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LETTER

Personalized laparoscopic radical resection of gallbladder cancer by staining of the liver draining area through ICG injection into the cholecystic artery

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Gallbladder cancer (GBC) is a common malignant tumor often diagnosed in advanced stages. Surgery is among the most important treatments for GBC. Radical resection of GBC involves removal of the gallbladder and the gallbladder bed [liver segments (S) 4b and 5], and hepatoduodenal ligament regional lymphadenectomy. The main GBC metastasis modes are blood and lymph node metastases. The scope of resection/wedge resection or regular S4b and S5 hepatectomy for blood metastasis is a matter of debate. A variety of hepatectomy methods have been proposed for T2 stage GBC, but no consensus has been reached regarding the scope of radical resection. Currently, the liver resection range is determined by branches of the portal vein. S4b and S5 hepatectomy is determined according to the liver portal vein branch perfusion area, but the rationale for liver resection for GBC is to eliminate potential metastasis from the cystic vein reflux area to the liver. In the case described herein, we used a novel technique and theoretical framework to conduct laparoscopic radical resection of gallbladder cancer (LRRGC) facilitated by staining of the liver draining area with an indocyanine green (ICG) injection into the cholecystic artery.

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LRRGC is feasible, but the extent of liver resection is debated

The primary technologies used in LRRGC are well established. According to the expert consensus on LRRGC, patients with stage T1b and T2 cancer without significant metastasis to the hepatoduodenal ligament lymph nodes are eligible for LRRGC at experienced laparoscopic surgery centers[1]. Although studies have reported the feasibility and safety of laparoscopic wedge resection or S4b/5 resection, no consensus exists regarding the optimal extent of hepatectomy. The 2019 edition of the "Guidelines for the Diagnosis and Treatment of Gallbladder Cancer" recommends simple cholecystectomy for Tis or T1a stage cancers. For T1b and T2a stages, a combined wedge resection of liver tissue at least 2 cm from the gallbladder bed is advised. For T2b stage cancers, surgical resection may involve either wedge resection of the liver or resection of S4b and S5; however, the superiority of either technique remains unclear. The 2023 CSCO guidelines also state that simple cholecystectomy is appropriate for Tis or T1a stages. For gallbladder cancer stages above T1b stage, combined wedge resection of liver tissue at least 2 cm from the gallbladder bed is recommended. For T2 and T3N0 stages, the liver resection approach includes S4b and S5.

A multicenter retrospective study by Lee et al. has indicated no significant differences in the 5-year survival rate or recurrence-free survival rate after wedge resection or IVb/V resection of the liver in patients with T2 GBC who underwent extended cholecystectomy, and other studies have reported similar results[2]. However, some reports have suggested that, compared with liver wedge resection, liver IVb and V

segmentectomy effectively prolongs the disease-free survival and overall survival times of patients with T2b GBC. Liver IVb and V segmentectomy is an independent protective factor in the prognosis of patients undergoing radical resection for T2 GBC[3].

Cholecystic venous drainage and its role in GBC metastasis

Currently, S4b and S5 hepatectomy is determined according to the liver portal vein branch perfusion area, but the rationale for liver resection for GBC is to eliminate potential metastasis from the cystic vein reflux area to the liver.

Some studies have reported that the sites of liver metastases correlate with areas of cholecystic venous drainage, particularly in concurrent and early postoperative metastasis (occurring within 6 months after surgery)[4,5]. A metastatic tumor in the S6 segment has been reported in one patient, and cholecystic venous drainage is not confined solely to S4a or S5 but may also extend to S4b, S3, S1, S2, and S8. The route of cholecystic venous flow can be classified into 2 patterns: cholecystic vein flow directly into the hepatic parenchyma adjacent to the gallbladder (type 1) or cystic vein flow into sites separate from the gallbladder (type 2)[6]. Another study has described 2 modes of drainage of the cystic veins. The first type is drainage from the fundus and corpus of the gallbladder through the liver bed, before merging into branches of the portal vein in S4b and S5 (primary), and S1, S6, and S8 (secondary). The second type is cystic duct drainage into the main trunk of the portal vein and around the left and right bifurcation through the triangle of Calot. Alternatively, drainage may occur alongside the peribiliary vein, into the portal vein supplying the anterior right lobe of the liver or intra-haptic branches of the portal vein in S4 and S1[7]. Overall, the reflux area of cystic vein occurs in segments other than S4a or S5.

