism in 3 patients (1.3%), hemorrhage in 4 patients (1.8%), and others in 12 patients (5.5%). Seven patients (3.2%) required reoperation.

Univariate and multivariate analysis of risk factors for grade B and grade C POPF

In the univariate analysis, seven variables, gender (male), gender (≥ 65), BMI (≥ 20), disease (other than pancreatic cancer), the size of the main pancreatic duct (< 3 mm), portal vein resection (not performed), and bile juice infection on day 1, were identified as significant risk factors for grade B and grade C POPF (Table 1). No statistical difference was found in the incidence of grade B or grade C POPF between patients undergoing only PTCD ($n=63$) and patients undergoing only retrograde drainage ($n=30$; 25% vs 27%, $p=0.73$). The performance or status of biliary drainage and the method of pancreaticojejunostomy were not significant risk factors for POPF. Multivariate analysis revealed that size of the main pancreatic duct (< 3 mm), BMI (≥ 20), and bile juice infection on day 1 were independent risk factors for grade B and grade C POPF (Table 2).

Status of the biliary drainage and the results of the culture of the bile juice infection on day 1 after pancreaticoduodenectomy

Relationship between the status of biliary drainage and bile juice infection on day 1 after pancreaticoduodenectomy are listed in Table 3. Positive culture of the bile juice on day 1 was found in 17 out of 97 patients (18%) without biliary drainage, 19 out of 48 patients (40%) undergoing only PTCD, and 19 out of 26 patients (65%) undergoing only retrograde biliary drainage. There was a significant relationship between the status of the biliary drainage and the culture of bile juice on day 1 after pancreaticoduodenectomy ($p<0.001$). The incidence of bile juice infection was significantly higher in patients with biliary drainage than that in patients without biliary drainage (52% vs 18%, $p<0.001$) and was significantly higher in patients with retrograde drainage than that in patients with only percutaneous drainage (40% vs 65%, $p=0.006$).

Results of the culture of the bile juice on day 1 are listed in Table 4. *Enterococcus* and *Enterobacter* are the leading bacteria in the bile juice on day 1.

Discussion

In the present study, we evaluated the risk factors for grade B and grade C POPF after pancreaticoduodenectomy based on the recent definition by the international study group in a Japanese high-volume center. As a result, size of the main pancreatic duct (< 3 mm), BMI (≥ 20), and bile juice infection on day 1 were independent risk factors for grade B and grade C POPF. Among the three risk factors, the former two variables would be associated with the

Table 1 Univariate analysis of risk factors for postoperative pancreatic fistula (grade B and grade C) after pancreaticoduodenectomy

Variables		No pancreatic fistula or POPF, grade A (n=156)	POPF, grade B or C (n=64)	p value
Patient characteristics				
Gender	Male	80	45	0.010*
	Female	76	19	
Age, years	≥65	69	43	0.002*
	<65	87	21	
Mean BMI	≥20	71	46	<0.001*
	<20	85	18	
Disease	Pancreatic cancer	91	17	<0.001*
	Other disease	65	47	
MPD dilatation	≥3 mm	110	19	<0.001*
	<3 mm	46	45	
Status of biliary drainage				
Preoperative biliary drainage	Performed	71	30	0.85
	Not performed	85	34	
Retrograde biliary drainage	Not performed	129	53	0.98
	Performed	27	11	
Percutaneous biliary drainage	Not performed	107	42	0.67
	Performed	49	22	
Surgical procedures				
Procedure of PD	SW	42	16	0.80
	PPPD	113	47	
Pancreaticojejunostomy	Duct-to-mucosa anastomosis	128	52	0.89
	Dunking method	28	12	
Length of operation, min	>9 h	77	25	0.16
	<9 h	79	39	
Blood loss, mL	≥800 ml	76	35	0.42
	<800 ml	80	29	
Portal vein resection	Not performed	47	7	0.003*
	Performed	109	56	
Postoperative information				
Culture of bile juice on day 1	Negative	93	26	<0.001*
	Positive	31	28	
	Not determined	32	10	
Mortality		0 (0%)	2 (3.1%)	0.03
Duration of hospital stay (days)		24 (9–83)	39 (21–324)	<0.001*

POPF postoperative pancreatic fistula, BMI body mass index, MPD main pancreatic duct, SW standard Whipple procedure, PPPD pylorus-preserving pancreaticoduodenectomy

