Original Article

Laparoscopic hepatectomy and near-infrared fluorescence based on the concept of "biliary territory" in the treatment of hepatolithiasis: a propensity score-matched study with videos

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Background: Hepatolithiasis, a common condition in East Asia, often requires surgical treatment. The aim of this study was to evaluate the safety and efficacy of near-infrared fluorescence (NIF)-guided laparoscopic hepatectomy (LH) using the 'biliary territory' concept for hepatolithiasis.

Methods: This retrospective study included 97 patients who had undergone LH for hepatolithiasis between June 2018 and November 2022. The patients were divided into two groups based on whether intraoperative NIF-guided (n=31) or traditional white light (WL) laparoscopy (n=66) had been performed. Propensity score matching (PSM) was used to create 27 pairs for comparison. Perioperative outcomes, stone recurrence, and recurrence-free survival (RFS) were assessed.

Results: Prior to PSM, NIF guidance was associated with reduced bleeding (P=0.01) and a lower conversion rate (P=0.001). After PSM, only the postoperative albumin concentration differed significantly between the two groups (P=0.003). The median duration of follow-up was 36 months. Before PSM, RFS differed significantly between the groups (P=0.009), whereas in the matched cohort, the stone recurrence rate was 33.3% in the WL group and 7.4% in the NIF group; however, the RFS did not differ significantly between these groups (P=0.09). Postoperative complications were identified by Cox regression analysis as an independent risk factor for recurrence (95% CI: 1.02–15.21, P=0.047).

Conclusions: NIF-guided LH is a safe and effective approach to the treatment of hepatolithiasis, long-term outcomes being comparable to those of traditional techniques. Future studies should be larger and have longer follow-up.

Keywords: Biliary territory; hepatolithiasis; laparoscopic hepatectomy (LH); near-infrared fluorescence (NIF)

Submitted Dec 05, 2023. Accepted for publication Apr 02, 2024. Published online Jun 19, 2024.

doi: 10.21037/hbsn-23-643

View this article at: https://dx.doi.org/10.21037/hbsn-23-643

Introduction

Hepatolithiasis denotes the presence of stones in the intrahepatic bile ducts. Clinically, it is characterized by abdominal pain, fever, and other symptoms. It may occur alone or in conjunction with extrahepatic biliary stones. The stones can form in any part of the liver but have a predilection for the left lateral section (1). The incidence of hepatolithiasis varies according to region and is relatively high in East Asian countries (2). Long-standing hepatolithiasis can lead to cholangitis, cholangitic liver abscess, and hepatic parenchymal injury; eventually, biliary cirrhosis, portal hypertension, and even cholangiocarcinoma may result (1,3). Treatment options for hepatolithiasis include percutaneous transhepatic cholangioscopic lithotripsy, choledochotomy with stone extraction, and hepatectomy. Hepatectomy is considered the optimal choice (4-6).

In the 1990s, various types of laparoscopic hepatectomy (LH) were developed and introduced, mostly for treating malignant tumors; however, a few early reports described LH for hepatolithiasis (7). More recently, in conjunction with improvements in equipment and techniques, the safety and range of resection of LH have expanded and the advantages of LH for hepatolithiasis have become more evident. It has been demonstrated that LH results in less trauma, less blood loss, fewer complications, shorter hospital stay, faster recovery, and better preservation of normal liver parenchyma than does open hepatectomy (8-10).

Indocyanine green (ICG), a safe, near-infrared fluorescence (NIF) imaging agent, does not involve ionizing radiation and has minimal effects on liver function (11). It is widely used in assessment of reserve liver function, diagnosis of liver disease, and provision of guidance during liver surgery (12). ICG administered via the portal vein can achieve fluorescence visualization of liver segments or lobes through positive- or negative-staining techniques (13). When using ICG during LH for hepatolithiasis, the biliary excretion principle is used to accurately assess the extent of atrophic liver, intrahepatic stones, and diseased bile ducts (14). After intraoperative peripheral intravenous injection of ICG solution, absence of fluorescence because of obstructed biliary drainage identifies the liver tissue to be resected: this represents a type of negative staining (15). In patients undergoing LH, short-term operative indicators such as intraoperative blood loss, bile duct dilatation, and postoperative inflammation are superior when intraoperative NIF guidance has been used (15).

We have found that, after preoperative assessment of reserve liver function using ICG, the diseased liver segments or lobes continue to exhibit fluorescence during surgery, providing guidance similar to that provided by positive staining. Additionally, when positive staining is weak, NIF imaging of non-diseased liver can be achieved by injecting ICG through an endoscopic nasobiliary drainage (ENBD) tube or via direct puncture of the common bile duct, assisting navigation as well as negative staining does. We have also discovered that there is less fluorescence drift with this fluorescence imaging technique than when ICG is injected via the portal vein. In this study, we propose the concept of "biliary territory" in the context of treatment of hepatolithiasis. Our aim was to evaluate the safety and effectiveness of NIF-guided LH for hepatolithiasis. We present this article in accordance with the STROBE reporting checklist (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-643/rc).

Highlight box

Key findings

- In this study comparing near-infrared fluorescence (NIF) guided laparoscopic hepatectomy (LH) for hepatolithiasis using the 'biliary territory' concept with traditional white light, we found that, after propensity score matching, outcomes were comparable except for higher albumin concentrations on Day 3 with NIF.
- The stone recurrence rate was lower in the NIF group; however, the difference in recurrence-free survival was not statistically significant.

What is known and what is new?

