ORIGINAL ARTICLE

One Thousand Fifty-Six Hepatectomies Without Mortality in 8 Years

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Background: Despite improvements in diagnostic and surgical techniques, operative mortality associated with liver resection is still greater than 2% in most of the recent studies.

Hypothesis: By refining preoperative and postoperative care and surgical skills, liver resection mortality can be decreased to zero.

Design: Retrospective cohort study to analyze postoperative morbidity and mortality in 1056 consecutive hepatectomies performed at a single medical center during 8 years.

Setting: Tertiary referral center.

Patients: A total of 915 patients who underwent 1056 consecutive hepatic resections: 532 for hepatocellular carcinoma, 262 for other primary and secondary liver malignancies, 57 for biliary tract malignancy, 174 for living donor liver transplantation, and 31 for other benign diseases.

Main Outcome Measures: Operative mortality and morbidity rates.

Results: No operative mortality occurred. Major complications, as defined by postoperative radiologic or surgical intervention, occurred in 3% of patients with hepatocellular carcinoma, 8% with other liver malignancy, 28% with biliary malignancy, and 5% of living donor liver transplantation donors. Using multiple logistic regression, independent risk factors associated with major complications were operative blood loss of 1000 mL or greater for hepatocellular carcinoma and total bilirubin level of 1.0 mg/dL or greater (≥17 μmol/L) and operative time greater than 6 hours for other liver malignancy. No independent factors associated with major complications were identified for biliary malignancy or for living donor liver transplantation donors among the variables investigated in this study.

Conclusions: Liver resection can be performed without mortality provided that it is carried out in a high-volume medical center by well-trained hepatobiliary surgeons paying meticulous attention to the balance between the liver functional reserve and the volume of liver to be removed.

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ALTHOUGH the notion that the liver could be successfully resected was established in the 1950s, liver resection has long been fraught with danger. Many obstacles, such as difficult access because of the high position of the liver under the costal margin, enormous vascularity, no avascular planes, invisible intrahepatic vascular structures concealed by the parenchyma, and a soft, friable structure that denies easy suture ligation, combined to delay the development of liver surgery. It is only during the past 2 decades that liver surgery has advanced dramatically pari passu with the evolution of radiologic imaging, including ultrasound and computed tomography. As a result, the mortality associated with liver resections has decreased to less than 5% in most of the recent studies[1-8] from high-volume medical centers and to 0% for selected indications such as liver metastases.[9,10] In parallel, the indications for liver resection have been extended, that is, repeated liver resection for recurrent colorectal metastases[11,12] and hepatocellular carcinoma (HCC),[13,14] extended hepatectomy for hilar bile duct carcinoma,[15] and living donor liver transplantation (LDLT) in the adult.[16,17] Yet, morbidity and mortality rates in patients with HCC, many of whom have underlying liver cirrhosis,[18-20] and in patients with hilar bile duct carcinoma in whom extensive resection of cholestatic liver often becomes necessary[15,21-25] are still high, and mortality in adult LDLT donors is presumed to be 0.5% to 1.0%.[26]

See Invited Critique at end of article

Table 1. Indications for Hepatic Resection

Indication	Patients, Total No.	Resections, Total No.	Patients With Repeated Hepatectomies, No. 2	3	4	5	Patients With Impaired Liver Function, No.*	Patients With Portal Embolization, No.	Patients With Biliary Drainage, No.	Major Hepatectomies, No.
Primary liver tumor										
Hepatocellular carcinoma	445	532	71	11	5	0	391	15	4	81
Cholangiocellular carcinoma	17	19	2	0	0	0	6	2	1	9
Cystadenocarcinoma	3	3	0	0	0	0	1	0	0	2
Metastatic liver tumor										
Colorectal metastasis	164	213	39	7	2	1	50	11	0	37
Other metastasis	24	27	3	0	0	0	6	1	0	6
Biliary malignancy										
Hilar bile duct carcinoma	47	47	0	0	0	0	37	19	25	45
Gallbladder carcinoma	10	10	0	0	0	0	4	4	3	4
Donor for LDLT	174	174	0	0	0	0	0	0	0	103
Other benign disease	31	31	0	0	0	0	6	0	0	18
Total	**915**	**1056**	**115**	**18**	**7**	**1**	**501**	**52**	**33**	**305**

Abbreviation: LDLT, living donor liver transplantation.
*Patients who showed an indocyanine green retention rate at 15 minutes greater than 10% or those who were compromised with obstructive jaundice.

We applied the same criteria to select patients indicated for hepatectomy and performed more than 1000 hepatectomies during the past 8 years using a consistent strategy. Many patients had been judged inoperable at the initial referring hospitals owing to advanced cancer involvement or impaired liver function. Nevertheless, we did not have a single case of mortality throughout this period. In this study, we review the postoperative course of these hepatectomies related to our policy in each step of preoperative, intraoperative, and postoperative patient management.