* $p < 0.05$

characteristics of the patients and the disease. On the other hand, bile juice infection on day 1 practically signifies the bile juice has already contaminated preoperatively. Bile juice contamination would be largely brought by preoperative biliary drainage. Actually, bile juice infection on day 1

was found in 18% of patients without biliary drainage, 40% of patients undergoing only PTCD, and 65% of patients undergoing retrograde biliary drainage. Although the performance of biliary drainage itself was not a significant risk factor for POPF, the above results may suggest that (1)

Table 2 Multivariate logistic regression of risk factors for postoperative pancreatic fistula (grade B and grade C) after pancreaticoduodenectomy

Factors	Odds ratio	95% confidence interval	p value
Size of the main pancreatic duct <3 mm	3.284	1.538–7.014	0.002
BMI ≥20	2.428	1.094–5.387	0.03
Bile juice infection on day 1	2.235	1.033–4.836	0.04

Table 3 Status of the biliary drainage and culture of bile juice infection on day 1 after pancreaticoduodenectomy

	Culture of bile juice on day 1		p value
	Negative (n=119)	Positive (n=59)	
No biliary drainage	80 (82%)	17 (18%)	<0.001
PTCD alone	29 (60%)	19 (40%)	
Retrograde drainage alone	7 (35%)	19 (65%)	
Both PTCD and retrograde drainage	3 (43%)	4 (57%)	

PTCD percutaneous transhepatic biliary drainage

preoperative biliary drainage will evoke the biliary infection, and (2) when biliary drainage is necessary, PTCD might be advantageous against retrograde drainage in the viewpoint of reducing biliary infection.

In this study, the definition of POPF was determined by the international definition recently proposed by the international study group of pancreatic surgery [7]. The incidence of POPF (48%) in our institute was much higher than the reported series [1–8]. However, we routinely measured the amylase concentration in the drainage fluid, and we carefully did not remove the drains until the amylase-rich or infected fluid goes out. Our relatively conservative management might further prolong the drain placement and increase the chance of second infection [13]. In some reports [3, 14], the incidence of POPF was very low, while the incidence of intra-abdominal hemorrhage and/or the mortality rate are high. In these studies, some patients with occult POPF [6] might be discharged, and they might be back to the hospital with intra-abdominal abscess or hemorrhage, which can lead to life-threatening events.

Bile juice infection on day 1 was associated with POPF and also with the performance or method of biliary drainage. Some randomized trials have revealed that preoperative biliary drainage increased surgical morbidity,

including wound infection and POPF [15, 16], which could explain that biliary infection caused by biliary drainage would increase infections complication. Povoski et al. reported that intra-abdominal infection, morbidity, and mortality were more often in patients with preoperative biliary drainage [15]. Because occult POPF can sometimes present with intra-abdominal abscess, we suppose that biliary infection, caused by biliary drainage, can increase the incidence of intra-abdominal infection and also the incidence of POPF. Others have reported that preoperative biliary drainage did not increase the surgical risks after pancreaticoduodenectomy [17–19]. Some randomized trial has denied the clinical significance of preoperative biliary drainage before pancreaticoduodenectomy, but most of the enrolled patients underwent palliative surgery, and any randomized trial considering for patients undergoing pancreaticoduodenectomy has never been conducted. In most reports, preoperative biliary drainage did not decrease surgical complications, and they concluded that it should be avoided if possible. Nevertheless, 50–70% of patients underwent pancreatic resection after preoperative biliary drainage [15–19]. This is partly because patients were referred to a high-volume center following biliary drainage in primary care centers. As persistent obstructive jaundice will provoke general fatigue, itching, and hepatobiliary dysfunction, biliary drainage will be absolutely necessary in some patients to improve the general condition.

In our study, the incidence of bile infection was higher in patients undergoing retrograde drainage than in patients undergoing percutaneous drainage. However, superiority of percutaneous or retrograde drainage prior to pancreaticoduodenectomy has not been elucidated by any randomized trials [20]. This issue should be further investigated by a prospective study.