- LH is increasingly being performed for hepatolithiasis despite long-term outcomes being unclear.
- To the best of our knowledge, this is the first study assessing NIF-guided LH for hepatolithiasis based on 'biliary territory'.
- We herein provide initial evidence that NIF guidance is safe and efficacious and has a lower rate of stone recurrence than the traditional technique.

What is the implication, and what should change now?

- NIF-guided LH for hepatolithiasis appears promising.
- Larger studies with longer follow-up are warranted to validate findings and refine technique.
- If confirmed, NIF-guided LH may become standard for selected patients with hepatolithiasis.

Methods

This study was approved by the Medical Ethics Committee on Biomedical Research, West China Hospital of Sichuan University (ethics number: 2021 Review 1682) and has

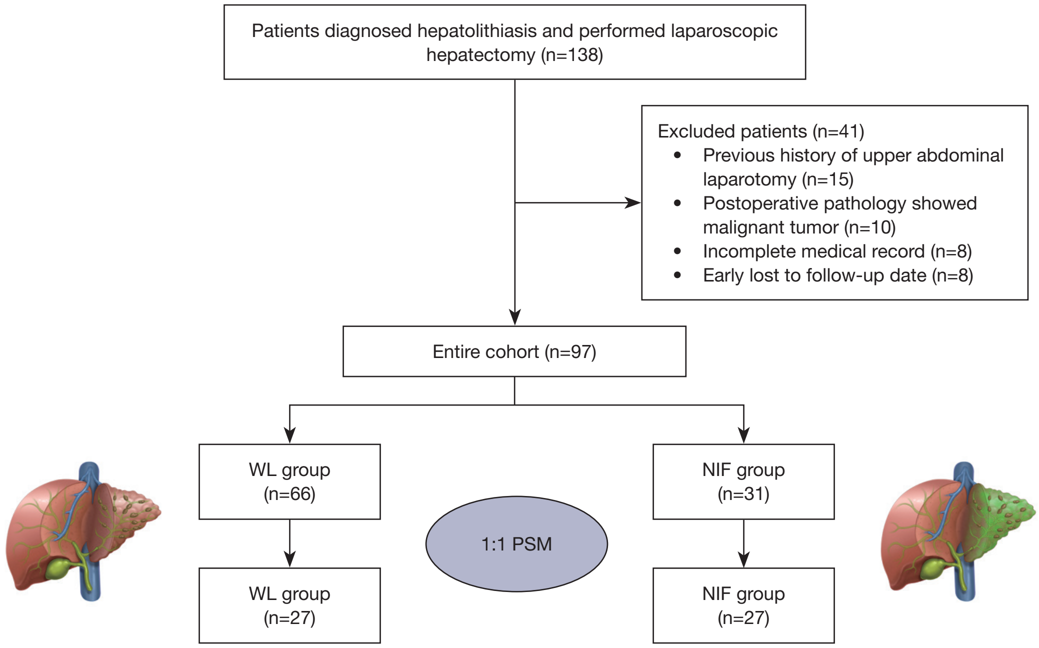

Figure 1 Study flowchart. NIF, near-infrared fluorescence; PSM, propensity score matching; WL, white-light.

been registered at www.researchregistry.com (registration number: researchregistry9528). Informed consent for treatment and for their data to be used for research purposes was obtained from all the participants. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Patients

We retrospectively reviewed relevant data of 138 patients with hepatolithiasis with or without extrahepatic stones who had undergone LH with or without choledocholithotomy in People's Hospital of Leshan between June 2018 and November 2022. Patients with Child-Pugh class B or C liver function, acute suppurative cholangitis, a history of open abdominal surgery or upper abdominal surgery other than laparoscopic cholecystectomy, comorbidities that precluded surgery, pathologically confirmed intrahepatic malignancy, incomplete clinical data (including intraoperative videos), and ICG allergy were excluded. We also excluded patients who had required bile duct reconstruction or biliary-enteric anastomosis and those lost to follow-up. After excluding 41 patients in accordance with these criteria, 97 were included for analysis and grouped. Those who had undergone LH using intraoperative NIF guidance were classified as the NIF group (31 patients), whereas those who had undergone surgery using traditional white-light (WL) laparoscopy were classified as the WL group (66 patients). Analyses were performed both before and after propensity score matching (PSM), which was performed in a 1:1 ratio (*Figure 1*).

Surgical procedures

General operative procedure

All surgeries were performed by the same hepatobiliary surgical team. The surgeons all had over 10 years of experience and each had completed more than 100 LHs. After induction of general endotracheal anesthesia, patients were placed in a supine position for LH. The intra-abdominal pressure was set at 10–14 mmHg. Central venous pressure was monitored and maintained below 5 cmH_2O. An ultrasonic scalpel (Harmonic scalpel; Ethicon, Cincinnati, OH, USA) was used to adequately mobilize the hepatic ligaments. Cholecystectomy was performed on patients with concurrent gallbladder stones or other benign gallbladder disease. When cholangioscope placement or transhepatic duct cholangioscopy for stone extraction was difficult, choledochoscopy and stone removal were performed via the common bile duct. Decisions to place a T-tube for drainage or perform primary bile duct closure were based on factors such as bile duct diameter and duodenal papillary function. The liver specimen was extracted through the umbilical incision, after which the pneumoperitoneum was deflated, puncture sites sutured, and the operation completed.

NIF-guided procedures

There are two procedures for implementation of intraoperative NIF: positive staining and negative staining via a biliary approach (*Figure 2*). For the positive staining method, ICG is injected intravenously 3 to 7 days before surgery to assess reserve liver function. When excretion of ICG-containing bile is obstructed because of bile duct stenosis, ICG accumulates behind the site of obstruction and the diseased bile duct drainage area is visible under fluorescent laparoscopy (*Figure 2A-2D* and Video S1). However, in some patients with distal bile duct stenosis on preoperative imaging, no fluorescence is visible during surgery. We implemented a negative staining method in such patients. We also used negative staining in patients who had undergone endoscopic retrograde cholangiopancreatography and ENBD before LH.

