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ORIGINAL ARTICLE

# 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

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## 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% base 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

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 Roticulator™ 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.

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

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

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-

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, PTCD might be or would be recommended for patients undergoing biliary drainage before pancreaticoduodenectomy.

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## References

1. Yeo CJ, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA et al (1997) Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. Ann Surg 226:248–257
2. Adam U, Makowiec F, Riediger H, Schareck WD, Benz S, Hopt UT (2004) Risk factors for complications after pancreatic head resection. Am J Surg 187:201–208
3. Muscari F, Suc B, Kirzin S, Hay JM, Fourtanier G, Fingerhut A, French Associations for Surgical Research et al (2006) Risk factors for mortality and intraabdominal complications after pancreatoduodenectomy: multivariate analysis in 300 patients. Surgery 139:591–598
4. Kazanjian KK, Hines OJ, Eibl G, Reber HA (2005) Management of pancreatic fistulas after pancreaticoduodenectomy: results in 437 consecutive patients. Arch Surg 140:849–854
5. Payne RF, Pain JA (2006) Duct-to-mucosa pancreaticogastrostomy is a safe anastomosis flowing pancreaticoduodenectomy. Br J Surg 93:73–77
6. Veillette G, Dominguez I, Ferrone C, Thayer SP, McGrath D, Warshaw AL et al (2008) Implications and management of pancreatic fistulas following pancreaticoduodenectomy: the Massachusetts General Hospital experience. Arch Surg 143:476–481
7. Bassi C, Dervenis C, Butturini G, Fingerhut A, Yeo C, Izbicki J, International Study Group on Pancreatic Fistula Definition et al (2005) Postoperative pancreatic fistula: an international study group (ISGPF) definition. Surgery 138:8–13
8. Pedrazzoli S, Liessi G, Pasquali C, Ragazzi R, Berselli M, Sperti C (2009) Postoperative pancreatic fistulas: preventing severe complications and reducing reoperation and mortality rate. Ann Surg 249:97–104
9. Shimada K, Sano T, Sakamoto Y, Kosuge T (2006) Clinical implications of combined portal vein resection as a palliative procedure in patients undergoing pancreaticoduodenectomy for pancreatic head carcinoma. Ann Surg Oncol 13:1569–1578
10. Sakamoto Y, Shimada K, Esaki M, Kajiwara T, Sano T, Kosuge T (2007) Wrapping the stump of the gastroduodenal artery using the falciform ligament during pancreaticoduodenectomy. J Am Coll Surg 204:334–336
11. Sakamoto Y, Kajiwara T, Esaki M, Shimada K, Nara S, Kosuge T (2009) Roux-en-Y reconstruction using staplers during pancreaticoduodenectomy: results of a prospective preliminary study. Surg Today 39:32–37
12. Wente MN, Bassi C, Dervenis C, Fingerhut A, Gouma DJ, Izbicki JR et al (2007) Delayed gastric emptying (DGE) after pancreatic surgery: definition by the International Study Group of Pancreatic Surgery (ISGPS). Surgery 142:761–768
13. Kawai M, Tani M, Terasawa H, Ina S, Hirono S, Nishioka R et al (2006) Early removal of prophylactic drains reduced the risk of intra-abdominal infections in patients with pancreatic head resection. Prospective study for 104 consecutive patients. Ann Surg 244:1–7
14. de Castro SM, Busch OR, van Gulik TM, Obertop H, Gouma DJ (2005) Incidence and management of pancreatic leakage after pancreaticoduodenectomy. Br J Surg 92:1117–1123
15. Povoski SP, Karpeh MS Jr, Conlon KC, Blumgart LH, Brennan MF (1999) Association of preoperative biliary drainage with postoperative outcome following pancreaticoduodenectomy. Ann Surg 230:131–142
16. Sohn TA, Yeo CJ, Cameron JL, Pitt HA, Lillemoe KD (2000) Do preoperative biliary stents increase postpancreaticoduodenectomy complications? J Gastrointest Surg 4:258–267
17. Sewnath ME, Birjmohun RS, Rauws EA, Huibregtse K, Obertop H, Gouma DJ (2001) The effect of preoperative biliary drainage on postoperative complications after pancreaticoduodenectomy. J Am Coll Surg 192:726–734
18. Pisters PW, Hudec WA, Hess KR, Lee JE, Vauthey JN, Lahoti S et al (2001) Effect of preoperative biliary decompression on pancreaticoduodenectomy-associated morbidity in 300 consecutive patients. Ann Surg 234:47–55
19. Martignoni ME, Wagner M, Krähenbühl L, Redaelli CA, Friess H, Büchler MW (2001) Effect of preoperative biliary drainage on surgical outcome after pancreatoduodenectomy. Am J Surg 181:52–59
20. Nagino M, Takada T, Miyazaki M, Miyakawa S, Tsukada K, Kondo S et al (2008) Preoperative biliary drainage for biliary tract and ampullary carcinomas. J Hepatobiliary Pancreat Surg 15:25–30
21. Bassi C, Falconi M, Molinari E, Mantovani W, Butturini G, Gumbs AA et al (2003) Duct-to-mucosa versus end-to-side pancreaticojejunostomy reconstruction after pancreaticoduodenectomy: results of a prospective randomized trial. Surgery 134:766–771
22. Langrehr JM, Bahra M, Jacob D, Glanemann M, Neuhaus P (2005) Prospective randomized comparison between a new mattress technique and Cattell (duct-to-mucosa) pancreaticojejunostomy for pancreatic resection. World J Surg 29:1111–1119
23. Yeo CJ, Cameron JL, Maher MM, Sauter PK, Zahurak ML, Talamini MA et al (1995) A prospective randomized trial of pancreaticogastrostomy versus pancreaticojejunostomy after pancreaticoduodenectomy. Ann Surg 222:580–592

