

Original article

Improvement of Post-hepatectomy Hepatic Complications by Applying Predictive Parameters of Preoperative Liver Function

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Short title: Improvement of posthepatectomy complications

This study was undertaken without any financial support. Non-randomized trial.

No conflict of interest.

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Abstract

Background/Purpose To prevent hepatic complications after hepatectomy, it is important to employ preoperative predictive parameters and determine indications of hepatectomy. In the present study, we evaluated risk parameters in patients who underwent hepatectomy from 1994 to 2003, and selected three to modify surgical indications. Using these indications before surgery, we compared the prevalence of postoperative complications in patients who underwent hepatectomy from 2004 to 2008.

Methods We examined 250 consecutive patients who underwent hepatectomy for liver disease. The 1994-2003 results constituted the early period and those from 2004 to 2008 constituted the later period.

Results In the early period, uncontrolled ascites was observed in 78 patients and hepatic failure was observed in 15 of 149 patients. Multivariate analysis identified volume of resected liver ($\geq 50\%$), intraoperative blood loss (≥ 500 ml), prothrombin activity ($< 70\%$), hyaluronic acid level (≥ 200 ng/ml) and LHL15 (< 0.85) as risk factors and the latter three parameters were evaluated as predictors of outcome. Since 2004, we used these three as indication criteria for hepatectomy in addition to ICGR15. Comparisons showed decreases in uncontrolled ascites (23% vs. 38%, $P=0.03$), hepatic failure (4% vs. 11%, $P=0.12$) and the rate of hepatic complications (17% vs. 50%, $P=0.003$) in patients of the later period compared with those of the early group.

Conclusions The use of prothrombin activity, and levels of hyaluronic acid and LHL15, as parameters of functional liver reserve, in selection of candidates for surgery lessened hepatic complications after hepatectomy.

Keywords Liver resection· prognostic parameters· liver function· post-hepatectomy complications.

Introduction

Postoperative morbidity and mortality rates in patients with liver disease have decreased markedly in the last decade due to advances in surgical techniques and improvements in anaesthesia and peri-operative management [1, 2]. However, surgical risk remains a factor in patients with liver dysfunction such as liver cirrhosis and obstructive jaundice and in those undergoing extended hepatic resection [3]. Hyperbilirubinaemia, uncontrolled ascites and intra-abdominal infection are troublesome complications of hepatic resection that could lead to prolonged hospitalisation and even life-threatening hepatic failure [4]. Reducing the incidence of postoperative hepatic complications requires careful preoperative planning and better patient selection using complication-associated parameters such as liver function tests, histopathological examination, and surgical history.

We previously examined the predictive value of assessing complication-specific parameters in patients undergoing hepatectomy [5-7]. We consecutively analysed a decade of past results in 2003 and modified our indications for hepatectomy accordingly. The same operations were then conducted in our institution from 2004 to 2008 using the modified criteria. The present study sought to clarify the efficacy of the modified indications for hepatic resection by analysing surgical results from the pre- and post-modification terms in 250 consecutive patients.

Material and methods

The subjects were 250 consecutive patients with liver injury who underwent hepatectomy in the Division of Surgical Oncology, Department of Translational Medical Sciences, Nagasaki University Graduate School of Biomedical Sciences from 1994 to 2008. They included 189 men and 61 women with a mean age of 64 ± 9 years (\pm SD; range, 28-82 years). The liver diseases warranting hepatic resection were hepatocellular carcinoma in 134 patients, metastatic liver carcinoma in 58, intrahepatic cholangiocarcinoma in 28, gall bladder carcinoma in 10, upper bile duct carcinoma in 12 and benign liver disease in 8 patients. Background liver diseases included chronic viral liver disease in 132 patients with cirrhosis in 62 of these (caused by hepatitis B virus in 75, hepatitis C virus in 51, and both viruses in 6), obstructive jaundice in 26 and fatty liver in 7. Eighty-five patients had normal liver.

Subjects were divided into two groups by the period of study: *the previous term* for the decade from 1994 to 2003, comprising 149 patients; and *the later term* for the 5 years from 2004 to 2008, comprising 101 patients.

