

Zero mortality in more than 300 hepatic resections: validity of preoperative volumetric analysis

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Abstract

Purpose We reviewed a series of patients who underwent hepatic resection at our institution, to investigate the risk factors for postoperative complications after hepatic resection of liver tumors and for procurement of living donor liver transplantation (LDLT) grafts.

Methods Between April 2004 and August 2007, we performed 304 hepatic resections for liver tumors or to procure grafts for LDLT. Preoperative volumetric analysis was done using 3-dimensional computed tomography (3D-CT) prior to major hepatic resection. We compared the clinicopathological factors between patients with and without postoperative complications.

Results There was no operative mortality. According to the 3D-CT volumetry, the mean error ratio between the actual and the estimated remnant liver volume was 13.4%. Postoperative complications developed in 96 (31.6%) patients. According to logistic regression analysis, histological liver cirrhosis and intraoperative blood loss >850 mL were significant risk factors of postoperative complications after hepatic resection.

Conclusions Meticulous preoperative evaluation based on volumetric analysis, together with sophisticated surgical techniques, achieved zero mortality and minimized intraoperative blood loss, which was classified as one of the most significant predictors of postoperative complications after major hepatic resection.

Keywords Hepatic resection · Complication · Mortality · Volumetry

Introduction

Hepatic resection is often performed for hepatocellular carcinoma (HCC) in patients with liver cirrhosis. The mortality and morbidity rates after hepatic resection have declined in recent years because of improved patient selection, surgical techniques, and perioperative care [1–4]. Many major centers have reported good perioperative results after hepatic resection for HCC, with operative mortality rates typically <2% in the high-volume centers in Japan [5, 6], and 5–8% in other countries [7, 8]. The mortality associated with adult living donor liver transplantation (LDLT) is presumed to be 0.5–1.0% [9]; however, the incidence of postoperative complications remains high in comparison with other types of general surgery.

In the 1980s, hepatic resection in the presence of cirrhosis was associated with high mortality, in the range of 10% at our institution [10, 11]. Since then, efforts have been made to reduce both mortality and morbidity: since 1994, nafamostat mesilate has been used perioperatively for hepatic resections, to stabilize the coagulant and fibrinolytic systems; since 1997, an intraoperative bile leakage test has been carried out routinely [12] and a selective hepatic vein-clamping method has been used in all hepatic resections; since 2000, steroid therapy has been given preoperatively to reduce surgical stress [13]. Surgical candidates, especially for right hepatectomy, were selected carefully based on a preoperative volumetric analysis [14] and donor selections were done using volumetric analysis based on 3-dimensional computed tomography (3D-CT) [15]. Based on these technical refinements and

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postoperative managements, we have performed about one hundred hepatic resections per year and achieved a hospital mortality rate of 0% in the recent year. In this study, we reviewed a series of patients who underwent hepatic resection at our institution, and investigated the risk factors for postoperative complications after hepatic resection for liver tumor and in donors of LDLT.

Methods

Patients

Between April 2004 and August 2007, 304 liver resections were performed at the Department of Surgery and Science, Kyushu University Hospital, without simultaneous procedures such as biliary reconstruction, colorectal resection, or stoma closure. Table 1 lists the indications for hepatic resection. Forty-three patients underwent intraoperative ablation therapy in addition to liver resection, 66 patients underwent right hepatectomy, and 120 patients were donors for LDLT. There were 208 men and 96 women (mean age 53.1 ± 18.5 years, range 19–85 years).

Before surgery, cardiac, pulmonary, and renal functions were evaluated by electrocardiogram, chest X-ray, and blood tests to exclude major disease, which could greatly increase the risk of hepatic resection. Hepatic function was also evaluated by the Child–Pugh classification [16] and the indocyanine green retention rate at 15 min (ICGR15). The definition of diabetes mellitus was a fasting serum glucose level above 126 mg/dL, abnormal results for a 75 g oral glucose tolerant test, or the need for insulin or an oral antihyperglycemic drug to control glucose levels. Preoperative multidetector helical computed tomography (MDCT) images were created with 2-mm thick slices represented on computed tomography (CT) machines. Enhancement was achieved by an intravenous bolus of a contrast nonionic medium (Iopamion, Schering, Erlangen, Germany) at a rate of 5 mL/s. Three-dimensional reconstruction of the liver, remnant liver, and graft was obtained from the MDCT data with Zio M900 (Zio Software Inc., Tokyo, Japan). The indications for hepatic resection and

