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DYNAMIC MANUSCRIPT

Real-time identification of aberrant left hepatic arterial territories using near-infrared fluorescence with indocyanine green during gastrectomy for gastric cancer

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Abstract

Background An aberrant left hepatic artery is frequently encountered during upper gastrointestinal surgery, and researchers have yet to propose optimal strategies with which to address this arterial variation. The objective of this study was to determine whether the areas perfused by an aberrant left hepatic artery can be visualized in real-time using near-infrared fluorescence imaging with indocyanine green.

Methods Patients with gastric adenocarcinoma who underwent minimally invasive radical gastrectomy from May 2018 to August 2019 were enrolled and retrospectively analyzed at a single-center. Patients with an aberrant left hepatic artery and normal preoperative liver function were examined. After the clamping of an aberrant left hepatic artery, indocyanine green was administered via a peripheral intravenous route during surgery. Fluorescence at the liver was visualized under near-infrared fluorescence imaging.

Results In 31 patients with aberrant left hepatic arteries, near-infrared fluorescence imaging was used without adverse events associated with indocyanine green. Six (19%) patients were reported to have an aberrant left hepatic artery upon preoperative CT imaging, while all other instances were detected during surgery. Fluorescence excitation on the liver was, on average, visible after 43 s (range, 25–65). Fluorescence across the entire surface of the liver was noted in 20 (65%) patients in whom the aberrant left hepatic artery could be ligated. Aberrant left hepatic arteries were safely preserved in 10 (32%) patients who showed areas of no or partial fluorescence excitation. Guided by near-infrared fluorescence imaging, ligation of aberrant left hepatic arteries elicited no significant changes in postoperative liver function.

Conclusion Near-infrared fluorescence imaging facilitates the identification of aberrant left hepatic arterial territories, guiding decisions on the preservation or ligation of this arterial variation.

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During upper gastrointestinal surgery, an aberrant left hepatic artery (ALHA) arising from the left gastric artery (LGA) is seen in approximately 6.5% to 34% of patients [1–7]. During radical gastrectomy with lymph node dissection for gastric cancer, the LGA should be ligated at its origin, thereby eliminating arterial flow from an ALHA. Although surgeons may desire to preserve an ALHA during gastrectomy for gastric cancer, as ligating it occasionally results in hepatic dysfunction or fatal hepatic necrosis, it is not always technically feasible and introduces the possibility of leaving metastatic lymph nodes behind [8, 9].

In recent studies, surgeons have attempted to develop tools of use in determining whether to preserve or ligate ALHAs based on accurate measurement of the diameters of the LGA and ALHAs, as well as anatomical information using advanced CT modalities [10, 11]. Meanwhile, a new surgical platform employing near-infrared fluorescence imaging (NIRFI) that allows surgeons to map the drainage patterns of the lymphatics, to assess vessel patency, and to identify primary or metastatic tumors has found use as a means with which to visualize biliary or vascular structures and to distinguish the boundaries of liver segments for fewer accidental injuries [12]. In patients with an ALHA, clinicians may be able to use this technology to visualize exclusive areas of the liver perfused by an aberrant artery in a real-time fashion.

In this study, we describe a novel, simple, and safe technique employing NIRFI to visualize ALHA territories on the liver during minimally invasive gastrectomy and its potential use in determining whether to ligate or preserve ALHAs during surgery.

Materials and methods

Patients

Patients with gastric cancer who had undergone radical gastrectomy via a laparoscopic or robotic procedure from May 2018 to July 2019 were retrospectively reviewed. All patients who were found to have an ALHA upon intraoperative laparoscopic exploration under NIRFI with ICG (Dongindang Pharmaceutical, Siheung, Korea) were included. We defined an aberrant hepatic artery (i.e., ALHA) in this study as an abnormally derived hepatic artery not originating from the celiac axis, the common hepatic artery, or the proper hepatic artery. An accessory ALHA was defined as an ALHA that partially vascularized the left hemi-liver and existed in addition to a normal left hepatic artery [13, 14]. A replacement ALHA was defined as an ALHA that vascularized segments 2, 3, and 4 of the left hemi-liver, with no other arterial supply to the left lobe of the liver or with poorly developed collaterals between the right and left lobes.