METHODS

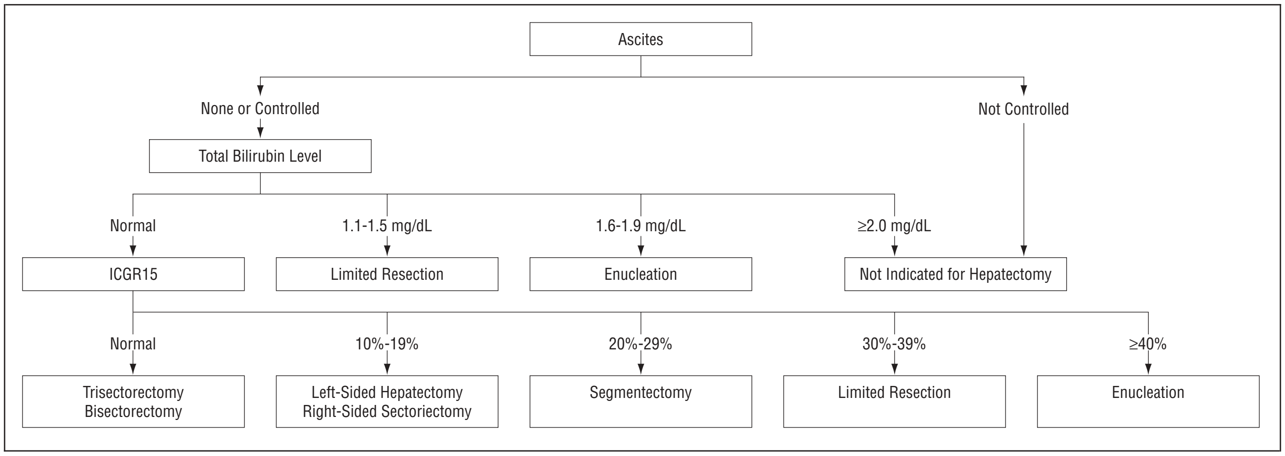
A total of 1056 liver resections were performed in 915 patients in the Division of Hepato-Biliary-Pancreatic Surgery at the University of Tokyo Hospital between October 1, 1994, when one of us (M.M.) headed the division, and May 31, 2002. There were 629 males and 286 females. The mean ± SD patient age at the time of hepatectomy was 62.9 ± 10.3 years (median, 64 years; range, 13-87 years). Indications for resection are listed in **Table 1**. Three hundred one hepatectomies were carried out in patients with liver cirrhosis. All of these patients underwent hepatectomy for the resection of HCC. Obstructive jaundice was a complaint in 33 patients.

PREOPERATIVE EVALUATION AND CARE

In addition to the routine screening test, liver function was evaluated via the indocyanine green retention rate at 15 minutes (ICGR15) in all patients except those with obstructive jaundice.[27] The liver volume to be resected and the liver part to remain after hepatectomy were calculated based on computed tomographic images for all patients in whom the resection of 2 or more Couinaud segments was scheduled regardless of the presence or absence of the underlying liver disease.[28] In patients with HCC, most of whom were compromised with cirrhosis, the safe limit of hepatectomy was determined by a criterion based on 3 variables: the presence or absence of ascites, the total bilirubin level, and the ICGR15 (**Figure**). In patients without ascites and with a normal bilirubin level, the ICGR15 becomes the main determinant of resectability. For example, right-sided hepatectomy can be tolerated if the ICGR15 is less than 10%. For patients with an ICGR15 of 10% to 19%, one third of the liver parenchyma can be resected, which corresponds to left-sided hepatectomy and right-sided paramedian or lateral sectorectomy. When the ICGR15 ranges from 20% to 29%, approximately one sixth of the liver parenchyma can be resected. This resection is roughly equivalent to Couinaud segmentectomy. Limited resection is indicated in patients whose ICGR15 is 30% or more. This decision criterion was also applied to patients without HCC whose liver function as evaluated by the ICG test was mildly impaired. If the scheduled operation corresponded to the removal of more than 60% of the entire hepatic volume in patients with a normal liver, for example, right-sided hemihepatectomy or left-sided trisectorectomy, or removal of 40% to 60% of the entire liver in patients who had slightly impaired liver function (ICGR15 of 10%-19%), preoperative portal vein embolization[29,30] was performed to induce the compensatory hypertrophy of the liver remnant after hepatectomy, thus reducing the risk of postoperative hepatic insufficiency. If the patients were compromised with obstructive jaundice, biliary decompression was carried out. Our policy is to perform unilateral biliary decompression of the hemiliver that is to remain after resection, even when communication between the right and left bile ducts is interrupted by tumor extension, to enhance the process of hypertrophy and reduce the incidence of catheter-related complications. In patients with impaired liver function, including liver cirrhosis, canrenoate potassium was administered daily beginning 3 days before surgery to prevent postoperative sodium retention. The dosage was calculated according to the ICGR15: 100 mg/d for patients with an ICGR15 of 10% to 19%, 200 mg/d for those with an ICGR15 of 20% to 29%, and 300 mg/d for those with an ICGR15 of 30% or greater.

