safe threshold rate of indocyanine green retention at 15 minutes after extreme hepatectomy in patients who have remnant liver volume < 40% of the standard volume as well as chronic liver disease, hepatic fibrosis or cirrhosis

junping gao
Guangxi Medical University Cancer Hospital
zhan lu
Guangxi Medical University Cancer Hospital
wanqiang liang
Wuxiang Hospital of the Third Affiliated to Guangxi Medical University
jie zhang
Guangxi Medical University Cancer Hospital
shangdong qin
Guangxi Medical University Cancer Hospital
jingfei zhao
Guangxi Medical University Cancer Hospital
juntao huang
Guangxi Medical University Cancer Hospital
wenfeng gong
Guangxi Medical University Cancer Hospital
bangde xiang (xiangbangde@163.com)
Guangxi Medical University Cancer Hospital

Research Article

Keywords: indocyanine green, hepatectomy, liver failure, chronic liver disease, hepatic fibrosis, cirrhosis

Posted Date: May 25th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1683360/v1

Abstract

Background

Indocyanine green (ICG) kinetics are used to assess hepatic function in the perioperative period of major liver resection and liver transplantation. Here, we aimed to determine the threshold rate of ICG retention at 15 min (ICG-R15) associated with clinically relevant post-hepatectomy liver failure (CRPHLF) among patients with underlying chronic liver disease, hepatic fibrosis or cirrhosis whose remnant liver volume was < 40% of the standard liver volume.

Methods

Data from 70 Chinese patients with a ratio of remnant to standard liver volume < 40% who underwent extreme hepatectomy at our medical center were analyzed prospectively. We investigated potential differences in several clinical and demographic factors between those who experienced CRPHLF and those who did not.

Results

Logistic regression showed that ICG-R15 was an independent predictor of the risk of CRPHLF. The ICG-R15 threshold for predicting CRPHLF risk was 5.25% across all patients, with an area under the receiver operating characteristic curve (AUC) of 0.740, sensitivity of 68.4%, and specificity 78.4%. The ICG-R15 threshold was 4.95% for patients with hepatic fibrosis (AUC 0.770, sensitivity 78.0%, specificity 74.0%), and 4.55% for patients with cirrhosis (AUC 0.768, sensitivity 87.5%, specificity 64.7%).

Conclusions

The risk of CRPHLF after extreme hepatectomy may be lower in Chinese patients when the ICG-R15 is below 5.25% in the presence of chronic liver disease, 4.95% in the presence of hepatic fibrosis, or 4.55% in the presence of cirrhosis. Our results suggest that ICG-R15 can be used to identify patients who may safely undergo extreme hepatectomy despite a low ratio of remnant to standard liver and different stages of hepatic fibrosis.

Background

Post-hepatectomy liver failure (PHLF) remains a significant complication after hepatectomy, and one of the leading causes of death after liver resection [1–4]. A major cause of PHLF is inadequate remnant liver volume (RLV) and function [5, 6]. Extreme hepatectomy increases the risk of PHLF due to insufficient RLV [7]. Therefore, accurate preoperative evaluation of RLV and residual liver function is crucial to avoid liver failure after extreme hepatectomy.

Criteria have not been standardized, in China or globally, for determining the threshold residual liver function that ensures adequate post-hepatectomy function. This is especially important for patients with underlying chronic liver disease, hepatic fibrosis or cirrhosis whose ratio of RLV to standard liver volume (RLV/SLV) < 40%. Normally, hepatectomy is considered only for patients whose RLV/SLV > 40% [8–10].

The integrity and function of liver cells is routinely assessed based on indocyanine green (ICG) clearance, and this assay is considered effective at predicting PHLF. In particular, the amount of ICG retained at 15 min after injection (ICG-R15) is the parameter most frequently used to assess residual liver function; it is included in decision-making protocols before hepatectomy [11–15]. Some algorithms stipulate ICG-R15 thresholds for ensuring adequate post-surgical liver function: for example, Makuuchi's algorithm indicates that patients with ICG-R15 < 10% can safely undergo extended hemi-hepatectomy or three-lobe resection, while those with 10–20% can undergo right hemi-hepatectomy [16]. The ICG-R15 threshold for predicting clinically relevant PHLF after extreme hepatectomy remains uncertain.

Here we determined the ICG-R15 threshold for extreme hepatectomy in patients with RLV/SLV < 40% and with different underlying liver diseases: chronic liver disease, fibrosis, or cirrhosis. All patients underwent right or extended right hemi-hepatectomy, which constitutes extreme hepatectomy because the right half of the liver accounts for 60–75% of total liver volume [17].

Methods

Ethics statement

This study was performed in accordance with the standards of the Declaration of Helsinki and approved by the Ethics Committee of Guangxi Medical University Cancer Hospital (Nanning, Guangxi, China). Written informed consent was obtained from all patients.