For negative staining, the diseased area is confirmed, after which the hepatic pedicle of the lobe or segment planned for resection is isolated and occluded using the Glissonean pedicle transection technique. Next, 40 to 60 mL of 0.25 mg/mL ICG solution is injected via the ENBD tube, ultimately achieving negative staining [technical note: the hepatoduodenal ligament must be clamped (Pringle maneuver) for 10 minutes to prevent ICG reflux into the duodenum] (*Figure 2E-2H* and Video S2). In patients who have not undergone endoscopic retrograde cholangiopancreatography, a 22-gauge needle is used to puncture the common bile duct for intraoperative cholangioscopy. While the hepatoduodenal ligament is clamped, 40 to 60 mL of 0.25 mg/mL ICG solution is injected directly to achieve negative staining (*Figure 2I-2L* and Video S3); this usually requires between 5 and 8 minutes.

Liver transection was performed under NIF guidance while the hepatoduodenal ligament was clamped (Pringle maneuver). The primary surgeon used an ultrasonic scalpel and bipolar forceps whereas the assistant used a suction-irrigation tube and dissecting forceps. Central venous pressure was maintained below 5 mmHg during resection. The relevant hepatic veins were divided using an endoscopic linear cutter. The remaining surgical steps were the same as described for the general operative procedure section.

Traditional LH

With the hepatoduodenal ligament clamped and low central venous pressure, the Glissonean technique was used to isolate and ligate the portal vein and hepatic artery of the liver segment or segments being resected, after which the vessels were divided. The diaphragmatic and visceral transection planes as determined on the basis of the demarcation line of liver ischemia were marked using an electric hook. The relevant parenchyma was then transected along the hepatic venous drainage using an ultrasonic scalpel. For resection of a single segment, after a hepatic venous approach, intraoperative ultrasonography was used to locate the area of interest, which was then resected using an ultrasonic scalpel. The remaining surgical steps were the same as described in the general operative procedure section.

Follow-up

All patients underwent computed tomography and T-tube cholangiography before discharge to check for any residual stones. After discharge, ultrasonography or computed tomography was performed every 3 months to identify recurrence of intra- and extra-hepatic stones. The date of last follow-up was 1 November 2023.

Histopathologic findings

Fluorescence images of resected specimens were captured using an Axio Observer microscope equipped with a charge-coupled camera (Zeiss, Oberkochen, Germany). Specimens were also stained with hematoxylin and eosin and examined microscopically.

Statistical analysis

Continuous variables were compared using Student's *t*-test, the Kruskal-Wallis test, or Mann-Whitney *U* test as appropriate. Categorical variables were compared using Pearson's χ^2 or Fisher's exact test. Recurrence-free survival (RFS) was defined as the time from the first postoperative imaging examination to show no residual stones to the time intrahepatic or extrahepatic stones were detected on follow-up imaging. Survival was analyzed using the Kaplan-Meier method and compared using the log-rank test.

To reduce confounding, PSM was performed to balance covariates between the WL and NIF groups in a 1:1 ratio. The following covariates were selected: T-tube placement, type of hepatectomy, and Tsunoda type of hepatolithiasis (16) (Figure S1). PSM resulted in 18 matched pairs. Univariate Cox proportional hazards regression was performed to