SURGICAL TECHNIQUE AND INTRAOPERATIVE CARE

J-shaped, inverted T-shaped, upper median, and right oblique incisions were made. In right-sided hepatectomy, a thoracoabdominal approach using a J-shaped incision through the ninth intercostal space or a right oblique incision through the eighth intercostal space was routinely applied. The liver was mobilized by dissecting its attachment to the posterior diaphragm, the triangular ligament, or both and by sectioning the falciform ligament. Thorough exploration of the liver via intraoperative ultrasound was performed routinely to detect the nod-



Decision criterion for selection of operative procedures in patients with impaired liver functional reserve. To convert total bilirubin from milligrams per deciliter to micromoles per liter, multiply by 17.1. ICGR15 indicates indocyanine green retention rate at 15 minutes. The Figure is adapted from Makuuchi et al.[27] Copyright 1993, Wiley-Liss. Reprinted by permission of Wiley-Liss Inc, a subsidiary of John Wiley & Sons Inc.

ules that were not identified by preoperative imaging studies and to identify the relationships among the intrahepatic vasculobiliary structures, tumor nodules, and parenchymal transection plane.

In patients with HCC, anatomic resection of tumor-bearing portal branches and corresponding liver parenchyma (Couinaud segmentectomy) for the prevention of vascular invasion–related recurrence was performed if permitted by the liver functional reserve.[27,31] Major resections such as hemihepatectomies were not necessarily indicated even when they were acceptable according to our discussed criterion. In cases of liver metastases, anatomic resection was not indicated as long as an adequate surgical margin was believed to be secured. Conversely, anatomic resection was scheduled in situations such as when a tumor was adjacent to or had invaded major branches of intrahepatic vascular structures, and resection of the vessels combined with removal of the corresponding region became mandatory, or if small multiple metastases were located in the right side of the liver and the removal of these tumors could be carried out more easily by right-sided hemihepatectomy than by multiple nonanatomic resections.[32] For metastases found at the same time as the primary tumor, hepatectomy was carried out simultaneously with the operation to remove the primary tumor. In cases of hilar bile duct tumors, extended right- or left-sided hemihepatectomy combined with caudate lobectomy according to the dominant site tumor location were the standard operations.[33] In LDLT donors, the type of hepatectomy was determined by the ratio of the graft volume to be obtained and the standard liver volume in the recipients.[34]

Liver transection was performed using the clamp crushing method or an ultrasonic dissector according to the surgeon's preference. The total inflow occlusion technique (the Pringle maneuver)[35] or the hemihepatic inflow occlusion technique[36] was applied in principle. Liver resections without any inflow occlusion were also performed sporadically. Inflow occlusion was applied in an intermittent manner, with 15 minutes of occlusion alternated with 5 minutes of reperfusion. During parenchymal transection, the round ligament was pulled ventrally and caudally to better expose the diaphragmatic surface and to decrease the hepatic venous pressure in the transection plane. The operating table was tilted in the right anterior oblique position for right-sided hepatectomy and in the left anterior position for left-sided hepatectomy. A sufficient level of anesthesia was maintained, an adequate dose of muscle relaxant was given, and the tidal volume of the ventilation was reduced to 30% to 40% of the standard volume in an attempt to decrease thoracic pressure. By using a combination of anesthesia and early intraoperative fluid restriction, central venous pressure was controlled below 5 cm H_2O to reduce venous hemorrhage during transection. Intraoperative fluid administration was set at a mandatory rate of 4.5 to 5.0 mL/kg per hour for patients with liver cirrhosis and 5.0 to 7.0 mL/kg per hour for those without liver cirrhosis.

During surgery, fresh frozen plasma, either autologous or homologous, was administered at a rate that exceeded the amount of blood loss by 10% to 20%. Whole blood was not transfused unless the amount of bleeding exceeded 1500 mL or the hematocrit value became less than 30% during surgery or less than 20% on postoperative days. A silicone tube was left along with each cut surface and was connected to a closed drainage system.

POSTOPERATIVE CARE

Immediately after surgery, blood discharge from the drain was monitored carefully; if it exceeded 100 mL/h, emergency surgery was performed. The amount of protein lost in the ascitic discharge was calculated and substituted by fresh frozen plasma to maintain the serum total protein value at 6.0 g/dL, which usually resulted in a dosage of 15 mL/kg per day of fresh frozen plasma in patients with cirrhosis. Canrenoate potassium was administered to reduce the ascitic discharge and to maintain the urine output regardless of whether they were compromised with ascites before or after surgery. Furosemide was given if there was a water retention tendency or if ascites could not be controlled solely by administration of canrenoate potassium. Patients with cirrhotic livers received a total fluid infusion of up to 40 mL/kg per day, compared with 45 mL/kg per day in those without cirrhosis. Histamine blockers were administered routinely during hospitalization. The thoracic tube was removed 2 to 4 days after surgery, when the amount of discharge decreased to less than 200 mL/d. Pleural effusion was checked routinely thereafter, and thoracocentesis was performed when effusion was detected. The abdominal drainage fluid was submitted for bacterial culture, and its bilirubin and protein levels were checked twice a week. The abdominal drainage tube was left for at least 1 week and then was removed by withdrawing it 2 to 3 cm daily after aseptic fluid discharge was confirmed. When the bilirubin level in the drainage fluid was more than twice that in the serum, removal of the drain was stopped and it was irrigated until the bilirubin level decreased to equal that of the serum. When the patient had a fever, the intra-abdominal space close to the raw surface of the remnant liver was investigated by ultrasound or computed tomography to determine whether there was any fluid collection. Any ab-