Patients with liver diseases, such as liver cirrhosis, that would hinder excretion of ICG; patients with abnormal liver function test results, including aspartate transaminase, alanine transaminase, total bilirubin, alkaline phosphatase, and gamma-glutamyl transferase levels, beyond standard reference values before the operation; patients who planned to undergo cholecystectomy; and patients with a prior history of hepatic or gastric operation were excluded from the study. Preoperative computed tomography (CT) scans for preoperative staging were taken at the referring hospital or at our institution with various protocols. In our institution, the preoperative gastric cancer CT protocol included arterial/portal phase axial and coronal reconstructed images of 3-mm thick sections obtained with a 16- or 64-channel multidetector CT scanner. Further details have been described in the literature [15]. All patients provided written informed consent for the procedure and were able to freely to choose totally laparoscopic or reduced-port totally robotic gastrectomy as described in previous reports [16]. Approval for this retrospective study was obtained from the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (4–2018-1117).

Operative technique

The operative procedures included totally laparoscopic (five-port) or robotic (reduced-port) gastrectomy. Detailed descriptions thereof have been provided elsewhere [16–18]. D2 lymph node dissection for clinically advanced cancer and D1 + lymph node dissection for early cancer were applied in accordance with appropriate guidelines on preoperative staging [19, 20].

NIRFI technique

To visualize areas perfused by ALHAs under NIRFI, we used the PINPOINT® Endoscopic Fluorescence Imaging System (Stryker, Kalamazoo, MI, USA) during laparoscopic and the Firefly® system integrated into the da Vinci Xi® surgical system (Intuitive Surgical, Sunnyvale, CA, USA) during robotic gastrectomy for gastric cancer. To identify the presence of an ALHA during liver retraction at the beginning of the operation, planned lymph node dissection proceeded until the root of the LGA was exposed. An endo-clamp was then applied to the ALHA near the left lobe of the liver. Afterward, 5 mg of ICG dissolved in 2 ml of sterile water was administered via a peripheral intravenous injection, and the operation view was switched to NIRFI to visualize fluorescence excitation of both lobes of the liver. During the procedure, there was no need to explore vascular anatomy in the porta hepatis or inflow vascular control, such as Pringle's maneuver. If there was no absence of fluorescence across the entire left lobe of the liver, the ALHA was ligated. If there was any absence or faintness of fluorescence excitation, the vascular clamp was unclamped, another 5 mg of ICG was injected, and fluorescence excitation was re-evaluated. When the previously absent fluorescence was restored after the second administration of ICG, the ALHA was endeavored to be left intact (Fig. 1). During laparoscopic surgery with the PINPOINT® system, we alternated among three different modes to better identify areas of less fluorescence on the liver: Pinpoint Fluorescence, real-time visualization of pseudocolor-fluorescence signals on white light images; SPY Fluorescence, black and white fluorescence images; or Color Segmented Fluorescence, a color scale ranging from gray for no perfusion to red for high degrees of perfusion.

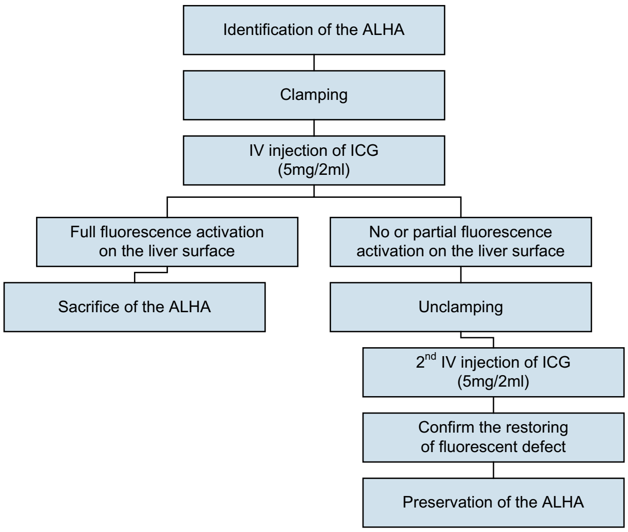

Fig. 1 Scheme for detecting areas on the left lobe of the liver exclusively supplied by an aberrant left hepatic artery (Color figure online)