In this cohort, 87 patients underwent limited resection, 60 had subsegmentectomy or segmentectomy, 64 underwent lobectomy, and 39 patients were treated by extended lobectomy. Postoperative hepatic dysfunction-associated complications occurred in 91 (36%) patients: persistent ascites or pleural effusion (defined as massive ascites unresponsive to diuretics for more than 2 weeks) in 78 patients and hepatic failure (defined by a total bilirubin of >3 mg/dl on postoperative day 7 or death without other cause) in 19 patients. Four patients died of hepatic failure within 30 days. Six patients experienced both hepatic dysfunction-associated complications and hepatic failure. The Ethics Review Board of our University approved the study protocol.

Clinical data (age and gender), conventional liver function tests (portal pressure, total bilirubin, alanine aminotransferase (ALT), platelet count, total cholesterol and prothrombin

activity)) and surgical data (resected volume, blood loss, and operative procedure) were analysed. Indocyanine green (ICG) was injected intravenously at a dose of 0.5 mg/kg body weight with 15-minute retention rates measured by a photopiece applied to the fingertip (RK-1000, Sumitomo Electric, Tokyo, Japan) without blood sampling [5, 6, 8, 9]. Patients received 3 mg (185 MBq) of ^{99m}Tc -GSA (Nihon Medi-Physics, Nishinomiya, Japan) as a bolus dose into the antecubital vein. The hepatic uptake ratio of ^{99m}Tc -GSA (LHL15) was calculated after injection of ^{99m}Tc -GSA by dividing the liver activity at 15 minutes by heart plus liver activity at 15 minutes (LHL15) [5, 7, 10]. Peripheral blood samples for analysis of hyaluronic acid (HA) levels were also collected early in the morning from every patient who was in a stable condition during hospitalisation [6]. Blood samples were centrifuged at 3000 rpm for 15 min, and serum was stored at -80°C . HA was assayed using a sandwich binding protein assay (SRL, Inc, Tokyo; normal range <50 ng/ml). The Liver Damage Grade based on the ICG retention rate at 15 min (ICGR15) was used instead of encephalopathy in determining the five Child-Pugh classification parameters of the 2000 Liver Cancer Study Group of Japan [11]. The staging and grading scores for hepatic fibrosis and the histologic activity index (HAI) score defined by Knodell et al. [12] were used for histopathological evaluations. Portal pressure was measured by cannulation of the portal trunk during surgery.

In our hospital, the volume of the liver to be resected is estimated before surgery based on ICGR15 results using the formula of Takasaki et al [13]. The liver volume, excluding the tumour (cm^3), is measured by computed tomography (CT) volumetry [14]. Essentially, the planned hepatectomy is performed when the permitted resected volume of the liver is greater than the estimated resected volume of the liver. In cases where the permitted resected volume is less than the estimated volume or the estimated volume is more than 65% in patients with normal liver and 50% in those with cirrhosis, a pre-operative portal vein embolisation (PVE) is performed [7, 15]. Although these ICGR15-based indications have been in force since 2004,

we applied referral hepatic functional parameters to decide the final indication for the extent of hepatectomy as follows: in cases where LHL15 was <0.85 , HA >200 ng/ml and prothrombin activity $<70\%$, the patient was deemed at high risk of severe hepatic complications after hepatectomy. The newly modified indication for hepatic resection applied beyond 2004 stipulated PVE alone, limited hepatectomy or avoidance of hepatectomy for patients with more than 2 of the above 3 risk factors.

Continuous data are expressed as mean \pm SD. Data of different groups was compared using one-way analysis of variance (ANOVA) and examined by Mann-Whitney's U-test. The optimal predictive cut-off value for posthepatectomy complications was determined for each parameter by analyzing receiver operating characteristic (ROC) curves. The Chi-square test was used to compare categorical data and logistic regression analysis was performed to determine the predictive value of risk factors. Potentially predictive variables were identified using a significance level of $P < 0.05$ by univariate analysis. Identified factors were then entered into logistic regression multivariate analysis, and a two-tailed P value < 0.05 was considered significant. Statistical analyses were performed using the STATISTICATM software (StatSoft, Tulsa, OK).