Table 2. Operative Data for 1056 Hepatic Resections*

Variable	HCC Group (n = 532)	Other Liver Malignancy Group (n = 262)	Biliary Malignancy Group (n = 57)	LDLT Donor Group (n = 174)	Other Benign Diseases Group (n = 31)
Operative time, min	360 (90-1150)	408 (100-1035)	668 (245-1065)	540 (315-1495)	333 (75-1030)
Blood loss, mL	635 (15-8200)	578 (0-6650)	913 (80-3136)	459 (35-2000)	580 (17-2100)
Red blood cell transfusion rate and amount, % (range)	6.9 (0-3200)	9.5 (0-2000)	8.9 (0-840)	0	0

Abbreviations: HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation.
*Data are expressed as median (range) except where indicated otherwise.

scess was drained percutaneously under ultrasound guidance. When the abscess cavity could not be drained percutaneously because of its location, although its drainage was thought to be mandatory, another laparotomy was performed. Bile leakage often follows drainage of an abscess at the site of liver resection. Management of the drain in such cases was performed in the manner described earlier in this paragraph.

OPERATIVE MORTALITY AND MORBIDITY

Operative mortality included intraoperative death, death within 30 days of surgery, and in-hospital death. All postoperative complications that affected the outcome or lengthened the hospital stay were considered. Postoperative hepatic failure was defined as a serum bilirubin concentration greater than 5.0 mg/dL (>85 μmol/L), a prothrombin time rate of less than 50% for 3 or more consecutive days, or both. Ascites was defined as drainage of ascitic fluid of more than 2 L/d for more than 3 days, drainage requiring paracentesis after the abdominal drain was removed, or postoperative hospitalization of more than 30 days owing to ascites control. In addition to any clinically evident intra-abdominal infection, patients who showed a positive bacterial culture finding in the drainage fluid were classified as having intra-abdominal infection. Bile leakage was considered when the bilirubin level of drainage fluid exceeded 5.0 mg/dL (>85 μmol/L) for more than 7 days or when intra-abdominal fluid collection showed a bilirubin level greater than 5.0 mg/dL (>85 μmol/L) after the puncture. Complications were defined as major when they resulted in organ failure, required another surgery or radiologic intervention, or required a red blood cell transfusion for any kind of postoperative bleeding; complications such as pleural effusion, wound infection, and biliary leakage healing spontaneously were classified as minor.[8]

DATA PRESENTATION AND STATISTICAL ANALYSES

Results are expressed as median (range). Operative data and complications were demonstrated and analyzed, classifying patients into 5 groups considering characteristics specific to each group: patients with HCC in whom some extent of liver functional impairment, if not cirrhosis, was presumed (HCC group); patients with primary and secondary malignant liver tumors other than HCC in whom no underlying liver disease can be presumed (other liver malignancy group); patients with biliary tract malignancy such as hilar bile duct or gallbladder carcinoma in whom biliary tract resection and reconstruction was an essential component of the operation and most of whom were compromised with obstructive jaundice (biliary malignancy group); LDLT donors whose general condition, including liver function, was completely within the reference range (LDLT group); and patients with other benign liver disease (other benign disease group).

In the analyses, comprehensive correlations between various perioperative variables and the occurrence of postoperative complications were investigated in the first 4 groups separately. The analysis was not performed in the other benign disease group because of the small number of hepatectomies and heterogeneous characteristics within the group. Various kinds of complications were grouped together, and patients were classified as those experiencing complications or those not experiencing complications. Variables to be analyzed were patient baseline characteristics such as age and sex, liver functional variables such as ICGR15 and total bilirubin values, operative variables such as operative time and blood loss, and other variables of clinical importance. A variety of variables were analyzed in an exclusive group-specific manner taking the characteristics of the group into account, for example, the presence or absence of cirrhosis and portal hypertension in the HCC group. Conversely, a variety of variables were excluded from analyses in a specific group, for example, ICGR15 and total bilirubin values from the biliary malignancy group since ICG tests were generally not performed owing to the presence of obstructive jaundice, and an operation was performed when the bilirubin value became less than 2 mg/dL (<34 μmol/L) after biliary decompression. All categorical or continuous variables were analyzed as dichotomous variables: the most appropriate cutoff point was chosen on the basis of the clinical relevance and according to the distribution and therefore was not necessarily consistent among the different groups. The risk of morbidity independently attributable to each variable was estimated using multiple logistic regression analyses and is expressed by an odds ratio (OR). Statistical significance was set at $P<.05$. Statistical analyses were performed using statistical software (JMP; SAS Institute Inc, Cary, NC).

RESULTS

Operative data and postoperative complications in 1056 hepatectomies are given in **Table 2** and **Table 3**, respectively. No kind of homologous blood transfusion was required in LDLT donors except in 1 donor who required fresh frozen plasma transfusion after surgery. In other patients, the overall rate of red blood cell transfusion was 6.2%.

There was no mortality during surgery, within 30 days of surgery, or during the same hospital admission.