Patient enrollment

This report is an interim analysis of an on-going prospective study involving liver cancer patients who were scheduled for right hemi-hepatectomy or extended right hemi-hepatectomy in the Department of Hepatobiliary Surgery at the Affiliated Cancer Hospital of Guangxi Medical University. Seventy patients were consecutively enrolled from July 2014 to January 2022. Inclusion criteria were as follows: (1) right hemi-hepatectomy or extended right hemi-hepatectomy for tumor resection; (2) age ≥ 18 years, preoperatively estimated RLV/SLV < 40% and ICG-R15 < 20%; (3) chronic liver disease, hepatic fibrosis or cirrhosis; (4) confinement of the main tumor to the right liver lobe; (5) computed tomography and enhanced examination within seven days before surgery; and (6) complete pre-, intra- and postoperative clinical data.

Patients were excluded from the study if they had (1) preoperative biliary obstruction or hepatic hilar cholangiocarcinoma; (2) other malignancies or other diseases treated at the same time, such as biliary tract infection or liver abscess; or (3) human immunodeficiency virus infection or other serious diseases.

ICG-R15 determination

ICG (Indocyanine Green for Injection, Dandong, China) was administered at 0.5 mg/kg through a peripheral vein and measured using pulse dye densitometry (DDG-3300K, NIHON KOHDEN, Japan). The ICG-R15 and plasma disappearance rate (ICG-k per minute) were calculated as described [16].

Clinical and laboratory tests

Baseline demographics and clinical data were collected from all patients before hepatic resection. All patients were analyzed using 128-slice spiral computed tomography (General Electric, Boston, MA, USA) one week before and one week after liver resection. The following tests were performed in each patient before resection: standard liver and renal function (total bilirubin, albumin, aspartate aminotransferase, alanine transaminase, creatinine), coagulation function [prothrombin time, (PT)], hematological examination (white blood cells, red blood cells, platelets, hemoglobin levels), screening for hepatitis B-virus (HBV) infection [HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), HBV e antigen (HBeAg), HBV e antibody (HBeAb), and HBV core antibody (HBcAb)], quantitation of HBV-DNA, and levels of the tumor marker alpha-fetoprotein (AFP).

Three-dimensional liver reconstruction

Three-dimensional (3D) liver reconstruction was performed before hepatectomy. Thin-slice (5 mm) computed tomography scans including the contiguous artery phase, portal venous phase and delayed phase were imported into a 3D surgical simulation operation system (Myrian XP Liver 1.30.79.4; Intrasense, Montpellier, France). Subsequent analysis was performed using portal venous phase images. Different colors were used to label different tissues, including liver, tumor, postcava, hepatic vein, and portal vein. The simulated volumes of liver, tumor, and blood vessels were calculated through 3D reconstruction of the tissue profile.

Simulated hepatic resection

Hepatectomy was simulated on a 3D model of the middle hepatic vein region, using the Myrian XP Liver system. The model was adjusted according to 2D images. Resected liver volume and RLV were calculated by the system (Fig. 1). SLV was calculated with the following formula:

SLV (mL) = 706.2 × body surface area + 2.4,

while standard RLV was calculated as remnant liver volume divided by body surface area [18].

Diagnosis of PHLF

PHLF was diagnosed according to the criteria of the International Study Group of Liver Surgery [19]. Patients were deemed to have PHLF if they experienced an increase in PT-international normalized ratio (PT-INR) and hyperbilirubinemia on or after postoperative day 5, based on the normal reference ranges defined by the local laboratory. If PT-INR or serum bilirubin increased preoperatively, PHLF was defined as

an increase in PT-INR and serum bilirubin level compared with the values of the previous day on or after postoperative day 5. Patients with PHLF who nevertheless required no adjustment to their clinical management were categorized as grade A; those who required adjustment but not invasive therapy, grade B; and those who required invasive therapy, grade C [19]. In the present study, we classified patients without PHLF or with grade A PHLF as having non-clinically relevant PHLF, and those with grades B or C as having clinically relevant PHLF (CRPHLF) [20].

Histological assessment

Hepatic fibrosis was diagnosed by two histologists independently, who estimated the degree of hepatic fibrosis using the METAVIR scoring system [21] (Fig. 2): F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; or F4, cirrhosis. Disagreements between histologists were resolved by discussion.

Statistical analysis

Continuous variables were reported as mean ± standard deviation, and inter-group differences were assessed for significance using Student's *t* test. Categorical variables were reported as frequencies, and differences were assessed using the chi-squared test. Independent risk factors for predicting CRPHLF were identified by logistic regression. The ICG-R15 threshold for predicting CRPHLF was estimated using receiver operating characteristic curves.

All analyses were conducted using two-sided tests in SPSS 19.0 (IBM, Chicago, IL, USA). Differences were considered significant if associated with p 0.05.