Results

Table 1 shows the relationship between hepatic complications and preoperative liver functional parameters by univariate and multivariate analysis from 1994 to 2003. During this period, uncontrolled ascites was observed in 78 patients (38%) and hepatic failure in 15 (11%). Univariate analysis identified 9 parameters as significant predictive factors between patients with or without hepatic complications. Cut-off values of 8 continuous data were defined by the ROC analysis (Table 1). The statistically significant parameters from the univariate analysis were selected as candidates for multivariate analysis (Table 2). Volume of resected liver ($\geq 50\%$), intraoperative blood loss (≥ 1500 ml), prothrombin activity ($< 70\%$) and HA level (≥ 200 ng/ml) were identified as independent risk factors for postoperative hepatic complications. In addition, LHL15 (< 0.85) tended to be a risk factor, although the *P* value was not significant. Blood loss and resected volume could not be used as preoperative risk parameters for selecting the surgical procedure, leaving preoperative liver function defined by prothrombin activity $< 70\%$, HA level ≥ 200 ng/ml, and LHL15 < 0.85 as supplementary predictive parameters to indicate hepatectomy or extent of hepatectomy based on the ICGR15 result. Since 2004, if more than two of these predictive factors were positive, the decision would be a) inoperable, b) minimisation of the extent of hepatectomy such as limited resection or c) consideration of indication for preoperative PVE in patients who needed major hepatectomy by the new protocol.

The prevalence of hepatic complications under the modified indications for hepatic resection since 2004 was compared to the 1994-2003 results (Fig. 1). Uncontrolled ascites was significantly decreased in the later period compared to the pre-modification series (23% vs. 38%). Hepatic failure in patients of the later period also tended to be lower than those of the early period (4% vs. 11%), although the difference was not significant. The rate of total hepatic complications in the later period was also significantly lower than that in the first series (17%

vs. 50%). Death following surgery occurred in 1 patient from the later series and in 3 from the early group.

Discussion

Previous reports list various risk factors associated with post-hepatectomy complications such as liver failure, massive ascites and intra-abdominal infection [16-20]. Liver surgeons carefully select the extent or type of hepatectomy according to the preoperative functional liver reserve to avoid hepatic failure. A fine balance must be achieved between tumour curability and operative risk in some patients scheduled for hepatectomy, and surgeons often debate the most important or reliable predictive parameters to minimise complications before proceeding with surgery [13, 15, 19]. ICGR15 seems to be the most reliable measure to determine the volume of hepatic resection in Japan currently [3, 8, 9, 13]. In the present series, the extent of hepatectomy was decided based on a formula using the ICGR15 in all patients, as proposed by Takasaki et al. [13] ICGR15 was thus excluded as a key predictor of post-hepatectomy complications, and supplementary data were analysed to improve the accuracy of preoperative predictions.

The present preliminary study correlated 15 clinicopathological and surgical parameters with post-hepatectomy complications in an earlier period from 1994 to 2003. During this period, surgical indications were decided based only on ICGR15 results. Nine parameters were significantly associated with hepatic complications by univariate analysis. Multivariate analysis then identified three independently predictive preoperative liver function parameters and two factors based on surgical records. As the latter two factors are not applicable as preoperative predictors, the three functional parameters were used to support the ICGR15 result to formulate surgical indications in the next step. The same three parameters have already been the subject of interest by previous investigators including our group [5-7].

A decrease in one of these parameters, prothrombin activity, reflects impaired liver function, and reduced prothrombin activity is classified as grade B according to the Liver Damage Grade of the Liver Cancer Study Group of Japan [11]. As the coagulation factors indicating prothrombin activity are liver-generated, rapid-turnover proteins, this parameter

accurately reflects the present liver functional reserve [21]. In the present study, prothrombin activity indicated the highest risk for hepatic complications of the candidate parameters.