Postoperative evaluation

For postoperative assessment of liver function, AST and ALT levels were evaluated at postoperative days 0, 1, 2, 3, and 5. Any complications that required additional pharmacologic, interventional, or surgical management were recorded and graded based on Clavien–Dindo classification [21]. Patients were recommended to be discharged from day 5 after the operation if there were no complications or dietary issues.

Measurement of operative outcomes and NIRFI results

Patient characteristics and operation-related variables were compared for the entire study group and in relation to ligation and preservation of ALHAs. Continuous variables are presented as means and ranges, while categorical variables are described as counts and percentages. All calculations and comparisons were conducted using R version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, NIRFI and ICG were utilized to visualize territories of ALHA perfusion in a total of 31 patients. No adverse events associated with the ICG injection, such as allergic reactions, were recorded. All gastrectomies were completed without conversion or additional port insertion. The preoperative characteristics of the patients, including 21 (68%) males and 10 (32%) females with normal liver function, are shown in Table 1. The mean age and body mass index value were 62.7 years (range, 40—84) and 23.7 kg/m^2 (range, 19.0—29.9), respectively. Clinical T1 cancer was suspected preoperatively in 27 (87%) patients. Six (19%) patients were reported to have an ALHA on preoperative CT scan: two had a replacement ALHA, another two had an accessory artery, and the other two were unspecified. All other instances of an ALHA were detected during surgery.

Table 1 Preoperative patient characteristics

Variables	(n=31)
Age, years	62.7 (40–84)
Sex	
Male	21 (67.7%)
Female	10 (32.3%)
Body mass index, kg/m^2	23.7 (19.0—29.9)
ASA class	
1	7 (22.6%)
2	15 (48.4%)
3	7 (22.6%)
4	2 (6.4%)
Depth of invasion, clinical	
cT1	27 (87.1%)
cT2/3	3 (9.7%)
cT4a	1 (3.2%)
Lymph node metastasis, clinical	
cN0	30 (96.8%)
cN +	1 (3.2%)
Presence of ALHA on preoperative CT scan	
Absent	25 (80.6%)
Present	6 (19.4%)
Replaced	2
Accessory	2
Not mentioned	2
Preoperative liver function test parameters	
Aspartate transaminase, IU/L	19.5 (9–30)
Alanine transaminase, IU/L	17.0 (8–45)
Total bilirubin, mg/dL	0.6 (0.2–1.3)
Alkaline phosphatase, IU/L	63.8 (31–113)
Gamma-glutamyl transferase, IU/L	19.7 (8–40)

ASA American Society of Anesthesiologists, *ALHA* aberrant left hepatic artery

All data are presented as a mean and range or number and %

Intraoperative results of NIRFI using indocyanine green

The presence of strong, uniform fluorescence excitation on the entire surface of the liver (Supplementary video 1) was found in 20 patients (group 1); fluorescence was absent or faint in parts of (Supplementary video 2) or along the entire left lobe of the liver (Supplementary video 3) in 11 patients (group 2). The ALHAs of the patients in group 1 were all ligated. The ALHAs of the patients in group 2 were first re-evaluated by additional administration of ICG after unclamping the ALHA and preserved upon confirmation of restored fluorescence. Intraoperative images for the patients in whom fluorescence was initially absent, but restored upon a second ICG injection and unclamping of the ALHA, are shown in Fig. 2 and Supplementary Fig. 1. All ALHAs in the patients in group 2 were successfully preserved, except in 1 patient (Patient No.11) due to technical difficulties.