In the multivariate analysis, BMI and the size of the main pancreatic duct were other risk factors for POPF. It has been repeatedly described that normal, soft pancreas with thin main pancreatic duct is closely associated with POPF [2, 3]. The incidence of POPF of patients with duct-to-mucosa anastomosis was similar with that of patients with dunking method (29% vs 30%, $p=0.89$). Although duct-to-mucosa anastomosis has been willingly introduced in order to reduce the incidence of POPF [5], no well-designed randomized trial has revealed the efficacy of duct-

Table 4 Results of culture of the bile juice on day 1 after pancreaticoduodenectomy

Positive/negative	n	Bacteria	n
Positive	59	<i>Enterococcus</i>	24
		<i>Enterobacter</i>	22
		<i>Klebsiella</i>	8
		<i>Pseudomonas</i>	6
		<i>Streptococcus</i>	4
		<i>Citrobacter</i>	4
		<i>Aeromonas</i>	3
		<i>Staphylococcus</i>	2
		<i>Bacteroides</i>	2
		<i>Stenotrophomonas</i>	2
		Other six bacteria	1
Negative	119		
Not determined	42		

to-mucosa anastomosis against conventional dunking method [21, 22]. It was reported that pancreaticogastrostomy was not superior to pancreaticojejunostomy in a randomized trial performed in a high-volume center [23]. Up to now, the best reconstruction method for the pancreatic duct during pancreaticoduodenectomy remains unclear.

Conclusion

Our multivariate analysis revealed that bile juice infection on day 1 was a significant and independent risk factor for POPF. As bile juice infection on day 1 was strongly associated with retrograde biliary drainage, not with percutaneous drainage, PTCO might be or would be recommended for patients undergoing biliary drainage before pancreaticoduodenectomy.

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Special Report**Report of the 18th follow-up survey of primary liver cancer in Japan**

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In the 18th Nationwide Follow-Up Survey of Primary Liver Cancer in Japan, 20 753 people were newly registered as patients with primary liver cancer at 544 medical institutions over a period of 2 years (from 1 January 2004 to 31 December 2005). Of these patients, 94.0% had hepatocellular carcinoma (HCC) and 4.4% had intrahepatic cholangiocarcinoma (ICC). In addition, 30 677 follow-up patients were registered in the survey. Epidemiological and clinicopathological factors, diagnosis and treatment were investigated in the newly registered patients. Compared with the 17th follow-up survey, 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. The cumulative survival rates of newly-registered patients between 1994 and 2005 were calculated for each histological type (HCC, ICC, and combined HCC and ICC) and stratified by background factors and treatment. The cumulative survival rates of newly-registered patients between 1978 and 2005 divided into three groups (1978–1985, 1986–1995 and 1996–2005) were also calculated. The data obtained in this follow-up survey should contribute to future research and medical practice for primary liver cancer.

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

INTRODUCTION

SINCE 1969, THE Liver Cancer Study Group of Japan (LCSGJ) has conducted 17 nationwide follow-up surveys of primary liver cancer in patients in member hospitals and cooperative institutions in Japan, with the goal of promoting research and clinical treatment of liver cancer.^{1–17} The 18th Nationwide Follow-up Survey of Primary Liver Cancer was conducted over a 2-year period from 1 January 2004 to 31 December 2005, and 20 753 patients with primary liver cancer

were newly registered at 544 institutions. In addition, 30 677 registered patients were followed up with a valid response rate of 74.2%. Items related to epidemiological and clinicopathological factors, diagnosis and treatment were investigated in the newly-registered patients. Cumulative survival rates of newly-registered patients between 1994 to 2005 were calculated for each histological type and based on background factors and treatment.

METHODS**Basic statistics**

THE SUBJECTS WERE 20 753 patients with primary liver cancer who were diagnosed clinically or by autopsy and underwent treatment or autopsy during a 2-year period from 1 January 2004 to 31 December 2005 at 544 institutions in Japan. Doctors in each institution completed a form developed by the Follow-up

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Table 1 Classification of primary liver cancer

Diagnosis	Male (n = 14 601)	Female (n = 6152)	Total (n = 20 753)
HCC	13 805	5 694	19 499 (94.0%)
ICC	561	344	905 (4.4%)
Combined	119	41	160 (0.8%)
Cystadenocarcinoma	14	13	27 (0.1%)
Hepatoblastoma	5	9	14 (0.1%)
Sarcoma	7	2	9 (0.0%)
Undifferentiated carcinoma	6	2	8 (0.0%)
Others	84	47	131 (0.6%)

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

Survey Committee of the Liver Cancer Study Group of Japan (chairperson, Masatoshi Kudo). In cases with an inconsistency between the clinical, pathological and autopsy diagnoses, the autopsy and pathological diagnoses were given first and second priority, respectively. Of the 20 753 patients, 94.0% had hepatocellular carcinoma (HCC) and 4.4% had intrahepatic cholangiocarcinoma (ICC) (Table 1). The results in the tables are categorized into HCC, ICC, and combined HCC and ICC, for which more than 100 newly-registered cases appeared in the current follow-up survey. The abbreviations in the tables conform to *The General Rules for the Clinical and Pathological Study of Primary Liver Cancer*, 2nd English edition and *Response Evaluation Criteria in Cancer of Liver* proposed by the Liver Cancer Study Group of Japan.^{18,19}