Another of the three parameters, serum HA level reflects the function of hepatic sinusoids and is a sensitive marker of liver endothelial cell dysfunction after liver ischaemia [22].

Measurement of serum HA level is therefore considered useful for evaluating liver damage as well as fibrosis. Yachida et al. [23], Das et al. [24] and our preliminary reports demonstrated the significance of serum HA levels in predicting postoperative ascites or hepatic failure [6, 24]. In the present study, the value of serum HA was also a significantly predictive parameter for hepatic complications, and concentrations of more than 150-200 ng/ml should be carefully evaluated before considering hepatectomy [6, 23].

^{99m}Tc-GSA is a recently reliable test of hepatic functional reserve, in which the uptake region shows live hepatic cells. The clinical significance of ^{99m}Tc-GSA scintigraphy has been demonstrated in patients with various hepatic backgrounds [25, 26], and results are often dissociated from the results of ICG testing in patients with hepatic vascular shunt or icteric liver [5, 27]. In these cases of liver disease, the results of ICGR15 do not accurately influence indications for hepatectomy. Application of ^{99m}Tc-GSA scintigraphy thus seems likely to address the limitations of ICG testing, to evaluate liver function on any background condition. In this regard, LHL15 is also a reliable parameter [28]. In our previous analysis, approximately 8% of patients with liver disease showed marked differences between ICGR15 and LHL15 [5].

Reviewing the data from 1994-2003 led us to modify our indication regime for hepatectomy and we have applied this modification since 2004; it applies ICGR15, prothrombin activity, serum HA levels and LHL15. The new strategy was evaluated after 5 years, as reported herein. Incidences of hepatic complications were markedly reduced, particularly uncontrolled ascites, giving promise for our new system. Other investigators have also reported modified formula to decide indications of hepatectomy [29-31], however, their

parameters were already popular in this era. For instance, diabetes mellitus used to be an important risk factor for hepatic complications [30], but most diabetes is now controlled adequately by improvements in the perioperative management of blood sugar. To our knowledge, this is the first new comprehensive evaluation of preoperative liver function, and the results recommend applying our combined evaluation. Hepatic complications were still reported even with the modified indication, thus further improvements will be considered in the future. The present patients showing hepatic failure comprised one case of chronic renal failure with artificial haemodialysis, one of blood loss over 6000 ml due to the presence of highly advanced tumour, and two with hyperbilirubinaemia around 2.0 mg/dl. These patients might therefore have contra-indications. Careful management of water balance by intake or the use of diuretics is necessary to manage uncontrolled ascites, and these measures were taken in the later series of patients (2004-2008). Reducing this complication will need improved management modalities in addition to better evaluation of preoperative risks.

In conclusion, since 2004 we have applied our new indication criteria for hepatectomy using prothrombin activity, serum HA level and LHL15 by ^{99m}Tc -GSA to be used hand in hand with ICGR15. The postoperative complications/outcomes were compared to a series of 149 patients who underwent hepatic resections from 1994 to 2003 in whom these criteria were used for selection/suitability for surgery. The findings showed significantly decreased hepatic complications in 101 patients following the use of the new indication criteria over the past 5 years. Comprehensive evaluation of functional liver reserve by the above four parameters could thus reduce the incidence of hepatic complications after hepatectomy.

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Table 1 Comparison of Continuous Parameters in Patients with and without Post-operative Hepatic Complications.

	Complication (-) (n=83)	Complication (+) (n=66)	P value	Predictive cut-off value
Resected volume (%)	27±19	45±19	<0.001	50
Blood loss (ml)	725±438	1421±635	<0.001	1500
LHL15	95.2±3.8	92.2±4.6	0.021	0.85
ALT (IU/L)	36±40	63±58	0.015	80
Total cholesterol (mg/dl)	180±42	153±37	0.009	150
Prothrombin activity (%)	97±12	76±15	0.013	80
Hyaluronic acid (ng/ml)	77±65	198±112	<0.001	150
HAI score	5.6±3.6	8.7±4.2	<0.001	8

Data are presented as mean ± standard deviation.

Predictive value calculated by the analysis of receiver operating characteristic (ROC) curves.