Perioperative results, including postoperative changes in liver function

Table 2 outlines perioperative parameters, including postoperative pathologic results, for the entire study cohort. The mean operation time for all 31 patients was 196 min (range, 97–278). Intraoperative mean blood loss was estimated at 82.3 mL (range, 10–286). Twenty-eight (90.4%) patients were diagnosed with stage I cancer. The mean number of retrieved lymph nodes was 39.2 (range, 20–73). The mean postoperative hospital stay was 7.4 days (range, 5–21). No patient required any medicine for liver protection, such as a liver extract, or experienced an elevation in liver enzymes after discharge. Also, no major complications (Clavien–Dindo system grade III or higher) related to hepatic ischemia or surgery were recorded during the study period.

The characteristics of fluorescence of ALHA territories are depicted in Table 3. Fluorescence excitation of the liver parenchyma began to be visible from the caudate lobe of the liver after a mean of 43 s (range, 25–65). Among the 11 patients in group 2, fluorescence was absent in segment 2 only ($n=2$), segment 3 only ($n=1$), segments 2 and 3 ($n=4$), segments 3 and 4 ($n=1$), and segments 2, 3, and 4 ($n=3$). The mean time to preserve the ALHA in 10 of the 11 patients was 13 min, 12 s (range, 8:24–21:02).

A comparison of surgical outcomes and postoperative complications in patients in whom ALHAs were ligated or preserved under NIRFI is shown in Table 4. There were no

Table 2 Operative and pathologic outcomes

Variables	($n=31$)
Operation method	
Laparoscopy	21 (67.7%)
Robot	10 (32.3%)
Extent of gastric resection	
Distal subtotal	25 (80.6%)
Proximal	4 (12.8%)
Total	2 (6.4%)
Extent of lymph node dissection	
D1 +	26 (83.9%)
D2	5 (16.1%)
Operative time, minutes	196.4 (97–278)
Estimated blood loss, mL	82.3 (10–286)
Pathological stage, AJCC 8th	
I	28 (90.4%)
II	2 (6.4%)
III	1 (3.2%)
Number of metastatic lymph nodes	0.4 (0–11)
Number of retrieved lymph nodes	39.2 (20–73)
Resumption of soft diet, POD	4.8 (4–16)
Hospital stay, POD	7.4 (5–21)
Clavien–Dindo classification (Grade III or severe)	0

AJCC American Joint Committee on Cancer, *POD* postoperative day
All data are presented as a mean and range or number and %

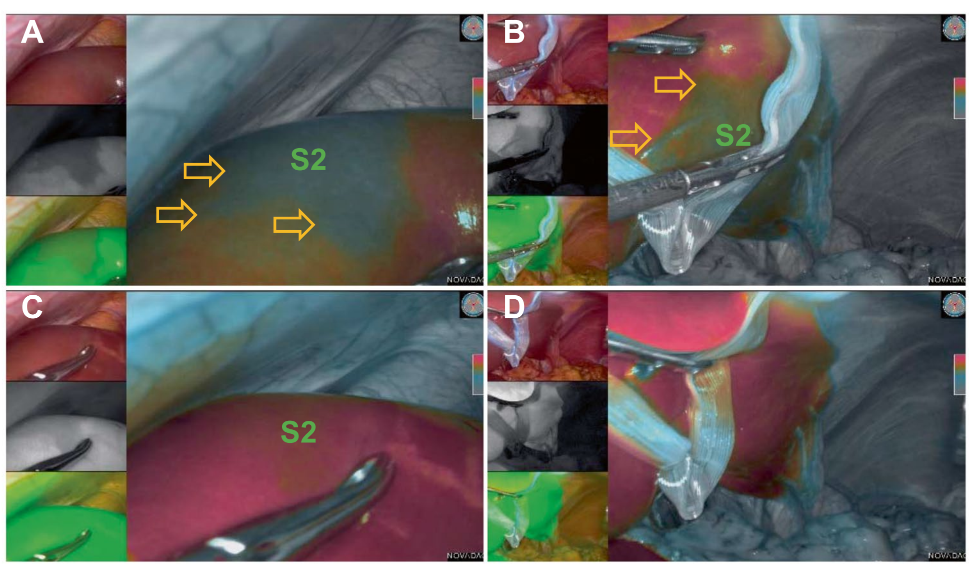

Fig. 2 Use of intraoperative near-infrared fluorescence imaging with indocyanine green to identify areas of the left lobe of the liver supplied by an aberrant left hepatic artery. **A** A lack of fluorescence (arrows) is noted along the upper surface of segment 2. **B** A lack of fluorescence is well visualized with the Color Segmented Fluorescence (CSF) mode. **C** Restored fluorescence at segments 2 and 3. **D** Restored fluorescence at segments 2 and 3 in the CSF mode (Color figure online)