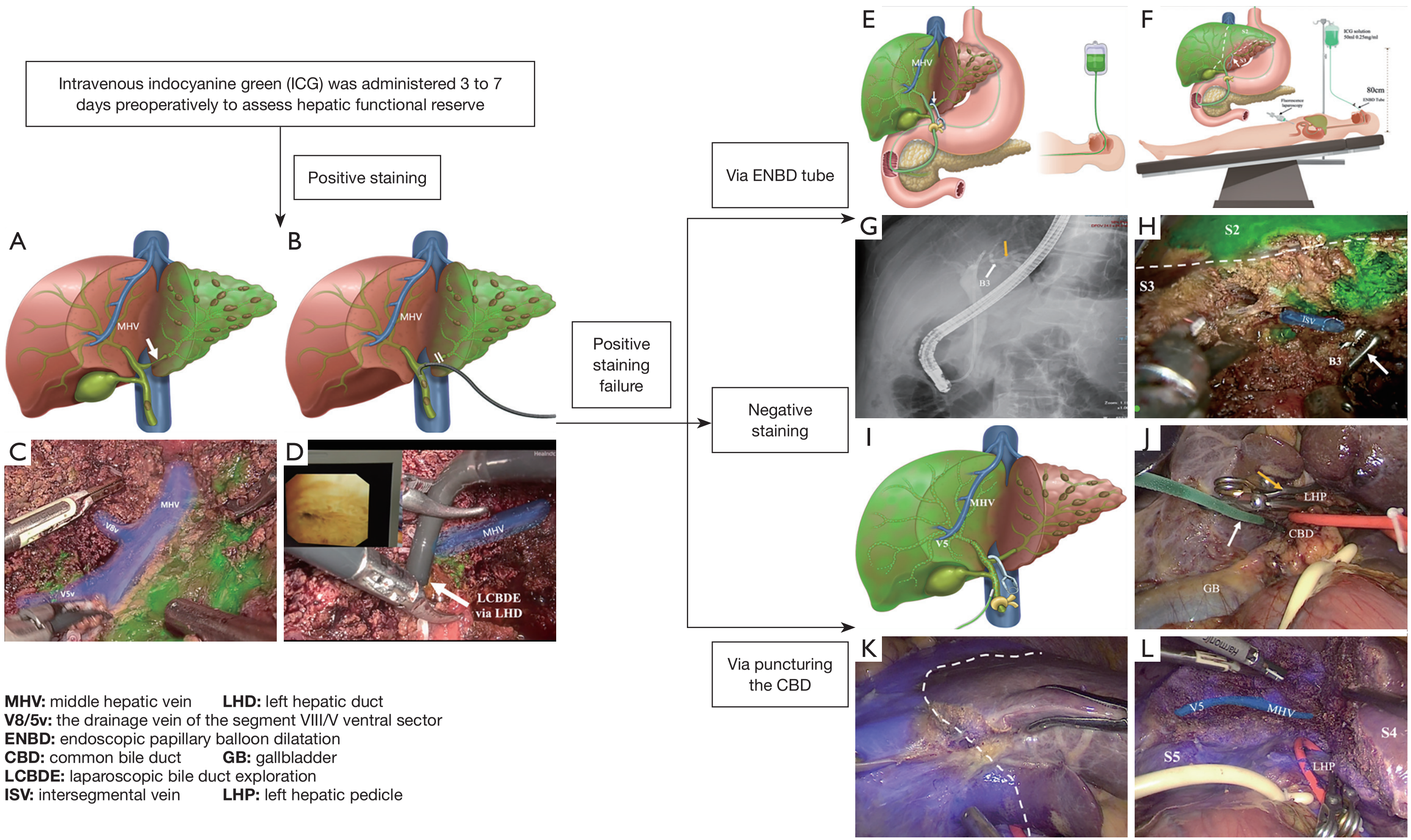

Figure 2 Intraoperative NIF guidance technology (positive and negative staining via a biliary approach). (A,B) Positive staining (the white arrow indicates stenosis of the proximal portion of the LHD). Choledochoscopy through the LHD stump (the double, white, horizontal lines indicate where the LHD has been clamped and transected). (C,D) Intraoperative images of a left hemihepatectomy under fluorescent laparoscopy. (E) Negative staining via an endoscopic nasobiliary drainage tube for left hemihepatectomy (white arrow: clip used to block the LHD). (F) LH for segment III. (G) Cholangiography after removal of common bile duct stones and nasobiliary drainage tube placement showing retained stones (white arrow) impacted in the hepatic duct of segment III and distal dilatation of the affected bile duct (yellow arrow). (H) The blue structure is the intersegmental vein coursing between segments II and III, which have no fluorescent staining. The white arrow indicates the clip used to block the hepatic duct of segment III. The white dotted line outlines the demarcation of fluorescence between segments II and III. (I) Negative staining via puncturing the common bile duct tube. (J) Intraoperative image of direct injection of indocyanine green into the common bile duct after puncture (white arrow: 22-gauge needle; yellow arrow: clip used to block the left hepatic pedicle). (K) The white dotted line outlines the fluorescent plane between the right and left hemi-livers after negative staining. (L) After splitting the hepatic parenchyma, the fluorescent plane inside the parenchyma clearly delineates the transection plane. LHD, left hepatic duct.

Table 1 Patient characteristics

Variables	Original dataset			1:1 matched dataset		
	WL group (n=66)	NIF group (n=31)	P	WL group (n=27)	NIF group (n=27)	P
Sex, male	20 (30.30)	13 (41.94)	0.26	8 (29.63)	11 (40.74)	0.39
Age, years	57.00 (51.00–67.00)	58.00 (52.50–67.00)	0.63	54.00 (50.00–64.00)	58.00 (53.00–67.00)	0.55
BMI, kg/m^2	22.05 (20.52–23.95)	22.80 (21.35–24.75)	0.15	21.50 (20.35–23.35)	22.80 (21.35–25.15)	0.07
Total bilirubin, μmol/L	9.10 (6.70–11.83)	10.20 (7.20–18.70)	0.15	7.60 (5.40–10.80)	10.20 (7.20–18.50)	0.06
Direct bilirubin, μmol/L	2.90 (1.92–5.18)	3.70 (1.95–7.60)	0.38	2.50 (1.85–5.25)	3.70 (1.90–6.45)	0.49
ALT, U/L	24.00 (17.00–38.75)	33.00 (22.00–70.50)	0.07	26.00 (18.50–42.50)	31.00 (22.00–61.50)	0.38
AST, U/L	24.00 (20.00–30.00)	28.00 (23.50–39.50)	0.042	27.00 (20.50–32.50)	28.00 (23.50–37.00)	0.42
Albumin, g/L	38.25 (34.47–41.15)	39.40 (36.90–42.10)	0.09	37.20 (33.15–40.85)	38.90 (36.40–42.10)	0.14
ICG R15, %	4.20 (2.82–5.70)	4.50 (2.70–8.45)	0.31	4.20 (2.40–5.45)	4.50 (2.70–8.20)	0.24
Tsunoda type			0.43			0.50
II	37 (56.06)	17 (54.84)		10 (37.04)	13 (48.15)	
III	22 (33.33)	13 (41.94)		14 (51.85)	13 (48.15)	
IV	7 (10.61)	1 (3.23)		3 (11.11)	1 (3.70)	
Hepatectomy type			0.037			0.49
LLH	54 (81.82)	20 (64.52)		23 (85.19)	20 (74.07)	
LRH	2 (3.03)	3 (9.68)		2 (7.41)	3 (11.11)	
LLLS	6 (9.09)	4 (12.90)		1 (3.70)	3 (11.11)	
LRPS	2 (3.03)	1 (3.23)		0	0	
LMS	2 (3.03)	3 (9.68)		1 (3.70)	0	
T-tube drainage			0.09			>0.99
Yes	36 (54.55)	24 (77.42)		20 (74.07)	20 (74.07)	
No	30 (45.45)	7 (22.58)		7 (25.93)	7 (25.93)	