LHL15, Hepatic uptake ratio by ^{99m}Tc-GSA; *ALT*, alanine aminotransferase; *HAI*, histological activity index.

Table 2 Logistical Multivariate Regression Analysis for Risk Factors associated with Post-operative Hepatic Complications between 1994 and 2003.

	Univariate		Multivariate	
	Odds ratio (95%CI)	P value	Odds ratio (95%CI)	P value
Volume of resected liver (≥ 50 vs. $< 50\%$)	2.5 (1.3-4.6)	< 0.01	7.0 (1.3-39.3)	0.027
Operative blood loss (≥ 1500 vs. < 1500 ml)	1.9 (1.1-3.3)	< 0.01	4.4 (1.6-12.5)	< 0.01
LHL15 (< 0.85 vs. ≥ 0.85)	5.1 (2.4-23)	0.022	3.6 (2.1-16.9)	0.083
ALT (≥ 80 vs. 80 IU/L)	1.6 (0.6-43)	0.094	1.2 (0.2-89)	0.857
Total cholesterol (< 150 vs. ≥ 150 mg/dl)	2.1 (0.7-6.7)	0.056	3.3 (0.7-15.3)	0.127
Prothrombin activity (< 70 vs. ≥ 70 %)	4.2 (1.9-18)	< 0.01	7.5 (2.0-28.4)	< 0.01
Liver Damage score (B vs. A)	8.5 (3.9-18.8)	0.015	2.7 (0.5-15.7)	0.274
Hyaluronic acid level (≥ 200 vs. < 200 ng/ml)	3.8 (1.6-8.9)	0.012	5.4 (1.2-18.9)	0.045
HAI score (≥ 8 vs. < 8)	1.6 (0.6-11.1)	0.090	1.8 (0.4-8.9)	0.452

LHL15, Hepatic uptake ratio by ^{99m}Tc -GSA; *ALT*, alanine aminotransferase; *HAI*, histological activity index; *95%CI*, 95% confidence interval.

Figure Legend

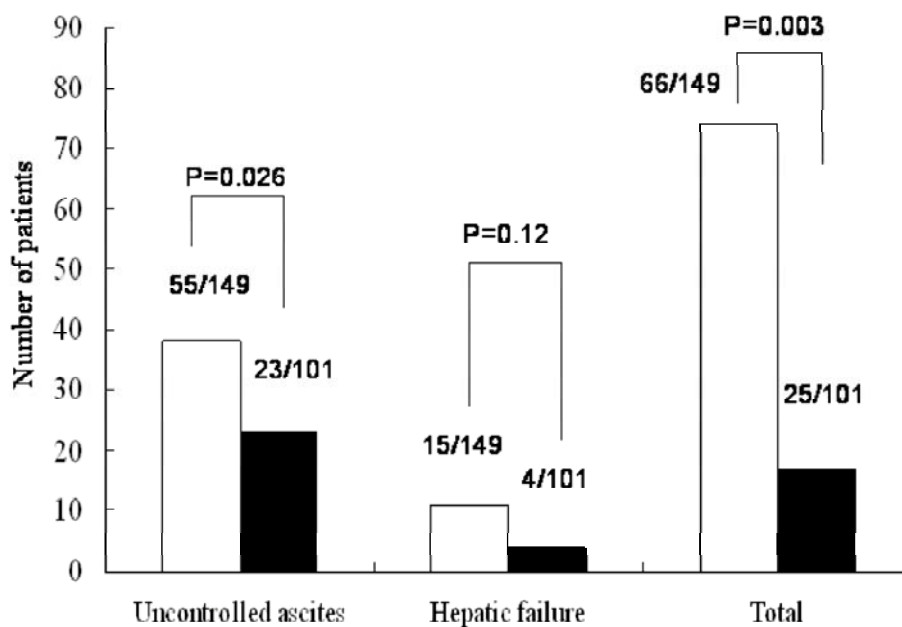


Fig 1. Changes in prevalence of hepatic complications after hepatectomy between 1994-2003 and 2004-2008.