Overall morbidity was 39.0% and major morbidity was 5.6%. Postoperative surgical intervention was required in 2.5% of hepatectomies. Results of multivariate logistic regression analyses to estimate independent relative risk for the overall and major complications are given in **Tables 4**, **5**, **6**, and **7**. In the HCC group, variables related to overall complications were blood loss greater than or equal to 1000 mL (OR, 2.72; 95% confidence interval [CI], 1.62-4.62) and thoracotomy (OR, 1.76; 95% CI, 1.13-2.74) (Table 4). Operative time greater than 6 hours was a marginally significant variable ($P=.07$), with an OR of 1.56 (95% CI, 0.97-2.52). A variable related to

Table 3. Postoperative Complications in 1056 Hepatic Resections

	HCC Group (n = 532)	Other Liver Malignancy Group (n = 262)	Biliary Malignancy Group (n = 57)	LDLT Donor Group (n = 174)	Other Benign Diseases Group (n = 31)
Complications, No.					
Pleural effusion	106	55	12	18	3
Bile leak	48	26	9	11	3
Intra-abdominal abscess	45	23	12	5	2
Atelectasis	42	16	1	5	2
Wound infection	26	12	3	1	1
Pneumonia	10	3	1	0	0
Intra-abdominal bleeding	2	5	2	0	0
Gastrointestinal tract bleeding	2	1	0	2	0
Cholangitis	1	0	6	0	0
Hepatic failure	1	0	0	0	0
Ascites	16	0	0	0	0
Others	1	2	0	7	0
Total	**300**	**143**	**46**	**49**	**11**
Patients with complications, No. (%)	208 (39)	108 (41)	31 (54)	43 (25)	10 (32)
Major complications, No. (%)*	15 (3)	20 (8)	16 (28)	8 (5)	0
Surgical intervention, No. (%)	7 (1)	8 (3)	5 (9)	6 (3)	0

Abbreviations: HCC, hepatocellular carcinoma; LDLT, living donor liver transplantation.
*Complications that required radiologic or surgical interventions.

Table 4. Logistic Multiple Regression of Predictive Factors for Postoperative Complications: HCC Group

	Overall Complications		Major Complications	
Preoperative Variable	***P* Value**	**Odds Ratio (95% CI)**	***P* Value**	**Odds Ratio (95% CI)**
Male sex	.39	1.25 (0.76-2.09)	.78	0.82 (0.22-4.02)
Age ≥65 y	.31	0.80 (0.53-1.22)	.11	0.35 (0.08-1.20)
Diabetes mellitus	.98	0.99 (0.61-1.60)	.22	0.27 (0.01-1.48)
Portal hypertension*	.35	1.26 (0.77-2.05)	.72	1.27 (0.31-4.84)
Liver cirrhosis	.92	1.02 (0.65-1.61)	.85	1.14 (0.32-4.31)
ICGR15 >10%	.34	1.27 (0.77-2.12)	.76	0.80 (0.20-3.60)
Albumin level ≤3.5 g/dL	.34	1.27 (0.78-2.08)	.46	1.70 (0.39-6.94)
Total bilirubin level ≥1.0 mg/dL (≥17 μmol/L)	.32	0.75 (0.43-1.31)	.27	0.30 (0.02-1.77)
Prothrombin time rate ≤70%	.69	0.87 (0.43-1.72)	.44	1.96 (0.29-9.68)
Child-Turcotte-Pugh class B	.33	1.52 (0.66-3.57)	.31	0.31 (0.03-3.08)
Major hepatectomy†	.82	1.07 (0.59-1.96)	.28	3.39 (0.54-67.2)
Combined resection‡	.44	1.35 (0.63-2.94)	.65	0.60 (0.03-3.74)
Repeated resection	.72	0.91 (0.55-1.50)	.45	1.65 (0.41-5.71)
Thoracotomy	.01	1.76 (1.13-2.74)	.53	1.51 (0.45-6.01)
Operative time >360 min	.07	1.56 (0.97-2.52)	.62	0.69 (0.15-3.02)
Blood loss ≥1000 mL	<.001	2.72 (1.62-4.62)	.04	4.17 (1.04-17.5)
Blood transfusion	.25	1.72 (0.71-4.53)	.66	0.60 (0.03-4.31)
Inflow occlusion time >60 min	.33	0.79 (0.48-1.27)	.85	1.15 (0.27-4.90)

Abbreviations: CI, confidence interval; HCC, hepatocellular carcinoma; ICGR15, indocyanine green retention rate at 15 minutes.
*Presence of varices, hypersplenism, or hepatofugal portal flow.[37]
†Resection of 2 or more Couinaud segments.
‡Extrahepatic resection performed at the same time as liver resection.

major complications in this group was blood loss greater than or equal to 1000 mL, with an OR of 4.17 (95% CI, 1.04-17.5). In the other liver malignancy group, variables related to overall complications were total bilirubin level greater than or equal to 1.0 mg/dL (≥17 μmol/L) (OR, 2.71; 95% CI, 1.07-7.24) and operative time greater than 6 hours (OR, 2.06; 95% CI, 1.07-4.02) (Table 5). Variables associated with major complications in this group were total bilirubin level greater than or equal to 1.0 mg/dL (≥17 μmol/L) (OR, 7.49; 95% CI, 2.01-28.1) and operative time greater than 6 hours (OR, 3.74; 95% CI, 0.98-16.9), although the significance of the latter was marginal (P=.06). In the biliary malignancy group, prothrombin time rate less than or equal to 80% was related to overall complications (OR, 3.98; 95% CI, 1.02-18.8), and no variables were identified as being associated with major complications (Table 6). In the LDLT group, the present analyses did not identify any variables as being related to overall or major complications (Table 7).