Exploration of fluorescence-guided personalized liver resection for GBC

Preliminary clinical practice has explored various techniques. One technique was described in 2004 for 4 hepatic resections of pT2 gallbladder cancer, involving ICG injection through the cystic artery. The distance between the demarcation line and the gallbladder ranged from 1.0 to 5.0 cm. The extent of the stained area differed among individuals, and 1 of the 4 resected livers had micrometastasis in the portal area 27 mm from the gallbladder wall. No recurrence was observed in any of the 4 patients at 16–26 months after operation[8]. This study involved laparotomy, and additional equipment was required to effectively demonstrate the range of fluorescence staining. One case report used ICG fluorescence imaging during laparoscopic radical surgery to delineate the gallbladder venous reflux area in a patient with T2 stage gallbladder cancer. No new complications were reported with this technique compared with traditional surgical methods[9]. The surgeon encircled Calot's triangle by using the Glissonean approach from the ventral side of the gallbladder plate, then taped the hilar Glissonean pedicles. Notably, ICG was administered intravenously, not directly through the cystic artery. The application of this method may be influenced by common variations in the hepatic artery, thus potentially influencing the staining results. In another study, 24 consecutive patients diagnosed with cT2 GBC underwent hepatic resection through laparotomy with ICG navigation. Microscopic liver metastasis was detected in the resected liver in 3 (20%) of 15 patients, and the liver sites were S6, S5, and S5. The resected liver weight with ICG navigation was significantly less than that with S4a/S5 segmentectomy. The extent of hepatectomy was individualized for each patient without excess or deficiency. Therefore, an insufficient remnant liver volume and postoperative complications may be avoided. In all patients, the disease-free survival rate was 59.1% at 5 years, and the overall survival rate was 86.2% at 5 years[10]. The study used laparotomy, which required an external fluorescence display device.

The techniques for laparoscopic radical cholecystectomy for gallbladder cancer are only in preliminary stages. However, no study has directly injected ICG through the cystic artery under laparoscopy to visualize the cystic vein reflux area in real time by using fluorescence laparoscopy. Accordingly, we conducted a preliminary exploration of this approach.

Achieving personalized LRRGC through ICG injection into the cystic artery

We present a video showing a 67-year-old woman undergoing radical laparoscopic GBC resection. No lung metastases were detected on preoperative CT, and no intrahepatic metastases were found on preoperative CT and intraoperative ultrasound. Gallbladder T2bN0M0 (stage IIb) stage cancer was confirmed

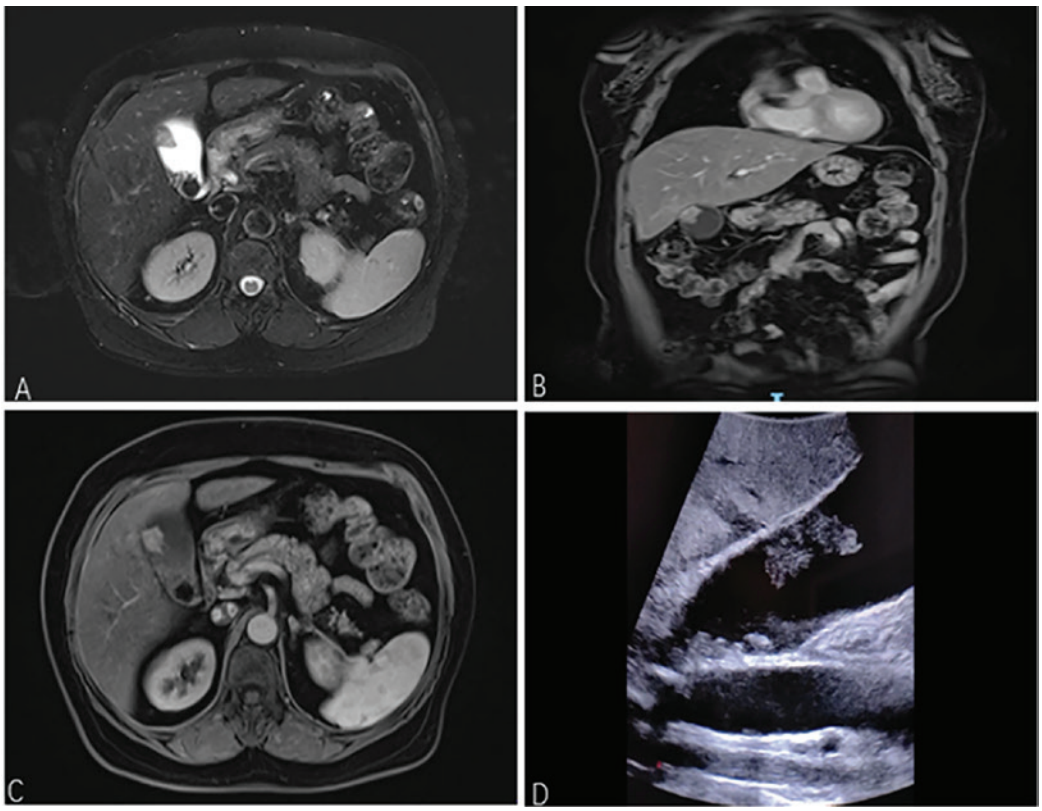

Figure 1 The gallbladder mass was located near the liver side of the gallbladder. The gallbladder mass was irregularly thickened, a nodular shadow protruded into the lumen, and the serosal surface of the gallbladder wall was smooth (A and B). An enhanced scan showed markedly enhancement of the gallbladder wall, a soft tissue mass, and sustained enhancement (C). An intraoperative ultrasound revealed a mass in the gallbladder cavity that did not penetrate the serous membrane (D).