Results

Demographic and clinical characteristics of patients

A total of 70 patients were enrolled, including 57 (82.3%) men and 13 (17.6%) women (Table 1), of whom 60 (85.7%) were HBsAg-positive. Sixty-eight patients underwent right hemi-hepatectomy and two patients, extended right hemi-hepatectomy. Postoperative liver tumor pathology identified 66 patients with hepatocellular carcinoma (HCC), and one patient each with intrahepatic cholangiocarcinoma, HCC-intrahepatic cholangiocarcinoma, adenocarcinoma, or low-grade dysplasia. Postoperative liver tissue pathology identified 10 (14.3%) patients with chronic liver disease without hepatic fibrosis or cirrhosis, 35 (50.0%) with hepatic fibrosis, and 25 (35.7%) with cirrhosis.

After surgery, obvious ascites appeared in five patients (7.1%), biliary leak in two (2.9%), and abdominal infection in one (1.4%). CRPHLF occurred in 19 (27.1%). No patient died during the perioperative period, from one week before surgery until one week after surgery. All patients recovered successfully.

Table 1
Demographic and clinical characteristics of the 70 patients in the study.

Characteristic	Value
Sex	57 (81.4)
Male	13 (18.6)
Female	
HBsAg	60 (85.7)
Positive	10 (14.3)
Negative	
Preoperative parameters	44.63 ± 3.73
Age (years)	21.75 ± 3.34
Body mass index (kg/m^2)	18.14 ± 30.75
Total bilirubin (μmol/L)	37.15 ± 4.21
Albumin (g/L)	56.83 ± 41.73
ALT (U/L)	73.30 ± 53.40
AST (U/L)	236.03 ± 93.97
Platelet count (10^9 /L)	12.58 ± 1.22
Prothrombin time (s)	76.73 ± 15.05
Creatinine (μmol/L)	41 (58.6)
HBV-DNA (IU/mL)	29 (41.4)
≥ 2 000	39 (55.7)
< 2000	31(44.3)
Alpha-fetoprotein (ng/mL)	10 (14.3)
≥ 400	60 (85.7)
< 400	66 (94.3)
Ascites	4 (5.7)
Yes	0
No	4.88 ± 3.11
Child–Pugh grade	248.25 ± 24.20
	35.03 ± 3.37

Values are n (%) or mean ± standard deviation.

Characteristic	Value
A	405.15 ± 52.09
B	513.0 ± 399.3
C	
ICG-R15 (%)	
SRLV (mL/m^2)	
RLV/SLV (%)	
RLV (mL)	
Tumor volume (mL)	
Intraoperative parameters	15 (21.4)
Blood transfusion	55 (78.6)
Yes	557.14 ± 474.13
No	273.74 ± 61.49
Blood loss (mL)	
Operative time (min)	
Postoperative parameters	10 (14.3)
Hepatic fibrosis stage (METAVIR)	35 (50.0)
No fibrosis (F0)	25 (35.7)
Fibrosis (F1-3)	14.09 ± 10.62
Cirrhosis (F4)	0
Hospital stay (days)	
Perioperative mortality (%)	
Values are n (%) or mean ± standard deviation.	

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HBsAg, hepatitis B virus surface antigen; HBV-DNA, hepatitis B virus DNA; ICG-R15, indocyanine green retention rate at 15 min; RLV, remnant liver volume; SLV, standard liver volume; SRLV, standard remnant liver volume.

Risk factors for CRPHLF

The ICG-R15 of patients who experienced CRPHLF was significantly higher than that of patients who did not (Table 2). Positive stepwise binary logistic regression was used to assess the potential relationship between ICG-R15 and CRPHLF, in which the threshold for model inclusion was 0.05, and the threshold for

exclusion was 0.1. This analysis identified ICG-R15 as an independent predictor of CRPHLF after extreme hepatectomy (Table 3).

Table 2. Comparison of clinicopathologic characteristics between patients who experienced CRPHLF or not.

Characteristic	No CRPHLF (n = 51)	CRPHLF (n = 19)	χ^2 (t test)	*p*
Sex			3.054	0.081
Male	39	18		
Female	12	1		
HBsAg			0.301	0.583
Positive	43	17		
Negative	8	2		
Preoperative parameters				
Age (years)	47.49±11.02	48.16±11.63	1.040	0.302
Body mass index (kg/m^2)	21.98±3.40	21.14±3.20	0.931	0.355
Total bilirubin (μmol/L)	14.43±5.24	28.02±58.38	-1.011	0.325
Albumin (g/L)	37.08±3.61	37.36±5.63	-0.201	0.842
ALT (U/L)	58.14±42.02	53.32±41.87	0.427	0.671
AST (U/L)	72.44±50.43	75.61±62.13	-0.22	0.827
Platelet count (10^9 /L)	234.15±97.13	241.06±87.19	-0.271	0.787
Prothrombin time (s)	12.49±1.23	12.83±1.18	-1.017	0.313
Creatinine (μmol/L)	75.25±14.72	80.68±15.60	-1.35	0.181
HBV-DNA (IU/mL)			0.301	0.583
≥ 2 000	22	9		
< 2000	19	10		
Alpha-fetoprotein (ng/mL)			0.05	0.823
≥ 400	28	11		
< 400	23	8		
Ascites			0.048	0.826
Yes	7	3		
No	44	16		
Child–Pugh grade			1.121	0.290
A	49	17		