Data are presented as median (IQR) or number (%). WL, white light; NIF, near-infrared fluorescence; ALT, alanine transaminase; AST, aspartate transaminase; ICG R15, indocyanine green retention rate at 15 minutes; IQR, interquartile range; LLH, laparoscopic left hemihepatectomy; LLLS, laparoscopic left lateral sectionectomy; LMS, laparoscopic monosegmentectomy; LRH, laparoscopic right hemihepatectomy; LRPS, laparoscopic right posterior sectionectomy.

determine hazard ratios (HRs) with 95% confidence intervals (CIs) to identify factors associated with stone recurrence. Statistical analyses were performed using R software version 4.0.3 (R Foundation, Vienna, Austria) and EasyR software (https://www.easyr.cc). All tests were two-sided. P<0.05 was considered to denote significance.

Results

Patient characteristics

Following PSM, the analysis included 27 patients in each group. Type of hepatectomy differed significantly between the WL and NIF groups (P=0.037) before PSM. After PSM, none of the studied variables differed significantly between the two groups. Patient characteristics in the entire and matched cohorts are shown in *Table 1*.

Surgical characteristics

In this study, we found that before PSM, the WL group had significantly higher rates of intraoperative bleeding (P=0.01), conversion to laparotomy (P=0.001), and incidence of alanine

Table 2 Surgical characteristics

Variables	Original dataset			1:1 matched dataset		
	WL group (n=66)	NIF group (n=31)	P	WL group (n=27)	NIF group (n=27)	P
Duration of surgery, min	300.00 (240.00–360.00)	300.00 (240.00–350.00)	0.88	260.00 (235.00–357.50)	305.00 (240.00–370.00)	0.35
Intraoperative bleeding, mL	150.00 (100.00–287.50)	100.00 (100.00–160.00)	0.01	200.00 (100.00–200.00)	100.00 (100.00–200.00)	0.052
Intraoperative blood transfusion			0.054			0.24
No	57 (86.36)	31 (100.00)		24 (88.89)	27 (100.00)	
Yes	9 (13.64)	0		3 (11.11)	0	
Conversion to laparotomy			0.001			>0.99
No	48 (72.73)	31 (100.00)		23 (85.19)	27 (100.00)	
Yes	18 (27.27)	0		4 (14.81)	0	
Postoperative hospital stay, day	12.00 (10.00–14.00)	12.00 (10.00–14.50)	0.85	13.00 (10.00–15.50)	12.00 (10.00–15.50)	0.97
Postoperative complications			0.058			0.13
No	43 (65.15)	26 (83.87)		17 (62.96)	22 (81.48)	
Yes	23 (34.85)	5 (16.13)		10 (37.04)	5 (18.52)	
Grade I	12 (18.18)	4 (12.90)	0.33	6 (22.22)	4 (14.81)	0.34*
Grade II	5 (7.58)	0	0.19	2 (7.41)	0	0.49*
Grade III	4 (6.06)	1 (3.23)	0.57*	1 (3.70)	1 (3.70)	>0.99*
Grade IV	2 (3.03)	0	>0.99*	1 (3.70)	0	>0.99*
Liver function on the third day after surgery						
Total bilirubin, μmol/L	15.30 (9.30–23.85)	15.60 (12.25–25.50)	0.56	18.05 (8.70–23.85)	14.90 (12.62–21.35)	0.89
Direct bilirubin, μmol/L	7.90 (3.92–14.05)	8.40 (5.45–14.10)	0.84	8.10 (4.05–16.50)	8.30 (6.05–12.45)	0.84
ALT ≥80 U/L	28 (42.42)	21 (67.74)	0.02	11 (40.74)	17 (62.96)	0.10
AST ≥80 U/L	10 (15.15)	8 (25.81)	0.56	5 (18.52)	6 (22.22)	0.74
Albumin, g/L	30.90 (28.23–33.70)	34.60 (32.05–36.10)	<0.001	31.30 (30.05–33.30)	34.40 (31.95–35.55)	0.003

Data are presented as median (IQR) or number (%). *, Fisher's exact test. WL, white light; NIF, near-infrared fluorescence; BMI, body mass index; ALT, alanine transaminase; AST, aspartate transaminase; IQR, interquartile range.

transaminase concentration ≥80 U/L (P=0.02). Additionally, the albumin concentration on postoperative day 3 was significantly higher in the NIF group (P<0.001). However, after PSM, only the albumin concentration on postoperative day 3 remained significantly higher in the NIF group (P=0.003). Furthermore, there was no significant difference in the grade of Clavien-Dindo (17) complications between the groups (P=0.058 before PSM, P=0.13 after PSM) (*Table 2*).

Stone recurrence and associated factors

The median duration of follow-up was 36 months for both groups. Prior to PSM, there were thirteen recurrences in the WL group and only two in the NIF group; this difference is significant (P=0.009). In the propensity score-matched cohort, stone recurrence occurred in 9 patients (33.3%) in the WL group and 2 (7.4%) in the NIF group.