COMMENT

Liver resection has been established as a distinct surgical specialty during the past 2 decades and has been in-

Table 5. Logistic Multiple Regression of Predictive Factors for Postoperative Complications: Other Liver Malignancy Group

	Overall Complications		Major Complications	
Preoperative Variable	***P* Value**	**Odds Ratio (95% CI)**	***P* Value**	**Odds Ratio (95% CI)**
Male sex	.45	1.25 (0.70-2.25)	.27	1.95 (0.63-7.04)
Age ≥65 y	.70	1.12 (0.63-2.01)	.25	1.87 (0.64-5.51)
Diabetes mellitus	.69	1.20 (0.49-2.86)	.14	2.70 (0.68-9.82)
ICGR15 >10%	.73	1.12 (0.57-2.18)	.73	0.81 (0.22-2.64)
Albumin level ≤3.5 g/dL	.76	1.19 (0.39-3.73)	.42	0.33 (0.01-2.95)
Total bilirubin level ≥1.0 mg/dL (≥17 μmol/L)	.04	2.71 (1.07-7.24)	.002	7.49 (2.01-28.1)
Prothrombin time rate ≤80%	.76	1.13 (0.51-2.47)	.35	0.36 (0.02-2.12)
Major hepatectomy*	.46	0.76 (0.37-1.57)	.25	2.38 (0.61-12.5)
Combined resection†	.24	1.55 (0.74-3.24)	.17	0.29 (0.03-1.38)
Repeated resection	.28	0.69 (0.35-1.33)	.22	0.46 (0.12-1.51)
Thoracotomy	.48	1.23 (0.69-2.20)	.82	0.88 (0.30-2.74)
Operative time >360 min	.03	2.06 (1.07-4.02)	.06	3.74 (0.98-16.9)
Blood loss ≥1000 mL	.26	1.56 (0.72-3.41)	.59	0.66 (0.13-2.91)
Blood transfusion	.42	0.65 (0.22-1.86)	.29	2.67 (0.39-16.1)
Inflow occlusion time >60 min	.49	1.25 (0.66-2.34)	.49	1.49 (0.47-4.73)

Abbreviations: CI, confidence interval; ICGR15, indocyanine green retention rate at 15 minutes.
*Resection of 2 or more Couinaud segments.
†Extrahepatic resection performed at the same time as liver resection.

Table 6. Logistic Multiple Regression of Predictive Factors for Postoperative Complications: Biliary Malignancy Group

	Overall Complications		Major Complications	
Preoperative Variable	***P* Value**	**Odds Ratio (95% CI)**	***P* Value**	**Odds Ratio (95% CI)**
Male sex	.27	2.07 (0.57-8.07)	.18	3.51 (0.64-29.1)
Age ≥65 y	.45	0.61 (0.17-2.25)	.63	0.69 (0.15-3.30)
Diabetes mellitus	.34	3.19 (0.37-69.7)	.56	1.84 (0.22-15.8)
Prothrombin time rate ≤80%	.05	3.98 (1.02-18.8)	.92	1.10 (0.87-19.7)
Combined resection*	.95	1.05 (0.22-5.11)	.19	2.81 (0.12-7.80)
Thoracotomy	.24	2.06 (0.62-7.15)	.49	0.53 (0.64-14.8)
Operative time >720 min	.64	1.43 (0.32-6.50)	.17	2.97 (0.07-3.23)
Blood loss ≥1000 mL	.93	0.94 (0.23-3.69)	.08	3.94 (0.64-15.6)

Abbreviation: CI, confidence interval.
*Extrahepatic resection performed at the same time as liver resection, excluding biliary tract resection.

Table 7. Logistic Multiple Regression of Predictive Factors for Postoperative Complications: LDLT Group

	Overall Complications		Major Complications	
Preoperative Variable	***P* Value**	**Odds Ratio (95% CI)**	***P* Value**	**Odds Ratio (95% CI)**
Male sex	.92	0.96 (0.46-2.06)	.34	2.28 (0.46-16.7)
Age ≥65 y	.72	1.15 (0.54-2.44)	.62	1.47 (0.31-7.09)
Total bilirubin level ≥1.0 mg/dL (≥17 μmol/L)	.45	1.54 (0.47-4.64)	.28	2.71 (0.34-15.1)
Right-sided hemiliver graft*	.78	0.76 (0.09-5.09)	.80	1.70 (0.05-65.1)
Thoracotomy	.10	5.26 (0.79-45.6)	.75	1.97 (0.05-75.8)
Blood loss ≥500 mL	.56	1.25 (0.59-2.63)	.34	0.45 (0.06-2.10)

Abbreviations: CI, confidence interval; LDLT, living donor liver transplantation.
*Odds ratio of right-sided hemiliver graft to other kinds of grafts (left-sided hemiliver, right lateral sector, and left lobe).

creasingly performed in high-volume medical centers by specialized surgeons. These medical centers have reported their experiences with more than 100 hepatectomies in patients with hilar bile duct carcinoma,[15] more than 300 hepatectomies in those with HCC,[38] and even more than 1000 hepatectomies in those with metastatic liver tumors of colorectal origin.[39] The most striking characteristics of the present series of 1056 hepatectomies in this context are the low rate of liver failure (1 of 1056 hepatectomies) and the zero mortality. A variety of lessons can be learned from this experience regarding strategies to perform hepatic resection safely.