B	2	2		
ICG-R15 (%)	4.27±2.95	6.51±3.02	-2.799	0.007*
SRLV (mL/m^2)	249.06±24.09	246.10±25.05	0.452	0.652
RLV/SLV (%)	35.19±3.4	34.61±3.33	0.633	0.529
RLV (mL)	407.06±53.19	400.02±50.05	0.50	0.619
Tumor volume (mL)	482.15±403.63	595.83±386.03	-1.06	0.293
Intraoperative parameters				
Blood transfusion			4.048	0.044*
Yes	14	1		
No	37	18		
Blood loss (mL)	520.73±456.89	608.62±501.08	-0.762	0.449
Operative time (min)	277.14±62.29	264.63±59.97	0.754	0.453
Postoperative parameters				
Hepatic fibrosis stage (METAVIR)			1.820	0.402
No fibrosis (F0)	9	1		
Fibrosis (F1-3)	25	10		
Cirrhosis (F4)	17	8		
Hospital stay (days)	11.33±6.36	21.47±15.51	-2.764	0.012*

Values are n or mean ± standard deviation. * $p < 0.05$

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; HBsAg, hepatitis B virus surface antigen; HBV-DNA, hepatitis B virus DNA; ICG-R15, indocyanine green retention rate at 15 min; RLV, remnant liver volume; SLV, standard liver volume; SRLV, standard remnant liver volume.

Table 3. Binary logistic regression analysis to identify factors related to CRPHLF.

Factor	Univariate analysis			Multivariate analysis		
	B	Odds Ratio (95% CI)	*p*	B	Odds Ratio (95% CI)	*p*
Sex (male)	1.712	5.538 (0.668–45.914)	0.172	1.470	4.347(0.451–41.865)	0.203
ICG-R15	0.231	1.259 (1.047–1.515)	0.014*	0.224	1.251(1.029–1.521)	0.024*
Creatinine	0.025	1.025(0.988–1.063)	0.182	0.022	1.023 (0.982–1.065)	0.281
Hepatic fibrosis stage						
Fibrosis(F1-3)	1.281	3.60(0.402–32.240)	0.252	0.956	2.602 (0.255–26.573)	0.420
Cirrhosis(F4)	1.443	4.235(0.455–39.401)	0.205	1.006	2.734 (0.252–29.686)	0.408

* $p < 0.05$.

Abbreviations: CI, confidence interval; ICG-R15, indocyanine green retention rate at 15 min.

ICG-R15 thresholds for predicting CRPHLF

Receiver operating characteristic curves showed that ICG-R15 predicted CRPHLF in our patients with high sensitivity and specificity, regardless of whether they had chronic liver disease, hepatic fibrosis, or cirrhosis. Across all patients, the ICG-R15 threshold for CRPHLF was 5.25%, which gave an area under the curve (AUC) of 0.740, sensitivity of 68.4%, and specificity of 78.4% (p = 0.002, Fig. 3A). In patients with hepatic fibrosis, the ICG-R15 threshold was 4.95%, which gave an AUC 0.770, sensitivity of 78.0%, and specificity of 74.0% (p = 0.001, Fig. 3B). In patients with cirrhosis, the threshold was 4.55%, which gave an AUC of 0.768, sensitivity of 87.5%, and specificity of 64.7% (p = 0.033, Fig. 3C).

Discussion

Preoperative assessment of RLV and liver function is crucial to prevent postoperative liver failure after extreme hepatectomy. However, the safe ICG-R15 threshold for extreme hepatectomy remains unclear for patients with chronic liver disease, hepatic fibrosis, or cirrhosis. Here we identified ICG-R15 as an independent predictor of CRPHLF, in agreement with previous studies reporting that SRLV and ICG-R15 are independent predictors of PHLF [22]. We found the safe ICG-R15 threshold to be 5.25% across our entire cohort, lower than the threshold of 10% in a Japanese study [16]. This difference may reflect the fact that we enrolled only patients who had underlying chronic liver disease, hepatic fibrosis or cirrhosis; whose RLV/SLV < 40%; and who underwent extreme hepatectomy.

Patients undergoing hepatectomy in China often present with hepatic fibrosis or cirrhosis [23], which can strongly affect preoperative liver function and regeneration of postoperative remnant liver. We found that the safe ICG-R15 threshold was 4.95% for patients with hepatic fibrosis and 4.55% for those with cirrhosis. Thus, the more severe a patient's hepatic fibrosis is, the lower their safe ICG-R15 threshold for predicting CRPHLF.