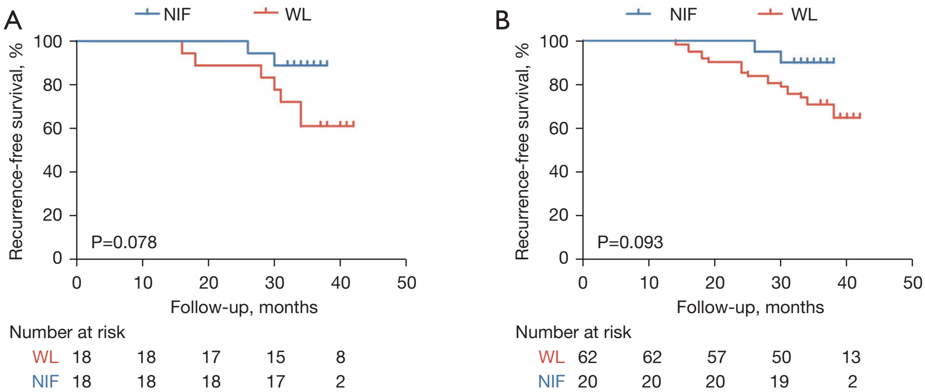

Figure 3 Kaplan-Meier curves for recurrence-free survival in the NIF and traditional WL laparoscopy groups in the propensity score-matched cohort (A) and entire cohort (B). NIF, near-infrared fluorescence; WL, white light.

The estimated median RFS was not reached in either group. RFS did not differ significantly between the PSM groups (P=0.09) (*Figure 3*).

Cox analysis

As shown in *Table 3*, univariate and multivariate Cox regression analysis showed a significant association between the occurrence of postoperative complications and stone recurrence. According to univariate analysis, the HR was 5.55 (95% CI: 1.66–18.52, P=0.005), whereas according to multivariate analysis, the HR was 3.94 (95% CI: 1.02–15.21, P=0.047). These findings suggest that the occurrence of complications increases the risk of stone recurrence. Furthermore, univariate analysis also identified prolonged hospital stay (P=0.01) and high preoperative ICG R15 (P=0.043) as indicators of stone recurrence; however, these associations were not statistically significant on multivariate analysis (hospital stay: P=0.18; ICG R15: P=0.052). Thus, the occurrence of complications appears to be an important risk factor for stone recurrence.

Pathological examination of specimens

Figure 4 demonstrates fluorescence imaging of a liver specimen that was resected using NIF guidance and the positive staining technique. Hematoxylin and eosin-stained photomicrographs are also shown.

Discussion

Most previous studies comparing traditional and NIF-guided LH have focused on treatment of hepatic malignancy (18-21). Chen *et al.* reported that NIF guidance was associated with a higher rate of R0 resection, shorter operation time, less blood loss, and lower incidence of postoperative complications (18). A PSM study reported a wider surgical margin in the NIF group (19). In a comparison of long-term outcomes of propensity-score matched patients, RFS and overall survival were superior in the NIF group (20). Cai *et al.* reported that NIF guidance can identify safe surgical margins for resection of colorectal liver metastases (21). A previous prospective randomized controlled trial comparing traditional and NIF-guided LH for hepatolithiasis, which was also the focus of our study, reported that numerous surgical indicators were superior in the NIF group (15). In a 2023 meta-analysis of 1,115 patients who had undergone LH, the R0 resection rate was higher and blood loss lower in the fluorescence than the conventional group; however, length of hospital stay, operation time, and incidence of complications did not differ significantly between these groups (22). Our study data on perioperative outcomes revealed that, after PSM, only the albumin concentration on postoperative day 3 remained significantly higher in the NIF group. However, we believe that this has little clinical significance because the sample size was small. Thus, our findings align with those of previous studies.

In the present long-term follow-up study, there was a significant difference in RFS between the two groups before performing PSM. However, after minimizing selection bias by PSM, there was no significant difference in stone recurrence between the two groups in the long-term. Of note, the RFS curves began to differ at approximately the 2-year point, reflecting the fact that hepatolithiasis recurrence is a chronic process and that studies with longer

Table 3 Results of univariate and multivariable Cox analysis

Variables	Data	Univariate Cox		Multivariable Cox	
		HR (95% CI)	P	HR (95% CI)	P
Sex					
Male	19 (35.19)	1.0			
Female	35 (64.81)	1.04 (0.31–3.46)	0.95		
Age, years	57.26±10.78	1.03 (0.97–1.09)	0.40		
BMI, kg/m^2	22.54±3.32	0.90 (0.75–1.08)	0.26		
Total bilirubin, μmol/L	12.16±10.49	0.98 (0.91–1.05)	0.56		
Direct bilirubin, μmol/L	5.71±7.41	0.96 (0.86–1.08)	0.52		
ALT, U/L	45.65±44.51	0.99 (0.98–1.01)	0.41		
AST, U/L	32.33±16.83	0.98 (0.94–1.02)	0.40		
Albumin, g/L	38.59±4.89	0.94 (0.84–1.06)	0.33		
ICG R15, %	4.76±2.74	0.72 (0.52–0.99)	0.043	0.72 (0.51–1.01)	0.052
Tsunoda type					
II	23 (42.59)	1.0			
III	27 (50.00)	0.98 (0.28–3.40)	0.98		
IV	4 (7.41)	3.62 (0.68–19.34)	0.13		
Hepatectomy type					
LLH	43 (79.63)	1.0			
LRH	5 (9.26)	0.94 (0.12–7.46)	0.96		
LLLS	4 (7.41)	1.07 (0.14–8.48)	0.95		
LMS	1 (1.85)	7.69 (0.91–65.18)	0.061		
T-tube drainage					
Yes	40 (74.07)	1.0			
No	14 (25.93)	0.90 (0.24–3.31)	0.87		
Liver function on postoperative day 3					
Total bilirubin, μmol/L	20.75±18.87	1.01 (0.99–1.03)	0.23		
Direct bilirubin, μmol/L	11.85±12.82	1.02 (0.99–1.05)	0.25		
ALT, U/L					
<80	26 (48.15)	1.0			
≥80	28 (51.85)	0.88 (0.28–2.72)	0.82		
AST, U/L					
<80	43 (79.63)	1.0			
≥80	11 (20.37)	2.22 (0.67–7.41)	0.19		
Albumin, g/L	32.57±2.98	0.91 (0.75–1.11)	0.36		