Cumulative survival rate

The cumulative survival rates of newly-registered patients in the 13th to 18th follow-up surveys between 1994 and 2005 whose final prognosis was determined to be survival or death (excluding patients with unknown outcomes) were calculated for each histological type (HCC, ICC, and combined HCC and ICC) and based on different background factors and treatment, including hepatectomy, local ablation therapy and transcatheter arterial embolization. The cumulative survival rates of newly-registered patients between 1978 and 2005 divided into three groups (1978–1985, 1986–1995 and 1996–2005) were also calculated. In this report, patients who had died from either liver-related or liver-unrelated causes were considered to be uncensored cases in estimating cumulative survival rates.

RESULTS

Basic statistics

Causes of death during the study period

FOR HCC, THE mortality of newly-registered patients during the study period was 15.7%: the death rate due to cancer was 55.8% and death rates due to hepatic failure, gastrointestinal bleeding and rupture of esophago-gastric varices were 18.8%, 2.1% and 4.1%, respectively. Of the patients who did not survive, 42 died within 30 days after surgery; these patients represented 0.7% of the 5794 patients who underwent surgery. For ICC, the mortality of newly-registered patients during the study period was 35.5% and death rates due to cancer and hepatic failure were 78.5% and 8.3%, respectively (Table 2).

Past history

Of patients with HCC, 76.2% and 60.0% had a past history of chronic hepatitis and liver cirrhosis, respectively, whereas only 19.9% and 9.4% of ICC patients had this history. Interferon therapy had been given to 15.7% of HCC patients due to concomitant chronic hepatitis, and 26.9% and 24.5% of HCC patients and 9.1% and 15.7% of ICC patients had a past history of blood transfusion and habitual alcohol intake, respectively.

Clinical diagnosis

Clinical diagnosis of primary liver cancer in patients with HCC was made at a mean age of 66.4 years in men and 69.9 years in women. For patients with ICC, the corresponding mean ages were 67.2 years in men

Table 2 Causes of death of patients with primary liver cancer

	HCC		ICC		Combined	
Alive	15 885		567		110	
Total deaths of between 2004 and 2005	2 952		312		46	
Cancer death	1 646	(55.8%)	245	(78.5%)	35	(76.1%)
Hepatic failure	554	(18.8%)	26	(8.3%)	7	(15.2%)
Gastrointestinal bleeding	62	(2.1%)	2	(0.6%)	0	(0.0%)
Rupture of esophageal varices	122	(4.1%)	2	(0.6%)	0	(0.0%)
Rupture of tumor	166	(5.6%)	0	(0.0%)	0	(0.0%)
Operative death	42	(1.4%)	4	(1.3%)	0	(0.0%)
Other causes	360	(12.2%)	33	(10.6%)	4	(8.7%)
Unknown	612		22		4	

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

and 66.6 years in women. The male : female ratios for HCC and ICC patients were 2.41 and 1.67, respectively.

In patients with HCC, the level of liver injury at the time of diagnosis, based on the liver damage classification of the LCSGJ, was class A, B and C in 60.4%, 32.2% and 7.4% of patients, respectively, whereas 71.0%, 23.6% and 5.4% of HCC patients were in the Child–Pugh class A, B and C categories, respectively (Table 3). Of the HCC patients, 37.1%, 36.3% and 26.6% had serum α -fetoprotein (AFP) levels of less than 15 ng/mL, 15–199 ng/mL and 200 ng/mL or more, respectively, and 64.3%, 5.2% and 30.6% of patients with HCC had serum levels of lectin-reactive AFP-L₃ of less than 10%, 10.0–14.9% and 15% or more, respectively. Of the HCC patients, 40.5%, 14.4% and 45.0% had a protein induced by vitamin K absence or antagonist-II (PIVKA-II) level of less than 40 mAU/mL, 40–99 mAU/mL and 100 mAU/mL or more, respectively. In patients with ICC, 60.0%, 13.9% and 26.2% had a carcinoembryonic antigen level of less than 5.0 ng/mL, 5.0–9.9 ng/mL and 10 ng/mL or more, respectively, and 30.5%, 18.0% and 51.4% had a carbohydrate antigen 19-9 level of less than 37 U/mL, 37–99 U/mL and 100 U/mL or more, respectively (Table 3).