Some studies have recommended that when selecting patients for hepatectomy, RLV/SLV should be > 40% if the patient has ICG-R15 < 10% as well as chronic liver disease or cirrhosis [8-10]. However, it is unclear whether hepatectomy is safe for patients whose RLV/SLV < 40% and who have underlying chronic liver disease, hepatic fibrosis or cirrhosis. Portal vein embolization (PVE) is a well-established method for increasing RLV in 4-6 weeks. However, more than 20% of patients may become ineligible for surgery during that period, either because their disease progresses or because the RLV after PVE is still insufficient [24-26]. More recently, the combination of liver partition and portal vein ligation for staged hepatectomy has been used to increase RLV in 1-2 weeks. However, this method remains controversial because of the high associated morbidity and mortality [27,28]. All 70 patients in our study underwent right hemi-hepatectomy or extended right hemi-hepatectomy, and although 19 (27.1%) developed CRPHLF, no patient in our study developed grade C PHLF or died during hospitalization. One explanation for this low perioperative mortality is that residual hepatocytes may release more liver-regenerating cytokines after right hemi-hepatectomy than after left hemi-hepatectomy [29-31]. We propose that hepatectomy can be safe in patients with RLV/SLV < 40% and with different stages of hepatic fibrosis, so long as ICG-R15 lies below a certain threshold. Nevertheless, two-staged hepatectomy may still need to be considered for such patients.

Since our study involved a small number of patients, the results should be interpreted with caution. Our results should be verified and extended in larger studies, preferably with concurrent analysis of postoperative complications. Future work should examine patients with RLV/SLV > 40% after hepatectomy, and it should search for additional risk factors for liver failure after extreme hepatectomy.

Conclusions

This small study suggests that ICG-R15 is an independent predictor of CRPHLF in patients who have chronic liver disease, hepatic fibrosis, or cirrhosis and who undergo extreme hepatectomy. Our results also propose safe ICG-R15 thresholds for each type of patient that, if validated in larger cohorts, may help guide their treatment and management. Our results suggest that ICG-R15 may help identify patients who can safely undergo hepatectomy despite having RLV/SLV < 40% and hepatic fibrosis.

Abbreviations

CRPHLF: clinically relevant posthepatectomy liver failure; ICG: indocyanine green; ICG-R15: indocyanine green retention rate at 15 minutes; PHLF: post-hepatectomy liver failure; RLV: remnant liver volume; SLV: standard liver volume; SRLV: standard remnant liver volume.

Declarations

Acknowledgments

None.

Author contributions

BX and WG designed the study. JG, ZL, WL, JZ, SQ, JZ and JH performed clinical examinations and collected patient data. BX and WG performed surgeries. JG and ZL drafted the manuscript, which all authors read and approved for submission.

Funding

This study was supported by the High-level Innovation Team and Outstanding Scholar Program in Guangxi Colleges and Universities, Key Laboratory of Early Prevention and Treatment for Regional High Frequency Tumor, Ministry of Education/Guangxi, Independent Research Project (project no. GKE-ZZ202111) and Guangxi Key Research and Development Program (program no. AA18221001, AB18050020). The funding bodies played no role in the design of the study or in the collection, analysis, or interpretation of the data.

Availability of data and materials

Data not shown directly in this publication can be obtained from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Guangxi Medical University Cancer Hospital. Written informed consent was obtained from patients or their legal guardians.

Consent for publication

Not applicable.

Competing interests

The authors state that there are no conflicts of interest to disclose.

References

1. Mullen JT, Ribero D, Reddy SK, Donadon M, Zorzi D, Gautam S, et al. Hepatic insufficiency and mortality in 1,059 noncirrhotic patients undergoing major hepatectomy. J Am Coll Surg. 2007;204:854–864, discussion 862-4.