(**Figure 1**). After the patient provided signed informed consent, we proceeded with the surgical procedure.

The cystic triangle was dissected, and the cystic duct was divided, ligated, and cut. Frozen pathologic evaluation revealed no residual tumor at the cut edge. The cystic artery was completely exposed, and an arterial clamp was used to temporarily occlude the cystic artery, after which a 2.5 mg dose of ICG was injected into the cystic artery with a 9 G needle. After the injection, the arterial clamp was released to prevent backflow from the injection. Subsequently, the perihepatic ligaments were mobilized, and fluorescence staining of the liver tissue was found to be consistent with the cystic vein reflux area. The boundary of the stained area in the liver parenchyma was marked by electrocautery before liver transection (**Figure 2**). Lymph nodes were dissected, including Nos. 13a, 12a/b/p, and 8a/p. The direction of lymph node dissection followed the lateral cephalic side of the foot side, from the left to the right side. The peripheral gallbladder nerves were cleaned. The Pringle maneuver was applied to control the blood flow, and the hepatic parenchyma was transected along the demarcation line marked by fluorescence. The operative time was 120 min, and the blood loss was 50 mL. No indications for blood transfusion were observed. The Pringle maneuver was applied twice for a total of 25 min. The postoperative recovery was uneventful. The patient was discharged on the fifth day postoperatively. Histopathologic evaluation revealed that the GBC was a T2 tumor without lymph node metastasis.

In conclusion, the scope of hepatectomy for GBC can be feasibly determined through injection of ICG into the cystic artery with fluorescence laparoscopy. We propose that using the gallbladder venous drainage area as a guide in fluorescence laparoscopic radical cholecystectomy facilitates precise and personalized resection of potential hepatic metastatic regions while optimizing preservation of the liver parenchyma. Furthermore, this method streamlines the determination of resection boundaries during laparoscopic liver surgery, thereby enhancing surgical efficiency. This method not only ensures the radical excision of tumors but also fosters

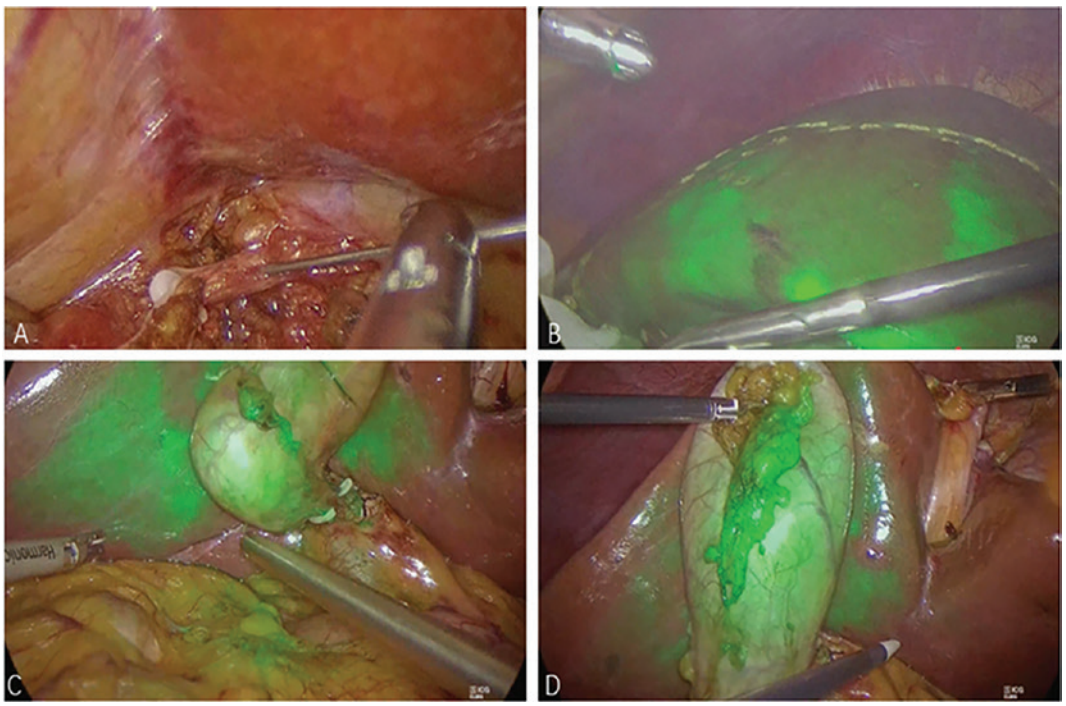

Figure 2 The cystic artery was completely exposed, and ICG (2.5 mg) was injected by puncturing the cystic artery with a 9 G needle (A). Fluorescence staining of the diaphragm surface of the liver (B). Fluorescence staining on the right side of the liver (C). Fluorescence staining on the left side of the liver (D).

expedited patient recovery and allows for prompt initiation of necessary postoperative treatments.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Wei Zhang.
Collected the data: Xu Bao, Dongyang Li.
Wrote the paper: Xu Bao, Dongyang Li.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

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