Of the patients with HCC, ICC, and combined HCC and ICC, those who were positive for hepatitis B virus surface antigen comprised 15.0%, 6.3% and 18.9%, respectively. The percentages of anti-hepatitis C virus antibody positive patients were 67.7%, 18.8% and 46.7%, respectively (Table 4).

Tumor size was determined using diagnostic imaging. Of patients with HCC, 33.5% and 45.5% had tumors of 2.0 cm or less and 2.1–5.0 cm, respectively.

The corresponding numbers for patients with ICC were 9.3% and 48.8%, respectively (Table 5). Of the tumors, 57.7% and 73.7% were solitary in patients with HCC and ICC, respectively. In patients with HCC, 93.2% had a tumor stain, 2.5% exhibited tumor rupture and 40.4% had esophagogastric varices of F2 or RC₁ or higher.

Major treatment

Of patients with HCC, 31.7%, 30.6% and 31.7% had undergone surgery (hepatectomy and liver transplantation), local ablation therapy and transcatheter arterial embolization, respectively. In patients with ICC, 67.1% and 26.5% had undergone surgery (hepatectomy) and chemotherapy, respectively, and in patients with combined HCC and ICC, 63.8% and 13.5% had undergone surgery (hepatectomy) and transcatheter arterial chemoembolization, respectively (Table 6). Among the HCC patients, 74.5%, 23.2% and 2.2% who underwent surgery, 60.6%, 34.7% and 4.7% of those treated with local ablation therapy, and 57.7%, 36.0% and 6.2% of those treated with transcatheter arterial embolization were in liver damage classes A, B and C, respectively.

Surgery

Of patients with HCC, 5646 underwent hepatectomy and 148 received a liver transplantation. Macroscopic analysis of the resected specimens showed that 59.0% of cases were of the single nodular type. Of patients with ICC, 492 underwent hepatectomy and two received a liver transplantation, and 63.1% of these cases were of the mass-forming type.

Table 3 Clinical profile of patients with primary liver cancer

	HCC		ICC		Combined	
Diagnosis	<i>n</i> = 35 472		<i>n</i> = 1693		<i>n</i> = 301	
Computed tomography	15 275	(43.1%)	701	(41.4%)	124	(41.2%)
Magnetic resonance imaging	2 815	(7.9%)	221	(13.1%)	30	(10.0%)
Ultrasonography	9 305	(26.2%)	378	(22.3%)	76	(25.2%)
Selective angiography	6 388	(18.0%)	186	(11.0%)	37	(12.3%)
Histopathological finding	1 504	(4.2%)	162	(9.6%)	29	(9.6%)
Others	185	(0.5%)	45	(2.7%)	5	(1.7%)
performance status	<i>n</i> = 16 364		<i>n</i> = 741		<i>n</i> = 137	
PS0	13 224	(80.8%)	575	(77.6%)	108	(78.8%)
PS1	2 100	(12.8%)	105	(14.2%)	18	(13.1%)
PS2	616	(3.8%)	30	(4.0%)	6	(4.4%)
PS3	273	(1.7%)	14	(1.9%)	4	(2.9%)
PS4	151	(0.9%)	17	(2.3%)	1	(0.7%)
Encephalopathy	<i>n</i> = 18 188		<i>n</i> = 813		<i>n</i> = 146	
None	17 494	(96.2%)	808	(99.4%)	145	(99.3%)
Mild	490	(2.7%)	3	(0.4%)	0	(0.0%)
Coma occasionally	204	(1.1%)	2	(0.2%)	1	(0.7%)
Ascites	<i>n</i> = 18 509		<i>n</i> = 830		<i>n</i> = 154	
Absent	16 135	(87.2%)	769	(92.7%)	138	(89.6%)
Slight	1 474	(8.0%)	19	(2.3%)	7	(4.5%)
Moderate	900	(4.9%)	42	(5.1%)	9	(5.8%)
Serum bilirubin (mg/mL)	<i>n</i> = 18 614		<i>n</i> = 852		<i>n</i> = 153	
0.0–0.9	10 342	(55.6%)	518	(60.8%)	104	(68.0%)
1.0–1.9	6 383	(34.3%)	195	(22.9%)	38	(24.8%)
2.0–3.0	1 140	(6.1%)	32	(3.8%)	4	(2.6%)
≥3.1	749	(4.0%)	107	(12.6%)	7	(4.6%)
Serum albumin (g/dL)	<i>n</i> = 18 481		<i>n</i> = 825		<i>n</i> = 152	
<2.8	1 470	(8.0%)	37	(4.5%)	9	(5.9%)
2.8–2.9	967	(5.2%)	23	(2.8%)	4	(2.6%)
3.0–3.5	5 255	(28.4%)	160	(19.4%)	40	(26.3%)
>3.5	10 789	(58.4%)	605	(73.3%)	99	(65.1%)
ICG R ₁₅ (%)	<i>n</i> = 10 794		<i>n</i> = 487		<i>n</i> = 106	
≤14	3 875	(35.9%)	341	(70.0%)	62	(58.5%)
15–24	3 286	(30.4%)	103	(21.1%)	31	(29.2%)
25–40	2 409	(22.3%)	32	(6.6%)	11	(10.4%)
>40	1 224	(11.3%)	11	(2.3%)	2	(1.9%)
Prothrombin activity (%)	<i>n</i> = 17 538		<i>n</i> = 775		<i>n</i> = 145	
<40	278	(1.6%)	15	(1.9%)	1	(0.7%)
40–49	372	(2.1%)	7	(0.9%)	1	(0.7%)
50–70	3 876	(22.1%)	70	(9.0%)	19	(13.1%)
71–80	3 900	(22.2%)	119	(15.4%)	31	(21.4%)
>80	9 112	(52.0%)	564	(72.8%)	93	(64.1%)
Platelet count (×10 ⁴ /mm ³)	<i>n</i> = 18 374		<i>n</i> = 847		<i>n</i> = 154	
<3.0	145	(0.8%)	4	(0.5%)	1	(0.6%)
3.0–4.9	942	(5.1%)	5	(0.6%)	0	(0.0%)
5.0–9.9	5 979	(32.5%)	53	(6.3%)	24	(15.6%)
10.0–14.9	5 419	(29.5%)	114	(13.5%)	46	(29.9%)
15.0–19.9	3 119	(17.0%)	216	(25.5%)	36	(23.4%)
20.0–99.9	2 697	(14.7%)	453	(53.5%)	47	(30.5%)
>100	73	(0.4%)	2	(0.2%)	0	(0.0%)