the operative procedure performed for each patient with liver disease were decided according to the preoperative ICGR15, as described previously [3]. Our criteria for hepatic resection were that ascites was not detected, or that it was controlled with diuretics, and a serum total bilirubin level of <2.0 mg/mL. The extent of resection was based on the ICGR15. Patients with an ICGR15 $\geq 30\%$ were selected for limited resection. Two-thirds of the nontumorous liver parenchyma could be removed if the ICGR15 was $\leq 10\%$, whereas less than one-third could be resected if it was 10–19%. Patients with an ICGR15 of 20–29% received single segmentectomy or less. Donor evaluation and selection for LDLT have been described previously [15, 17]. Briefly, the left lobe (LL) is preferred for the graft and is generally used. The right lobe (RL) is chosen if the estimated LL with the caudate lobe volume of the donor is $<35\%$ of the standard liver volume of the recipient. If the remnant liver volume is $<35\%$ of the total liver volume, the person will be excluded as a donor candidate.

Surgical procedures

Intraoperative ultrasonography was performed to mark the plane of transection. In major liver resection, extraparenchymatous control of the hepatic artery and the portal and hepatic veins was attempted. Parenchymal transection was performed using the Cavitron Ultrasonic Surgical Aspirator (CUSA system, Valleylab Inc., Boulder, CO, USA) and the monopolar dissecting sealer (TissueLink, TissueLink Medical Inc.). Inflow vascular control was performed with an intermittent hemi- or total Glisson's sheath occlusion (Pringle maneuver) and, if required, with a selective hepatic vein-clamping method. Inflow occlusion was applied intermittently with 15 min of occlusion alternating with 5 min of reperfusion. A bile leakage test was performed using an indocyanine green injection via a cannula placed inside the common bile duct through the cystic duct after transection. Two closed-suction drainage tubes were usually placed at the Winslow's foramen, near the raw surface of the liver.

Postoperative management

Antibiotics were continued for 24 h postoperatively. Oral intake was started on postoperative day (POD) 1 and the drainage tubes were usually removed on POD 3 if no abnormality was observed. All patients underwent routine CT on POD 7 to assess vessel and parenchymal integrities. Operative mortality was defined as intraoperative death, death within 30 days of surgery, or in-hospital death.

Surveillance for complications was carried out prospectively by physicians. The total bilirubin level of the drainage fluid was measured postoperatively, and bile

Table 1 Indications for hepatic resection

	Number of patients
Hepatocellular carcinoma	145 (47.7%)
Donor for LDLT	120 (39.5%)
Metastatic liver tumor	24 (7.8%)
Cholangiocellular carcinoma	9 (3.0%)
Other	6 (2.0%)

LDLT living related liver transplantation

leakage was diagnosed when the level exceeded 5.0 mg/dL and continued for more than 7 days [18]. Ultrasonography-guided paracentesis or insertion of a second drainage tube was performed in patients with an intra-abdominal collection accompanied by fever or a raised white blood cell count. A sample of the intra-abdominal collection was sent for bacteriological culture. Pleural paracentesis was performed to relieve symptoms if the patient had a fever or dyspnea and severe pleural effusion. Local wound complications included wound infection, delayed stitch-out, or keloid formation. Postoperative intra-abdominal bleeding was considered when bleeding from the drainage tubes exceeded 100 mL/h. In this study, postoperative complications were classified as Clavien's grade II or more [19]. Postoperative liver failure after hepatic resection was diagnosed according to the Belghiti 50–50 criteria (serum bilirubin >50 $\mu\text{mol/L}$ (2.9 mg/dL) and prothrombin ratio <50%) on POD 5 [20].

Statistical analysis

Categorical variables were compared using the Chi-square test and Fisher's exact test. Continuous variables are presented as the median (range) and compared using the Mann–Whitney *U* test. Logistic regression analysis was performed to identify the independent variable for postoperative complications. Differences were considered significant at $p < 0.05$. All statistical analyses were performed using the StatView 5.0 (Abacus Concepts, Berkeley, CA, USA).

Results

Ninety-six of the 304 (31.6%) patients suffered postoperative complications, as detailed in Table 2. The most

Table 2 Postoperative complications in the 304 patients

Complications	Number of patients
Local wound complications	63 (20.7%)
Bile leakage	18 (5.9%)
Pleural effusion needing aspiration	11 (3.6%)
Intra-abdominal infection	9 (3.0%)
Intra-abdominal collection needing aspiration	7 (2.3%)
Ileus/intestinal obstruction	5 (1.6%)
Pneumonia	3 (0.99%)
Intra-abdominal bleeding	1 (0.33%)
Liver failure	0 (0%)
Hospital death	0 (0%)
No. of patients with complications	96 (31.6%)

common was local wound complications, followed by bile leakage. There was no mortality during surgery, within 30 days of surgery, or during the same hospital admission. Only one patient died of rapid growth of recurrent HCC on POD 64, after re-admission to our hospital.