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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.

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## 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

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 esophagogastric 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-$L_3$ 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 $RC_1$ 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 | $n = 35\,472$ | | $n = 1693$ | | $n = 301$ | |
| 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 | $n = 16\,364$ | | $n = 741$ | | $n = 137$ | |
| 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 | $n = 18\,188$ | | $n = 813$ | | $n = 146$ | |
| 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 | $n = 18\,509$ | | $n = 830$ | | $n = 154$ | |
| 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) | $n = 18\,614$ | | $n = 852$ | | $n = 153$ | |
| 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) | $n = 18\,481$ | | $n = 825$ | | $n = 152$ | |
| <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 $R_{15}$ (%) | $n = 10\,794$ | | $n = 487$ | | $n = 106$ | |
| ≤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 (%) | $n = 17\,538$ | | $n = 775$ | | $n = 145$ | |
| <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 ($\times 10^4/mm^3$) | $n = 18\,374$ | | $n = 847$ | | $n = 154$ | |
| <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-$L_3$, 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 $R_{15}$, indocyanine green retention rate at 15 min; LCSGJ, Liver Cancer Study Group o 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 | *n* = 18 317 | | *n* = 809 | | *n* = 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 | *n* = 5 436 | | *n* = 219 | | *n* = 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 | *n* = 4 731 | | *n* = 160 | | *n* = 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 | *n* = 3 410 | | *n* = 94 | | *n* = 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 | *n* = 3 338 | | *n* = 84 | | *n* = 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 | *n* = 18 624 | | *n* = 828 | | *n* = 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) | *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; $Fc\text{-}Inf^-$, absence of cancerous infiltration of the tumor capsule, $Fc\text{-}Inf^+$, 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.

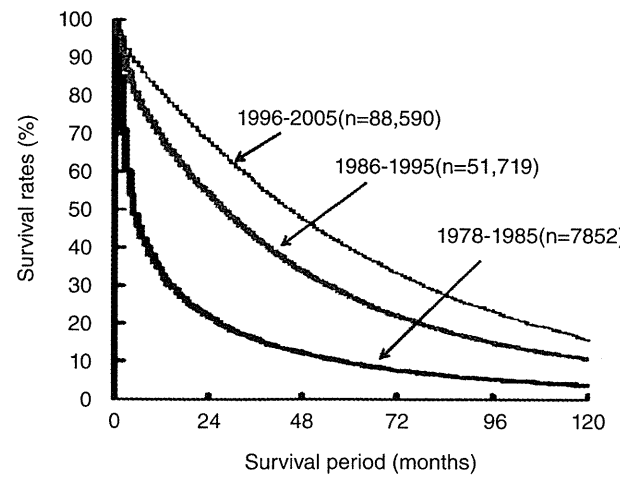


**Figure 1** Cumulative survival rates of newly-registered patients in the 5th to 18th follow-up surveys (1978–2005) divided into three groups (1978–1985, 1986–1995 and 1996–2005) are shown. The 3- and 5-year cumulative survival rates were 15.7%, 9.5% in patients between 1978 and 1985 ($n = 7852$), 42.1%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