Table 3 *(continued)*

Table 3 *(continued)*

Variables	Data	Univariate Cox		Multivariable Cox	
		HR (95% CI)	P	HR (95% CI)	P
Postoperative complications					
No	39 (72.22)	1.0			
Yes	15 (27.78)	5.55 (1.66–18.52)	0.005	3.94 (1.02–15.21)	0.047
Group					
WL	27 (50.00)	1			
NIF	27 (50.00)	0.27 (0.06–1.27)	0.09		
Duration of surgery, min	302.19±92.64	1.00 (1.00–1.01)	0.38		
Intraoperative bleeding, mL	169.07±115.39	1.00 (1.00–1.01)	0.91		
Length of hospital stay after surgery, day	13.78±5.22	1.13 (1.03–1.25)	0.01	1.07 (0.97–1.19)	0.18

Data are presented as mean ± standard deviation or number (%). ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; ICG R15, indocyanine green retention rate at 15 minutes; LLH, laparoscopic left hemihepatectomy; LLLS, laparoscopic left lateral sectionectomy; LMS, laparoscopic monosegmentectomy; LRH, laparoscopic right hemihepatectomy; LRPS, laparoscopic right posterior sectionectomy; WL, white light; NIF, near-infrared fluorescence; HR, hazard ratio; CI, confidence interval.

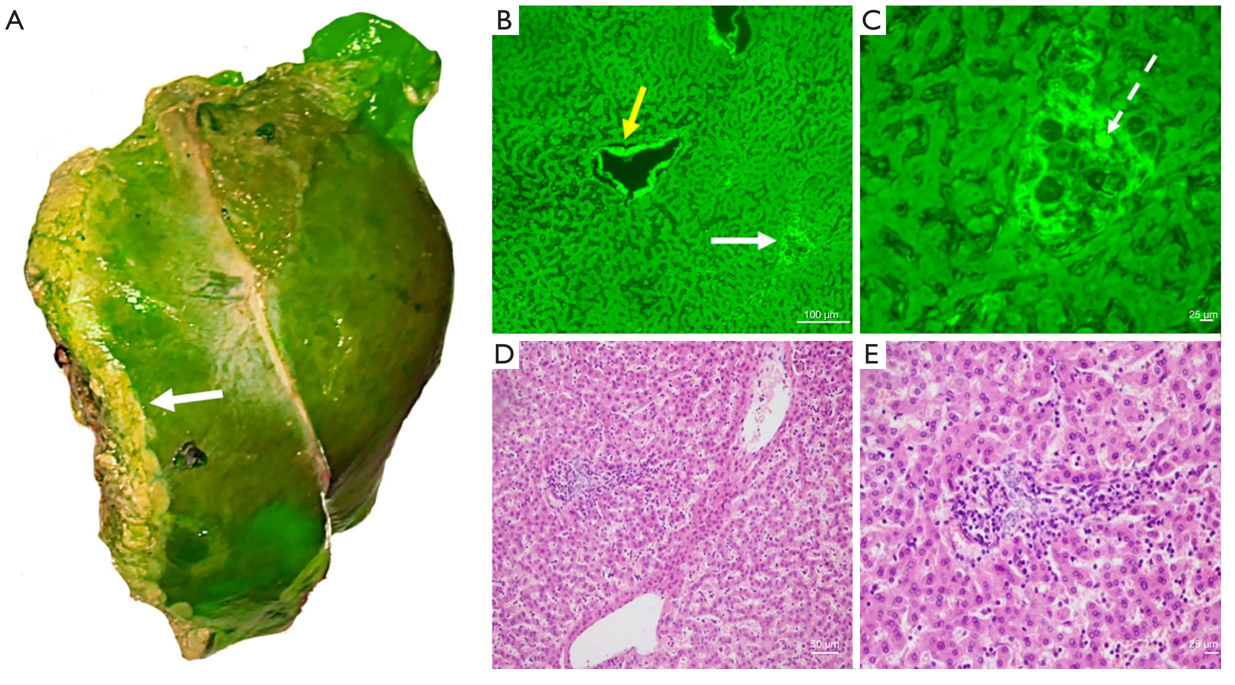

Figure 4 Hematoxylin and eosin-stained photomicrographs of a liver specimen from a patient in the NIF group. (A) Gross operative specimen from a patient with Tsunoda type III left hepatolithiasis who underwent LH using near-infrared fluorescence and the positive staining technique. White arrow: site from which specimens were sampled for microscopy. (B) Liver lobule structure observed under a fluorescence microscope showing deposition of indocyanine green in hepatic sinusoids, hepatocytes, central veins, and portal areas (scale bar =100 μm). Yellow arrow: deposition in the endothelial layer of the central vein; white arrow: deposition in the portal area. (C) Magnified image of the area indicated by the white arrow in (B) (scale bar =25 μm). White dashed arrow: deposition of indocyanine green in intrahepatic bile ducts between lobules. (D,E) Photomicrographs after hematoxylin and eosin staining showing normal liver cell cords and mild lymphocytic infiltration in the portal area (hematoxylin and eosin staining, scale bars =50 μm, 25 μm, respectively).

follow-up are needed. The main causes of recurrence after hepatectomy for hepatolithiasis are residual stones, infection caused by postoperative bile leakage, and persistent biliary stricture or angulation (3). We identified occurrence of postoperative complications as an independent risk factor for stone recurrence, which is consistent with conclusions reached by previous researchers.