Liver failure is one of the most dreadful complications of liver resection, and this concern is more profound in patients with liver cirrhosis because hepatectomy results in removal of functional liver tissue from an organ that already has marginal function. The extent of resection and the degree of baseline functional impairment are the main independent risk factors for postoperative complications, including liver failure. Our decision criterion denotes that hepatectomy was not indicated in patients who show any sign of decompensated cirrhosis, as reflected in an elevated bilirubin level or uncontrollable ascites. The Child-Turcotte-Pugh (CTP) classification, originally proposed for deciding operative indications for portal hypertension, has been applied widely for evaluating liver functional reserve in patients with chronic liver disease.[40,41] However, this classification does not indicate how much liver parenchyma can be removed in patients with associated chronic liver disease. In the present series of patients with HCC, 80% and 20% of patients were classified into CTP classes A and B, respectively. However, ICGR15 values in CTP class A patients showed a wide range. According to our decision criterion, a hepatectomy of more than 50% would have been theoretically possible in 26% of CTP class A patients, a one-third hepatectomy in 45%, a one-sixth hepatectomy in 13%, limited resection in 15%, and enucleation in 1%. Incorporation of the ICG clearance test gives a more refined criterion for the indication of hepatectomy than the conventional CTP classification. Other investigators[3,20,42] have also emphasized the practical relevance of the ICG test. Bruix et al[43] insisted that the presence of portal hypertension is a major risk factor for postoperative complications. In the present series, the presence of portal hypertension was not a contributing factor to the overall postoperative complications in patients with HCC. Investigating its relation to each kind of complication separately, portal hypertension is a risk factor for postoperative ascitic complications (OR, 16.2; 95% CI, 3.63-71.93) (Fisher exact test). These patients' ascitic complication could be controlled by conventional means.

Postoperative liver failure is also a matter of concern in patients with hilar bile duct carcinoma because extensive hepatic resection, mostly an extended right-sided hemihepatectomy, is preferable in terms of radical tumor excision, although most of them experience cholestasis-induced impairment of liver function.[15,21-25] In fact, the incidence of liver failure after hepatectomy for hilar bile duct carcinoma has been reported to range from 2.5% to 29%, with overall surgical mortality ranging from 2.3% to 14% (median, 9.5%).[15,21-25] Despite cholestasis being a well-known risk factor associated with liver surgery,[5,44] several controlled studies[45-47] have shown that preoperative biliary drainage offered no effect in reducing morbidity and mortality rates. However, these studies included only a few major hepatic resections, and a major disadvantage of biliary drainage in these studies was catheter-related infections, the rate of which increases with the number of stents.[22] We claim that biliary drainage carried out with technical expertise is an essential preoperative maneuver and that only a hemiliver to remain after hepatectomy should be drained.

We conduct volumetric measurement of the remaining liver after hepatectomy for all cases in which the resection of 2 or more Couinaud segments was scheduled regardless of whether the patients were presumed to have underlying liver disease. Because the ratios of left- and right-sided hemiliver and each sector volume to total liver volume varies considerably among individuals,[48] especially after partial resection of the liver, the amount of liver parenchyma to be removed cannot be predicted simply by the type of scheduled operation. Based on the liver volumetric data thus obtained, we indicated portal vein embolization for patients in whom the liver volume ratio to remain after hepatectomy was less than 40%. Fan et al[49] reported that 70% of hepatectomies can be carried out safely on the basis of their experience of donor hepatectomies of LDLT. We consider this 10% difference to be a safety margin. On the other hand, portal vein embolization was not indicated in 45% of patients undergoing right-sided hemihepatectomy in the present series because liver volumetry revealed that the major part of the right-sided hemiliver was occupied by the tumor or that the liver was already atrophied by portal venous branch occlusion.

Likewise, we routinely perform the ICG test on all patients in whom hepatectomy was scheduled. Twenty-four percent of patients in the other liver malignancy group had an ICGR15 exceeding the reference range vs 0% in the LDLT group. These results indicate that patients with a malignant liver tumor, although not associated with underlying liver disease, may have some extent of liver functional impairment presumably because of advanced age, previous chemotherapy, and tumor burden and that the precise estimation of liver functional reserve is a mandatory preoperative step.

Minimization of intraoperative blood loss is a widely accepted goal since the amount of blood loss and blood transfusion have been shown to adversely affect patient outcome.[50,51] We routinely applied an inflow occlusion technique, either totally or selectively, to all kinds of hepatectomies in an intermittent manner. Although recent randomized studies[52,53] have shown that the inflow occlusion technique is a method that safely reduces the amount of bleeding during parenchymal resection and that an intermittent manner is superior to a continuous manner, the upper limit of total occlusion time that can be applied safely is a matter of debate. Clavien et al[54] insisted that continuous occlusion preceded by preconditioning is preferable to intermittent occlusion. We constantly applied an intermittent occlusion technique. Furthermore, on every occasion when the integrated occlusion time exceeds 60 minutes, we alternated a 10-minute reperfusion interval instead of 5 minutes based on our own experience. In the present series, the occlusion time exceeded 60 minutes and 90 minutes in 46% and 23% of patients undergoing liver resection under the inflow occlusion technique, respectively. The maximum length of the occlusion was 330 minutes for patients without cirrhosis and 210 minutes for those with cirrhosis without any adverse effect to the liver integrity as evaluated by liver function tests. Feasibility of the prolonged duration of intermittent occlusion alternated by a sufficient reperfusion interval can never be underestimated in the present era, when hepatectomy for multiple liver metastases of colorectal origin or minor anatomic resections such as segmentectomies are frequently carried out. Both procedures are complex and require precision. In many cases, the surface of the transected parenchyma is greater and the parenchymal transection time is longer than with classic major hemihepatectomies.