We prospectively investigated the relationship between the actual and the estimated remnant liver volume, using 3D-CT volumetry, in 66 patients who underwent right hepatectomy. The mean actual remnant liver volume and the mean estimated remnant liver volume using 3D-CT volumetry were 497 (range 219–909) and 443 cm^3 (range 266–892), respectively. The mean error ratio was 13.4% (range 0.2–59.8; Fig. 1). The mean error ratio was 13.2% (range 0.2–32.7) in the donor group ($n = 48$) and 13.7% (range 1.9–59.8) in the liver disease group ($n = 18$). The error ratio of these two groups was not divided significantly. The mean actual and the mean estimated remnant liver volumes using 3D-CT volumetry for 18 patients with liver disease who underwent right hepatectomy were 348 (range 176–605) and 328 mL/m^2 (range 232–594), respectively. Five of the 18 patients had an estimated remnant liver volume of <250 mL/m^2 , using 3D-CT volumetry, but the actual remnant liver volume in three of these patients was greater than 250 mL/m^2 . Only 1 of 13 patients with an estimated remnant liver volume greater than 250 mL/m^2 on 3D-CT volumetry had an actual remnant liver volume of <250 mL/m^2 . None of these six patients, whose estimated remnant liver volume using 3D-CT volumetry or the actual remnant liver volume was <250 mL/m^2 , had diabetes mellitus.

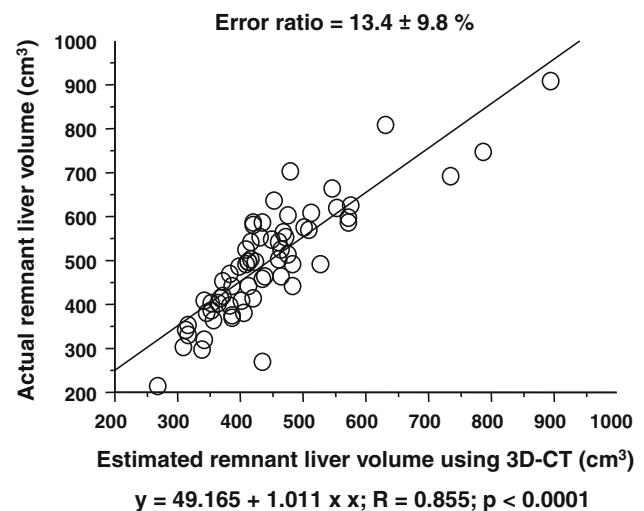


Fig. 1 Relationship between the actual and the estimated remnant liver volumes based on 3D-CT volumetry. The relationship was linear: $y = 49.165 + 1.011 \times x$ ($R = 0.855$, $p < 0.0001$). The mean error ratio was 13.4 ± 9.8%, calculated as follows: error ratio = $|E - A|/A \times 100$ (%). 3D-CT 3-dimensional computed tomography, A actual remnant liver volume (cm^3), E estimated graft volume (cm^3)

Table 3 Clinicopathological data for patients with and without complications

Variables	With complications (<i>n</i> = 96)	Without complications (<i>n</i> = 208)	<i>p</i>
Age (years) ^a	61.5 (20–83)	54.0 (10–85)	0.0108
≥55 years old ^b	64 (66.7%)	99 (47.6%)	0.002
Sex (male/female) ^b	69/27	139/69	0.4268
Positive HBs-Ag ^b	10 (10.4%)	16 (7.7%)	0.5073
Positive HCV-Ab ^b	41 (38.7%)	55 (30.3%)	0.038
Child–Pugh classification ^c			0.7304
A	92 (95.8%)	202 (97.1%)	
B	4 (4.2%)	6 (2.9%)	
Diabetes mellitus ^b	23 (24.0%)	27 (13.0%)	0.0192
Hypertension ^b	28 (29.2%)	45 (21.6%)	0.1493
Type of hepatic resection ^b			0.3256
Major	42 (43.8%)	104 (50.0%)	
Minor	54 (56.2%)	104 (50.0%)	
Donors for LDLT ^b	27 (28.1%)	93 (44.7%)	0.0078
Repeat hepatic resections ^b	13 (13.5%)	25 (12.2%)	0.7119
Intraoperative local ablation therapy ^b	18 (18.8%)	25 (12.2%)	0.1557
Operation time (min) ^a	405.5 (158–634)	395 (150–748)	0.3858
≥490 min ^b	22 (22.9%)	28 (13.5%)	0.0473
Intraoperative blood loss (cc) ^a	600 (90–4800)	550 (33–2482)	0.0728
>850 cc ^b	31 (32.3%)	33 (15.9%)	0.0014
Intraoperative red blood cell transfusions ^b	10 (10.4%)	14 (6.7%)	0.2631
Histological liver cirrhosis ^b	31 (32.3%)	30 (14.4%)	0.0006
Postoperative hospital stay (days) ^a	19 (9–141)	13 (7–62)	<0.0001