Localization of fluorescence was achieved in the positive staining cases using the association between biliary obstruction and impaired ICG excretion in bile. This association can also be used in other situations where there is localized cholestasis. Both Han *et al.* and Harada *et al.* reported cases of biliary obstruction and localized cholestasis caused by tumor compression; both of these research groups successfully completed LH using fluorescence imaging of the obstructed region (23,24). Yang *et al.* also reported using this procedure in hepatectomy for intrahepatic cholangiocellular carcinoma; they found that imaging the site of bile duct obstruction achieved valid demarcation in 93.8% of patients (25). In our study, in cases where preoperative magnetic resonance cholangiopancreatography indicated an obvious bile duct stricture, we observed a higher success rate for traditional staining. Positive staining was successful in 75% of attempts. Failure of this procedure in the remaining cases may have been related to a relatively long interval between preoperative ICG injection and intraoperative fluorescence imaging. Alternatively, in some patients, the bile duct stenosis identified by preoperative imaging may not have impaired excretion of bile.

When positive staining failed to delineate the liver region to be resected, we proceeded with negative staining, which can serve as a valuable supplement to our NIF technique. Previous researchers have reported administration of ICG solution via an ENBD tube to detect bile leakage at the transection plane during laparoscopic deroofing of liver cysts (26,27). In our study, five patients had incomplete biliary stenosis. Although incomplete stenosis may alter intrahepatic biliary hydrodynamics and induce stone formation, partially patent ducts would not cause accumulation of ICG-containing bile in the diseased region. In such cases, fluorescence would not be observed. Furthermore, intrahepatic bile duct dilatation can cause compression and narrowing of portal veins within the same Glissonean pedicle, making it difficult to achieve puncture of the affected vascular territory. Anatomical variations in intrahepatic bile ducts are reportedly extremely common and the drainage territories of the portal vein and intrahepatic bile duct do not precisely match (28). Given that intrahepatic bile duct stones are distributed along the biliary tree, the area of hepatectomy should be based on biliary territory rather than the traditional Couinaud's liver segmental anatomy. In our experience, fluorescence imaging of the biliary tract, whether by positive or negative staining, provides sharp and stable demarcation without significant fluorescence drift. Examination of resected liver specimens from patients in whom positive staining was successful showed that ICG had accumulated in the liver sinusoids, hepatocytes, and confluence areas and around the central veins. In paraffin-embedded sections, positively stained normal hepatic lobules still exhibited persistent and uniformly distributed fluorescence, indicating durability and stability of effect. In our study, negative staining was achieved in five cases by injecting ICG into the common bile duct. To the best of our knowledge, this is the first report of implementing this procedure worldwide.

Cholestasis is characterized by accumulation of conjugated bile acids and bilirubin in the blood. Of note, high plasma bilirubin concentrations result in increased liver retention of ICG. Given that uptake of conjugated bile acids is primarily mediated by sodium taurocholate cotransporting polypeptide (NTCP), it is likely that bile salts inhibit NTCP-mediated uptake of ICG during cholestasis (14). Thus, we hypothesize that NTCP also plays a role in transporting ICG molecules from bile into hepatocytes. However, the mechanism of negative staining is not yet fully understood. Further basic science studies are warranted.

This study had several limitations. The sample was small and follow-up was relatively short. Furthermore, there may have been selection bias regarding group assignment. Future studies with larger patient cohorts and longer follow-up are needed, as are studies to determine optimal ICG concentration and injection volume for fluorescence mapping of the biliary tree.

Conclusions

NIF-guided LH based on the biliary territory concept is a safe and effective procedure for treating hepatolithiasis. Our new technique provided useful intraoperative visual information and may achieve a significantly improved RFS than traditional WL LH in future studies with longer follow-up. Further research is needed to validate our findings, examine long-term outcomes, and refine the technique.

Acknowledgments

We thank Dr. Trish Reynolds, MBBS, FRACP, from Liwen Bianji (Edanz) (http://www.liwenbianji.cn/) for editing the English text of a draft of this article.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-643/rc

Data Sharing Statement: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-643/dss

Peer Review File: Available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-643/prf

Funding: This work was supported by grants from the National Natural Science Foundation of China (82173124, 82103533, 81972747, and 82203823); the Natural Science Foundation of Sichuan Province (2023NSFSC1877); the Science and Technology Program of Sichuan Province (2023JDR0077, 2022YFQ0077).

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://hbsn.amegroups.com/article/view/10.21037/hbsn-23-643/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This retrospective study was approved by the Medical Ethics Committee on Biomedical Research, West China Hospital of Sichuan University (ethics number: 2021 Review 1682). This clinical study has been registered at www.researchregistry.com with the registration number researchregistry9528. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent for treatment and for their data to be used for research purposes was obtained from all the participants.

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Cite this article as: Gao F, Xie Q, Zhao X, Yang M, Jiang K, Mao T, Yang J, Wu H. Laparoscopic hepatectomy and near-infrared fluorescence based on the concept of “biliary territory” in the treatment of hepatolithiasis: a propensity score-matched study with videos. HepatoBiliary Surg Nutr 2025;14(2):194-206. doi: 10.21037/hbsn-23-643