Table 3 Continued

	HCC		ICC		Combined	
Liver damage classification by LCSGJ	n = 15 574		n = 706		n = 138	
A	9 400	(60.4%)	596	(84.4%)	100	(72.5%)
B	5 016	(32.2%)	82	(11.6%)	35	(25.4%)
C	1 158	(7.4%)	28	(4.0%)	3	(2.2%)
Child-Pugh classification	n = 18 032		n = 790		n = 149	
A	12 799	(71.0%)	667	(84.4%)	121	(81.2%)
B	4 254	(23.6%)	101	(12.8%)	21	(14.1%)
C	979	(5.4%)	22	(2.8%)	7	(4.7%)
AFP (ng/mL)	n = 17 804		n = 562		n = 145	
<15	6 608	(37.1%)	449	(79.9%)	59	(40.7%)
≤199	6 466	(36.3%)	77	(13.7%)	38	(26.2%)
≤399	1 000	(5.6%)	11	(2.0%)	7	(4.8%)
≤999	994	(5.6%)	7	(1.2%)	11	(7.6%)
≤9 999	1 549	(8.7%)	12	(2.1%)	17	(11.7%)
≤99 999	761	(4.3%)	3	(0.5%)	9	(6.2%)
≥100 000	426	(2.4%)	3	(0.5%)	4	(2.8%)
AFP-L ₃ (%)	n = 7904		n = 126		n = 62	
ND	2 661	(33.7%)	71	(56.3%)	14	(22.6%)
<5.0	1 785	(22.6%)	21	(16.7%)	10	(16.1%)
≤9.9	634	(8.0%)	4	(3.2%)	1	(1.6%)
≤14.9	411	(5.2%)	0	(0.0%)	3	(4.8%)
≤19.9	250	(3.2%)	0	(0.0%)	3	(4.8%)
≥20.0	2 163	(27.4%)	30	(23.8%)	31	(50.0%)
PIVKA-II (mAU/mL)	n = 16 114		n = 389		n = 140	
<40	6 531	(40.5%)	311	(79.9%)	61	(43.6%)
≤99	2 327	(14.4%)	32	(8.2%)	17	(12.1%)
≤299	1 998	(12.4%)	12	(3.1%)	18	(12.9%)
≤499	781	(4.8%)	6	(1.5%)	7	(5.0%)
≤999	842	(5.2%)	6	(1.5%)	11	(7.9%)
≤2 999	1 087	(6.7%)	5	(1.3%)	9	(6.4%)
≤9 999	975	(6.1%)	8	(2.1%)	8	(5.7%)
≥10 000	1 573	(9.8%)	9	(2.3%)	9	(6.4%)
CEA (ng/mL)	n = 6 192		n = 758		n = 113	
<2.5	2 329	(37.6%)	236	(31.1%)	38	(33.6%)
≤4.9	2 319	(37.5%)	219	(28.9%)	34	(30.1%)
≤9.9	1 219	(19.7%)	105	(13.9%)	27	(23.9%)
≤19.9	223	(3.6%)	60	(7.9%)	6	(5.3%)
≤49.9	57	(0.9%)	58	(7.7%)	0	(0.0%)
≤99.9	19	(0.3%)	27	(3.6%)	1	(0.9%)
≥100	26	(0.4%)	53	(7.0%)	7	(6.2%)
CA 19-9 (U/mL)	n = 4 807		n = 737		n = 108	
<37	3 023	(62.9%)	225	(30.5%)	49	(45.4%)
≤99	1 224	(25.5%)	133	(18.0%)	26	(24.1%)
≤299	422	(8.8%)	110	(14.9%)	15	(13.9%)
≤999	95	(2.0%)	82	(11.1%)	9	(8.3%)
≤2999	24	(0.5%)	51	(6.9%)	4	(3.7%)
≤9999	12	(0.2%)	64	(8.7%)	2	(1.9%)
≥10 000	7	(0.1%)	72	(9.8%)	3	(2.8%)