Values are expressed as numbers with percentages in parentheses or as the median (range)

HBs-Ag hepatitis B surface antigen, HCV-Ab hepatitis C virus antibody, LDLT living related liver transplantation

^a Mann–Whitney *U* test

^b Chi-square test

^c Fisher's exact test

The clinicopathological data for patients with and without complications are compared in Table 3. Those with complications were significantly older ($p = 0.0047$), a greater proportion had positivity for the hepatitis C virus antibody (HCV-Ab) ($p = 0.0380$), a greater proportion had diabetes mellitus ($p = 0.0192$), a lower proportion were donors for LDLT ($p = 0.0078$), the operation time was

Table 4 Multivariate analysis of risk factors for postoperative complications

Variables	Odds ratio (95% CI)	<i>p</i>
Age ≥55 years old	1.762 (0.633–4.903)	0.2777
HCV (+)	0.904 (0.454–1.801)	0.7748
Diabetes mellitus (+)	1.515 (0.757–3.031)	0.2409
Donor for LDLT (–)	0.941 (0.329–2.696)	0.91
Operation time ≥490 min	1.452 (0.718–2.934)	0.2992
Intraoperative blood loss >850 mL	2.167 (1.166–4.027)	0.0145
Histological liver cirrhosis	2.118 (1.078–4.164)	0.0295

HCV-Ab hepatitis C virus antibody, LDLT living related liver transplantation, CI confidence interval

≥490 min ($p = 0.0473$), intraoperative blood loss was >850 mL ($p = 0.0014$), and a greater proportion had histological liver cirrhosis ($p = 0.0006$). The median postoperative stay in hospital was significantly longer in patients with complications.

Logistic regression analysis of factors including age, positivity for HCV-Ab, diabetes mellitus, donor for LDLT, intraoperative blood loss, operation time, and histological liver cirrhosis revealed that histological liver cirrhosis [odds ratio 2.118 (95% confidence intervals (CI) 1.078–4.164); $p = 0.0295$] and intraoperative blood loss >850 mL [odds ratio 2.167 (95% CI 1.166–4.027); $p = 0.0145$] were independent predictors of a significantly higher rate of postoperative complications after hepatic resection (Table 4).

In the liver tumor group ($n = 184$), histological liver cirrhosis [odds ratio 2.096 (95% CI 1.044–4.206); $p = 0.0373$] and intraoperative blood loss >850 mL [odds ratio 2.735 (95% CI 1.267–5.902); $p = 0.0256$] were independent predictors of a significantly higher rate of postoperative complications after hepatic resection, based on logistic regression analysis. In the LDLT donor group ($n = 120$), no variables were identified as predictive of postoperative complications.

Discussion

The surgical techniques for liver resection have improved greatly in recent years, in parallel with decreased postoperative mortality rates. Many large studies have documented acceptable perioperative results, with operative mortality rates typically lower than 2% in the high-volume centers of Japan [5, 6] and 5–8% in other countries [7, 8]. However, there are few series of hepatic resection with no mortality. Midorikawa et al. [18] reported zero mortality in 277 hepatic resections, without postoperative hepatic insufficiency or hospital death, while Imamura et al. [21]