2. Farges O, Malassagne B, Flejou JF, Balzan S, Sauvanet A, Belghiti J. Risk of major liver resection in patients with underlying chronic liver disease: a reappraisal. Ann Surg. 1999;229:210–215.
3. Dan RG, Cret¸u OM, Mazilu O, Sima LV, Iliescu D, Blidis¸el A et al. Postoperative morbidity and mortality after liver resection. Retrospective study on 133 patients. Chirurgia (Bucur). 2012;107:737–741.
4. Nishio T, Taura K, Koyama Y, Tanabe K, Yamamoto G, Okuda Y, et al. Prediction of posthepatectomy liver failure based on liver stiffness measurement in patients with hepatocellular carcinoma. Surgery. 2016;159:399–408.
5. Sparrelid E, Jonas E, Tzortzakakis A, Dahlén U, Murquist G, Brismar T, et al. Dynamic evaluation of liver volume and function in associating liver partition and portal vein ligation for staged hepatectomy. J Gastrointest Surg. 2017;21(6):967–74.
6. Ribero D, Zimmitti G, Aloia TA, Shindoh J, Fabio F, Amisano M, et al.Preoperative cholangitis and future liver remnant volume determine the risk of liver failure in patients undergoing resection for hilar cholangiocarcinoma. J Am Coll Surg. 2016;223(1):87–97.
7. Kishi Y, Abdalla EK, Chun YS, Zorzi D, Madoff DC, Wallace MJ, et al. Three hundred and one consecutive extended right hepatectomies: evaluation of outcome based on systematic liver volumetry. Ann Surg. 2009;250(4):540-8.
8. Vauthey JN, Dixon E, Abdalla EK, Helton WS, Pawlik TM, Taouli B, et al. Pretreatment assessment of hepatocellular carcinoma: expert consensus statement. HPB (Oxford). 2010;12(5):289-299.
9. Suda K, Ohtsuka M, Ambiru S, Kimura F, Shimizu H, Yoshidome H, et al. Risk factors of liver dysfunction after extended hepatic resection in biliary tract malignancies. Am J Surg. 2009;197(6):752-758.
10. Oldhafer KJ, Stavrou GA, Van Gulik TM. ALPPS-Where do we stand, where do we go?: Eight recommendations from the first international expert meeting. Ann Surg. 2016;263(5):839-841.
11. Huo TI, Lin HC, Huo SC, Lee PC, Wu JC, Lee FY, et al. Comparison of four model for end-stage liver disease-based prognostic systems for cirrhosis. Liver Transplant. 2008;14 (6):837–844.
12. Manizate F, Hiotis SP, Labow D, Roayaie S, Schwartz M. Liver functional reserve estimation: state of the art and relevance for local treatments: the Western perspective. J Hepatobiliary Pancreat Sci. 2010;17:385-8.
13. Yokoyama Y, Nishio H, Ebata T, Igami T, Sugawara G, Nagino M. Value of indocyanine green clearance of the future liver remnant in predicting outcome after resection for biliary cancer. Br J Surg. 2010;97:1260-8.
14. Yokoyama Y, Ebata T, Igami T, Sugawara G, Mizuno T, Yamaguchi J, et al. The Predictive value of indocyanine green clearance in future liver remnant for posthepatectomy liver failure following hepatectomy with extrahepatic bile duct resection. World J Surg. 2016;40:1440-7.
15. Kim JM, Kwon CH, Joh JW, Park JB, Lee JH, Kim GS, et al. Can the model for end-stage liver disease score replace the indocyanine green clearance test in the selection of right hemihepatectomy in Child-Pugh class A? Ann Surg Treat Res. 2014;86:122-9.

16. H. Imamura, K. Sano, Y. Sugawara, N. Kokudo, M. Makuuchi. Assessment of hepatic reserve for indication of hepatic resection: decision tree incorporating indocyanine green test. J Hepatobiliary Pancreat Surg. 2005;12 (1):16–22.
17. Pickhardt PJ, Malecki K, Hunt OF, Beaumont C, Kloke J, Ziemlewicz TJ, et al. Hepatosplenic volumetric assessment at MDCT for staging liver fibrosis. Eur Radiol. 2017;27(7):3060–8.
18. Li J, Lei B, Nie X, Lin L, Tahir SA, Shi W, et al. A comprehensive method for predicting fatal liver failure of patients with liver cancer resection. Medicine. 2015;94(17):e784.
19. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). Surgery. 2011;149(5):713–24.
20. Navarro JG, Yang SJ, Kang I, Choi GH, Han DH, Kim KS, Choi JS. What are the most important predictive factors for clinically relevant posthepatectomy liver failure after right hepatectomy for hepatocellular carcinoma? Ann Surg Treat Res. 2020;98(2):62-71.
21. Bedossa P, Poynard T. An algorithm for the grading of activity in chronic hepatitis C. The METAVIR Cooperative Study Group. Hepatology. 1996;24(2):289-93.
22. Du ZG, Li B, Feng X, Yin J, Yan LN, Wen TF, et al. Combined indocyanine green test and standard remnant liver volume to predict post hepatectomy hepatic insufficiency for the patients with hepatocellular carcinoma. Zhonghua Wai Ke Za Zhi. 2010;48(3):189–92.
23. Lei Z, Li J, Wu D, Xia Y, Wang Q, Si A, et al. Nomogram for preoperative estimation of microvascular invasion risk in hepatitis B virus-related hepatocellular carcinoma within the Milan criteria. JAMA Surg. 2016;151(4):356–63.
24. Shindoh J, Vauthey JN, Zimmitti G, et al. Analysis of the efficacy of portal vein embolization for patients with extensive liver malignancy and very low future liver remnant volume, including a comparison with the associating liver partition with portal vein ligation for staged hepatectomy approach. J Am Coll Surg. 2013;217(1): 126-133; discussion 133-124.
25. Vauthey JN, Dixon E, Abdalla EK, et al. Pretreatment assessment of hepatocellular carcinoma: expert consensus statement. HPB (Oxford). 2010;12(5):289-299.
26. Aloia TA. Associating liver partition and portal vein ligation for staged hepatectomy: Portal vein embolization should remain the gold standard. JAMA Surg. 2015;150(10): 927-928.
27. Oldhafer KJ, Stavrou GA ,van Gulik TM. ALPPS-Where do we stand, where do we go?: Eight recommendations from the first international expert meeting. Ann Surg. 2016;263(5):839-841.
28. Schadde E, Raptis DA, Schnitzbauer AA, et al. Prediction of mortality after alpps stage-1: An analysis of 320 patients from the international ALPPS registry. Ann Surg. 2015;262(5):780-785; discussion 785-786.
29. Maldonado G, Greenland S. Simulation study of confounder-selection strategies. Am J Epidemiol. 1993;138(11):923–36.
30. Myronovych A, Murata S, Chiba M, Matsuo R, Ikeda O, Watanabe M, et al. Role of platelets on liver regeneration after 90% hepatectomy in mice. J Hepatol. 2008;49(3):363–72.