AFP, α -fetoprotein; AFP-L₃, lectin-reactive α -fetoprotein; CA 19-9, carbohydrate antigen 19-9; CEA, carcinoembryonic antigen; combined, combined hepatocellular and cholangiocarcinoma; HCC, hepatocellular carcinoma; ICC, intrahepatic cholangiocarcinoma; ICG R₁₅, indocyanine green retention rate at 15 min; LCSGJ, Liver Cancer Study Group of Japan; ND, not detectable; PIVKA, protein induced by vitamin K absence or antagonist.

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

	HCC		ICC		Combined	
HBsAg	<i>n</i> = 18 317		<i>n</i> = 809		<i>n</i> = 148	
Negative	15 550	(84.9%)	758	(93.7%)	120	(81.1%)
Positive	2 754	(15.0%)	51	(6.3%)	28	(18.9%)
Undetermined	13	(0.1%)	0	(0.0%)	0	(0.0%)
HBsAb	<i>n</i> = 5 436		<i>n</i> = 219		<i>n</i> = 62	
Negative	4 293	(79.0%)	181	(82.6%)	46	(74.2%)
Positive	1 107	(20.4%)	38	(17.4%)	16	(25.8%)
Undetermined	36	(0.7%)	0	(0.0%)	0	(0.0%)
HBcAb	<i>n</i> = 4 731		<i>n</i> = 160		<i>n</i> = 55	
Negative	2 200	(46.5%)	105	(65.6%)	28	(50.9%)
Positive	2 515	(53.2%)	54	(33.8%)	27	(49.1%)
Undetermined	16	(0.3%)	1	(0.6%)	0	(0.0%)
HBeAg	<i>n</i> = 3 410		<i>n</i> = 94		<i>n</i> = 42	
Negative	2 829	(83.0%)	91	(96.8%)	38	(90.5%)
Positive	570	(16.7%)	3	(3.2%)	3	(7.1%)
Undetermined	11	(0.3%)	0	(0.0%)	1	(2.4%)
HBeAb	<i>n</i> = 3 338		<i>n</i> = 84		<i>n</i> = 39	
Negative	1 723	(51.6%)	50	(59.5%)	16	(41.0%)
Positive	1 580	(47.3%)	31	(36.9%)	23	(59.0%)
Undetermined	35	(1.0%)	3	(3.6%)	0	(0.0%)
HCVAb	<i>n</i> = 18 624		<i>n</i> = 828		<i>n</i> = 150	
Negative	5 998	(32.2%)	671	(81.0%)	80	(53.3%)
Positive	12 610	(67.7%)	156	(18.8%)	70	(46.7%)
Undetermined	16	(0.1%)	1	(0.1%)	0	(0.0%)

Combined, combined hepatocellular and cholangiocarcinoma; HBcAb, antibody to hepatitis B core antigen; HbeAb, antibody to hepatitis B e antigen; HbeAg, hepatitis B e-antigen; HbsAb, hepatitis B surface antibody; HbsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma; HCVAb, hepatitis C virus antibody; ICC, intrahepatic cholangiocarcinoma.