reported no operative mortality among 1056 hepatic resections, including donors for LDLT, since 1994. In the present study, we achieved zero mortality among 304 patients who underwent hepatic resections. Moreover, none of our patients suffered liver failure or severe infection, which are common causes of postoperative hospital death. Liver failure is one of the most serious complications of liver resection, and patients with liver cirrhosis are at especially high risk because functional liver tissue is resected from an organ with marginal function. Among 80 patients who underwent major hepatic resections of no less than bisegmentectomy for HCC between 1990 and 1996 at our hospital, 7 died of postoperative liver failure within 6 months. All of the patients who died had undergone right hepatectomy, with a remnant liver volume of $<250 \text{ mL/m}^2$. According to another study, the only significant risk factor for liver failure in patients with a remnant liver volume of $<250 \text{ mL/m}^2$ was diabetes mellitus [14]. In this study, 18 of 66 patients who underwent right hepatectomy of the liver had liver disease and 5 of these 18 patients had an estimated remnant liver volume of $<250 \text{ mL/m}^2$, based on 3D-CT volumetry, but none of these 5 had diabetes mellitus. Thus, postoperative liver failure might occur if the estimated remnant liver volume after right hepatectomy of the liver, using 3D-CT volumetry, is $<250 \text{ mL/m}^2$ in patients with diabetes mellitus. We think that the strict preoperative patient selection using our criteria, including preoperative ICGR15 and volumetric analysis, preoperative steroid administration to reduce surgical stress, and the perioperative administration of nafamostat mesilate to stabilize the coagulant and fibrinolytic systems, helped to prevent liver failure in patients undergoing hepatic resections.

Preoperative liver volumetry based on 3D-CT has improved outcomes significantly in comparison with that based on 2D-CT [22]. In fact, the estimated remnant liver volume using 3D-CT volumetry was reported to be associated with an error ratio of 5–25% in comparison with the actual remnant liver volume [23, 24]. In our study, the mean error ratio was 13.4%, which is consistent with other reports. Thus, we need to develop methods to decrease the error ratio [25].

Our study clearly demonstrated that histological liver cirrhosis and intraoperative blood loss $>850 \text{ mL}$ were significant risk factors. Many major centers have published data on mortality and morbidity after hepatic resection for HCC, which usually develops from chronic hepatitis or liver cirrhosis [6–8]. In general, cirrhosis usually causes more problems, including ascites, pleural effusion, septic complications, and liver failure during hepatic resection [26]. Liu et al. [27] reported that underlying liver cirrhosis and intraoperative blood loss $>1500 \text{ mL}$ were independent and significant factors associated with postoperative

morbidity. On the other hand, Chok et al. [28] reported that histological liver cirrhosis did not exist significantly more often in patients with than in those without postoperative complications after hepatic resection for HCC. In the present study, histological liver cirrhosis was an independent risk factor of postoperative complications after hepatic resection for liver tumors and to procure tissue for LDLT from donors with a healthy normal liver. This is compatible with the fact that patients with liver cirrhosis have significantly higher rates of postoperative complications after hepatic resection than those without liver cirrhosis. Recently, transient elastography (FibroScan; Echosens, Paris, France) has become available for the assessment of liver fibrosis as a rapid and noninvasive method of measuring liver stiffness from outside the body [29]. This application might be useful to assess liver cirrhosis preoperatively in patients with chronic liver disease. Intraoperative blood loss is also a well-established risk factor of postoperative complication after hepatic resection [3, 27, 28]. The cutoff intraoperative blood loss volume has been reported as 1500 mL [27]–2000 mL [30]. In the present study, an intraoperative blood loss of $>850 \text{ mL}$ was found to be a significant risk factor after hepatic resection. The Pringle maneuver and a selective hepatic vein-clamping method help control bleeding in hepatic resection [3]. Moreover, we have recently begun using the monopolar dissecting sealer. These devices and techniques probably contributed to decreasing the mean estimated intraoperative blood loss (687 mL; range 33–4800). Therefore, the cutoff value of the intraoperative blood loss scored lower than reported previously. A randomized controlled trial to verify the validity of using the monopolar dissecting sealer during hepatic resection is warranted.

The incidence of postoperative complications after hepatic resection is reported to range from 20 to 55.5% [1, 8, 28]. In the present study, the overall complication rate was 31.6%, with local wound complications being the most common (20.7%). Patients with local wound complications had significantly greater intraoperative blood loss and a greater proportion of these patients had histological liver cirrhosis (data not shown). Intraoperative blood loss reduces the concentration of antibiotics and is thought to predispose to surgical site infection [31]. Underlying cirrhosis and hypoalbuminemia also inhibit normal wound healing [32]. This concurs with our finding that significantly more patients with histological liver cirrhosis suffered local wound complications.

In conclusion, with strict preoperative clinical evaluation based on volumetric analysis, sophisticated surgical techniques, and careful postoperative management, major hepatic resection can be a safe procedure without a significant risk of mortality. According to our findings, patients with histological liver cirrhosis and intraoperative

blood loss >850 mL are at risk of developing postoperative complications.

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