31. Gruttadauria S, Parikh V, Pagano D, Tuzzolino F, Cintorino D, Miraglia R, et al. Early regeneration of the remnant liver volume after right hepaectomy for living donation: a multiple regression analysis. Liver Transpl. 2012;18(8):907–13.

Figures

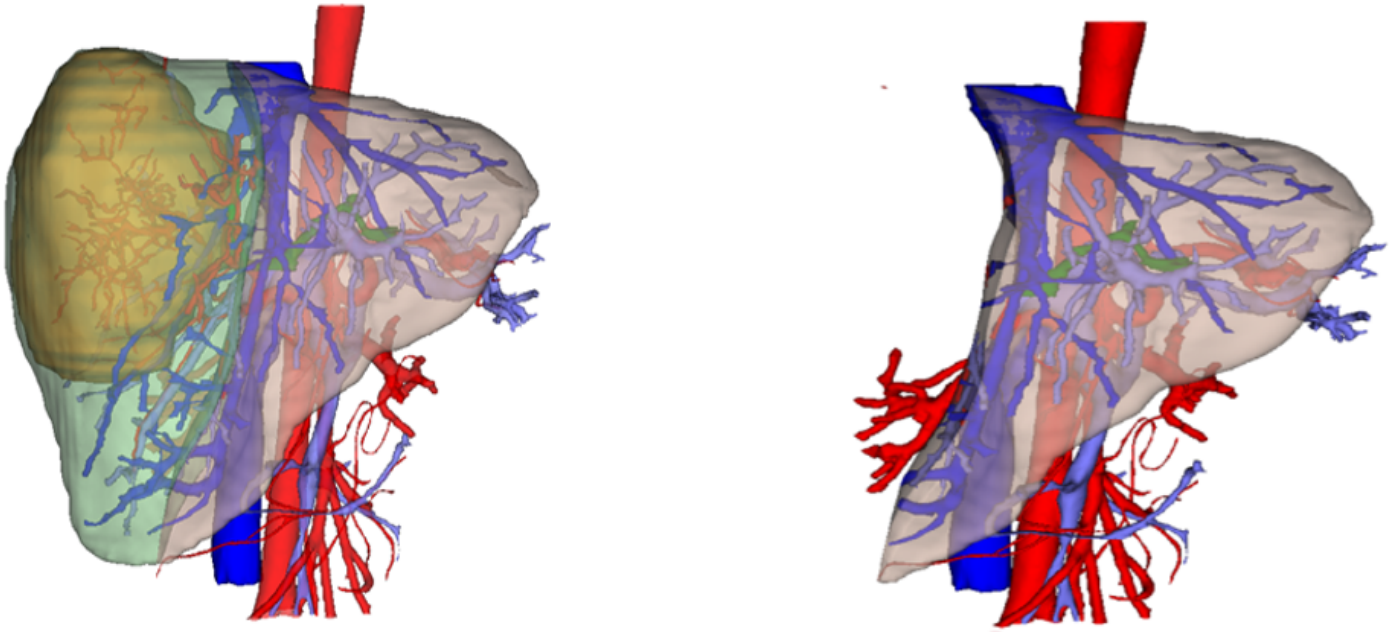

Figure 1

Representative images of 3D simulations of right hemi-hepatectomy: yellow, tumor; light green, excised liver tissue; gray, remnant liver tissue; blue, vein; red, artery; light blue, portal vein; green, biliary duct.