Macroscopic results from the resected specimens are shown in Table 7. In the HCC patients who underwent hepatectomy, tumors of size 2.0 cm or less, 2.1–5.0 cm and 5.1–10.0 cm were found in 17.7%, 54.9% and 20.2% of patients, respectively, and 74.3% of the tumors were solitary. Vascular invasion in the portal vein, hepatic vein and bile duct were found in 16.2%, 7.3% 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%, 49.0% and 42.1% of the patients, respectively. The extent of surgical resection was Hr0, HrS, Hr1, Hr2 and Hr3 in 30.7%, 23.4%, 22.6%, 20.8% and 2.5% of the patients, respectively (Table 7).

In patients with ICC, tumors of size 2.0 cm or less, 2.1–5.0 cm and 5.1–10.0 cm were found in 9.3%, 52.1% and 33.9% of patients, respectively, and 83.8% of the tumors were solitary.

Local ablation therapy

Of patients with HCC, 6673 underwent local ablation therapy. Ethanol injection therapy, microwave coagulation therapy and radiofrequency ablation therapy were given to 18.6%, 8.5% and 72.1% of these patients, respectively, suggesting a marked increase in the use of radiofrequency ablation therapy (Table 8). Percutaneous treatment was given in 86.3% of these cases, and of these patients, 71.2% had one tumor, 59.3% had a tumor of size 2.0 cm or less, and 28.5% had a tumor of 2.1–3.0 cm. Treatment outcomes of complete response (CR) and partial response (PR) at 6 months after treatment occurred in 80.3% and 9.9% of patients, respectively.

Transcatheter arterial embolization

Transcatheter arterial embolization was conducted in 8188 patients with HCC. Of these patients, lipiodol

Table 5 Tumor characteristics by imaging studies

	HCC		ICC		Combined
Tumor size by imaging studies (cm)	<i>n</i> = 17 804		<i>n</i> = 746		<i>n</i> = 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	<i>n</i> = 18 255		<i>n</i> = 792		<i>n</i> = 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	<i>n</i> = 17 455		<i>n</i> = 727		<i>n</i> = 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	<i>n</i> = 16 688		<i>n</i> = 694		<i>n</i> = 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	<i>n</i> = 16 536		<i>n</i> = 691		<i>n</i> = 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	<i>n</i> = 5 251		<i>n</i> = 33		<i>n</i> = 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	<i>n</i> = 17 986		<i>n</i> = 732		<i>n</i> = 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	<i>n</i> = 1 388		<i>n</i> = 158		<i>n</i> = 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)	<i>n</i> = 5277		<i>n</i> = 451		<i>n</i> = 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	<i>n</i> = 5336		<i>n</i> = 458		<i>n</i> = 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	<i>n</i> = 5189		<i>n</i> = 465		<i>n</i> = 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	<i>n</i> = 5105		<i>n</i> = 424		<i>n</i> = 83
Eg	4731 (92.7%)		196 (46.2%)		60 (72.3%)
Ig	374 (7.3%)		228 (53.8%)		23 (27.7%)
Capsule formation	<i>n</i> = 5047		<i>n</i> = 416		<i>n</i> = 80
Fc ⁻	1147 (22.7%)		379 (91.1%)		54 (67.5%)
Fc ⁺	3900 (77.3%)		37 (8.9%)		26 (32.5%)
Capsule infiltration	<i>n</i> = 4702		<i>n</i> = 288		<i>n</i> = 65
Fc-Inf ⁻	2768 (58.9%)		265 (92.0%)		52 (80.0%)
Fc-Inf ⁺	1934 (41.1%)		23 (8.0%)		13 (20.0%)
Septum formation	<i>n</i> = 4968		<i>n</i> = 398		<i>n</i> = 79
Sf ⁻	2313 (46.6%)		374 (94.0%)		51 (64.6%)
Sf ⁺	2655 (53.4%)		24 (6.0%)		28 (35.4%)
Serosal invasion	<i>n</i> = 5016		<i>n</i> = 429		<i>n</i> = 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	<i>n</i> = 4910		<i>n</i> = 449		<i>n</i> = 83
Absent	4858 (98.9%)		312 (69.5%)		70 (84.3%)
Present	52 (1.1%)		137 (30.5%)		13 (15.7%)
Portal vein invasion	<i>n</i> = 5228		<i>n</i> = 445		<i>n</i> = 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	<i>n</i> = 5088		<i>n</i> = 434		<i>n</i> = 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	<i>n</i> = 5057		<i>n</i> = 429		<i>n</i> = 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