The necessity of thoracotomy has been argued for a long time. We routinely adopted a thoracoabdominal approach through a J-shaped incision for right-sided hepatectomy. With this incision, gentle but adequate mobilization of the liver can be achieved easily, and the surgical field, including the retrohepatic inferior vena cava and hepatic veins, can be just in front of the surgeon. In addition, the right lobe of the liver can be lifted together with the diaphragm using the surgeon's left hand in the pleural cavity, and the patency of the right hepatic vein can be controlled by clamping this vein with the fingers of the surgeon's left hand if necessary. All these advantages in controlling hepatic venous pressure are important when considering the necessity of total vascular exclusion, another issue of debate for a long time.[55,56] In many patients in our series, the tumor was located in the caudate lobe or involvement of the inferior vena cava was suspected. Nevertheless, total vascular exclusion became necessary in a single patient in whom tumor thrombus from liver metastases from gastrointestinal leiomyosarcoma was present in the inferior vena cava.[57] Thoracoabdominal incisions have been thought to be associated with an increase in pulmonary complications. In the present series, the incidence of pulmonary complications such as pleural effusion and atelectasis was higher when patients underwent thoracotomy. The OR in patients overall was 3.2 (95% CI, 2.32-4.43) (Fisher exact test) and in patients with HCC was 3.0 (95% CI, 1.91-4.67), and this contributed to the increased incidence of overall complications in this group. These morbidities were minor and well managed. Investigating the effect of thoracotomy exclusively in its relation to the occurrence of pneumonia, it was no longer a contributing factor. We believe that the marked advantages obtained by thoracotomy compensated well for these minor morbidities.

The necessity of the drain placement in liver surgery is another matter of debate. Fong et al[58] argued against its effectiveness. A small but persistent amount of bile leakage from the cut surface is a unique but common phenomenon in liver surgery. In many patients in the present study, the drainage tube was removed without evoking any clinical symptoms, and the discharge subsided within a week and was not counted as a bile leak, whereas in other cases it persisted for a prolonged period and drain removal was postponed until 3 to 4 weeks after surgery, although the patients remained asymptomatic. We believe that in the absence of drains, ultrasound-guided puncture or another laparotomy would have been necessary in many of these patients owing to bile collection and subsequent infection. Drain placement is a mandatory procedure in liver resection, but the drain should be placed in a proper position to be effective.

Another variable that may be related to the postoperative morbidity but that could not be addressed based on the present results is the effect of hospital volume. Since the landmark article by Luft et al[59] in 1979 on the effect of volume on outcomes after high-risk surgical procedures, several researchers[60-62] have highlighted this volume-outcome effect in respective surgical procedures, including esophagectomy, pancreaticoduodenectomy, liver resection, and liver transplantation. In addition to the surgical expertise of one consultant surgeon (M.M.) who has performed more than 2000 hepatectomies, a multidisciplinary approach and active postoperative management 7 days a week might be important factors attributable to the present outcome achieved in a single high-volume medical center.

In conclusion, with the evolution of surgical technique and perioperative care, liver resection can be performed without mortality given that it is carried out in a high-volume medical center by well-trained hepatobiliary surgeons paying meticulous attention to the balance between the liver functional reserve and the volume of liver to be removed.

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Invited Critique

Today there is a heightened focus on mortality and cost as related to hospital and individual surgeon volumes for increasing numbers of major operative procedures. As such, liver resection has been included in the outcomes' spotlight.

In this article by Imamura et al, the authors present their mortality and morbidity results from 915 patients undergoing 1056 hepatic resections. Clearly, the authors are to be lauded for their excellent operative outcomes in this large, heterogeneous group of patients. The results speak for themselves: postoperative liver failure in only one patient; single-digit major complication rates in patients with hepatocellular carcinoma, many of whom had concurrent cirrhosis; and no operative mortality in the entire series.

After reviewing this study, the liver resectionist should take particular note of the authors' preoperative algorithm for deciding on extent of resection. It is this systematic approach to these patients that separates this article from other reports and, in fact, allowed the authors to experience a postoperative hepatic failure rate of only 0.095%. Unfortunately, the indocyanine green retention study, utilized so effectively by the authors as a measure of hepatic function, is not widely employed in the United States. Many of the authors' intraoperative and postoperative techniques are currently used by other liver surgeons, having been described elsewhere in the literature.

However, without detracting from the excellent results, the reader should take into consideration that the authors do not enumerate the actual types of resections performed. While they do report the number of "major hepatectomies" within each group (described in Table 1), it would have been more instructive to have included the number and extent of resections. It is not surprising that major hepatectomies accounted for only 15% of resections in hepatoma patients, but the rate of 18% in the 240 patients with metastatic liver tumors is lower than in other reported series.

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