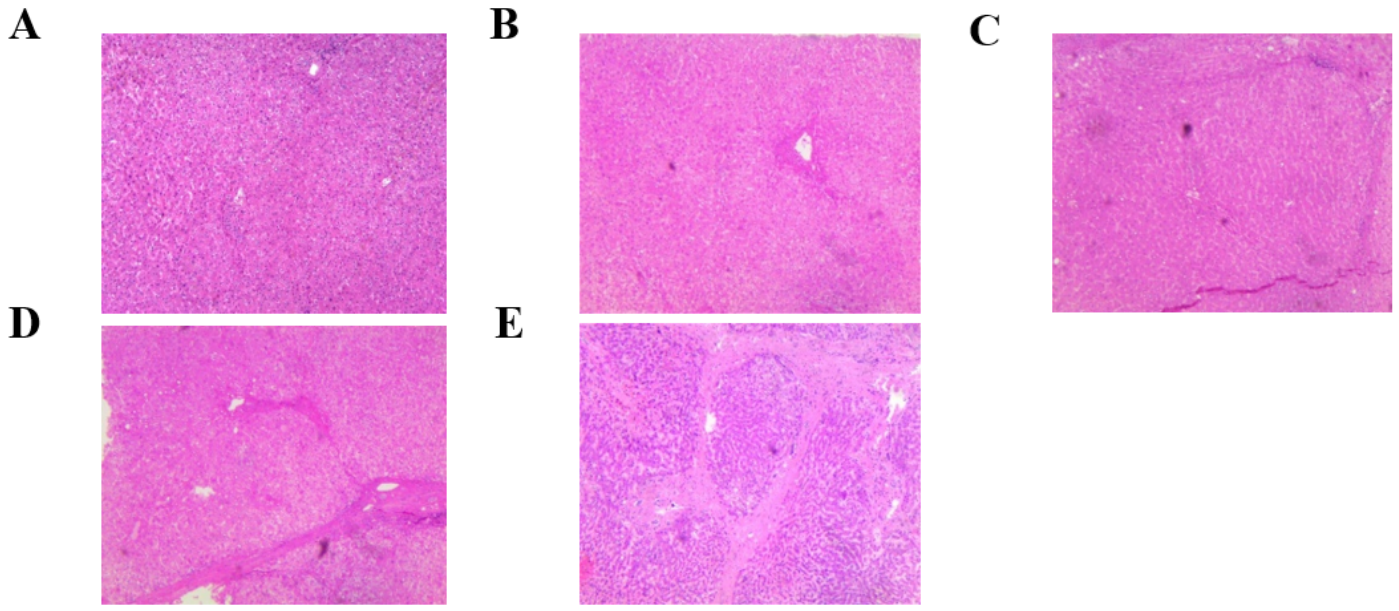

Figure 2

Representative micrographs of liver tissue (stained with hematoxylin-eosin) showing different grades of hepatic fibrosis. (A) F0. (B) F1. (C) F2. (D) F3. (E) F4. Magnification, 20x.

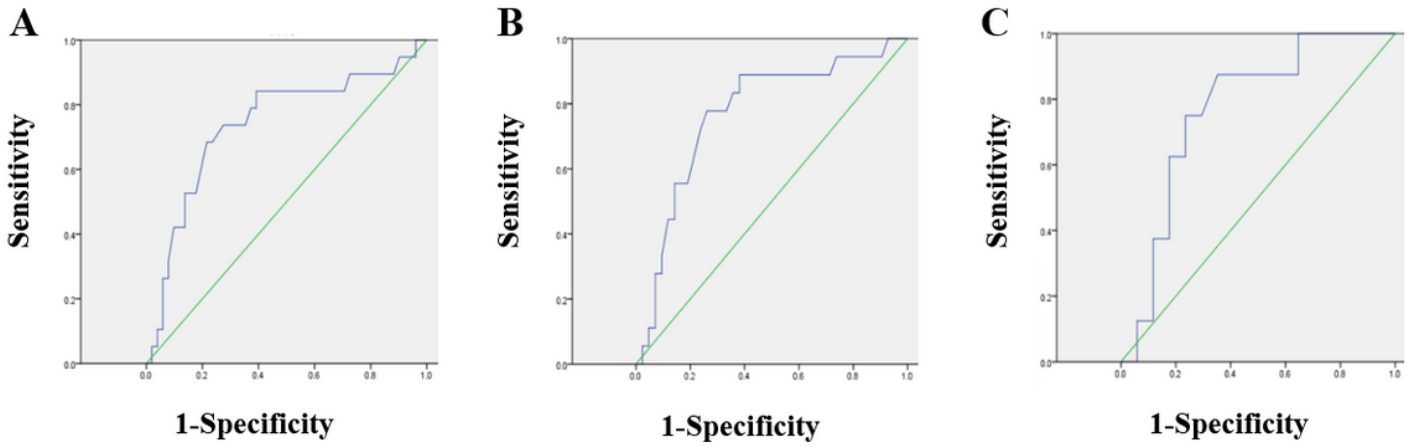

Figure 3

Receiver operating characteristic curves to assess the ability of indocyanine green retention rate at 15 min (ICG-R15) to predict clinically relevant post-hepatectomy liver failure in **(A)** all patients in our cohort, **(B)** the subgroup of patients with hepatic fibrosis, or **(C)** the subgroup of patients with cirrhosis.