Table 3 Evaluation of aberrant left hepatic arteries

Variables	($n=31$)
Time to fluorescence on the liver, seconds	43.1 (25–65)
Strong, uniform fluorescence along the entire left lobe of the liver	
Present	20 (64.5%)
Absent/Faint	11 (35.5%)
Segment 2	2
Segment 3	1
Segments 2, 3	4
Segments 3, 4	1
Segments 2, 3, 4	3
Management of ALHAs	
Ligation	20 (64.5%)
Preservation	10 (32.3%)
Attempted to preserve	1 (3.2%)
Intraoperative complication	0
Time to preserve the ALHA, minutes:seconds*	13:12 (8:35–21:02)

ALHA aberrant left hepatic artery

*Time to preserve the ALHA for patients (n = 10) in whom the ALHA was not ligated

All data are presented as a mean and range or number and %

significant differences in operation time, retrieved lymph nodes, blood loss, or hospital stay. No major complications related to hepatic ischemia or surgery were recorded upon ALHA ligation after identification of perfused territories of the liver using the NIRFI technique. Except for mean AST on the operation day, the mean AST and ALT levels for all enrolled patients ($n=31$) were within the upper limits of normal. Overall, AST levels were highest on the operation day, whereas ALT levels were highest on the second day after surgery.

Postoperative liver function test results on days 0, 1, 2, 3, and 5 after surgery are depicted for groups 1 (ALHA ligation) and 2 (ALHA preservation) separately in Fig. 3. In group 1, mean AST/ALT levels on each day were within the normal limit, and the maximum AST/ALT level was below two times the upper limit of normal during hospitalization, except in 1 patient. The highest postoperative mean AST was recorded on the operation day at 32.4 IU/L (range, 23–54), while the highest mean ALT was recorded on day 2 after surgery at 33.1 (range, 11–145). The patient who had the highest elevations in AST (maximum value of 111 at postoperative day 2) and ALT (maximum value of 145 at postoperative day 2) recovered well without the need for liver protecting medication. Meanwhile, in group 2, slight and transient elevations in AST/ALT within 1.5 times the upper limit of normal were noted. The patient in whom preservation of the ALHA was not successful experienced an elevation in AST (maximum value of 57 in immediate postoperative blood test), but none in ALT, beyond the reference value. Raw data are provided in Supplementary Table 1.

Discussion

In this study, we found the use of NIRFI after injection of ICG to be feasible in helping surgeons to determine whether ALHAs can be safely ligated or whether they need to be preserved during gastrectomy to ensure proper postoperative liver function. Strong, uniform fluorescence excitation on the entire surface of the liver demonstrated that ALHAs were accessory and could be safely ligated, whereas as a lack of or faint fluorescence indicated ALHAs were replacement arteries likely critical to the function of the liver, thus warranting preservation. Overall, our results are important because current radiologic imaging studies do not always describe the presence or type of an ALHA variation, and applying our technique could prevent the need for more radio-hazardous CT scans to better identify the arterial variation, such as CT angiography, which poses increased radiation exposure to patients.

Due to its proven safety and exclusive biliary excretion without metabolism, ICG is the only FDA approved fluorescent agent. NIRFI-guided surgery using ICG has recently been adopted and has been widely used to provide better visualization of anatomic and functional structures that are obscure under white light. Applications of NIRFI-guided surgery using ICG in the gastric cancer field include its use to identify sentinel lymph nodes and infrapyloric arteries for pylorus-preserving gastrectomy and to assess the completeness of lymph node dissection during radical gastrectomy [22–25]. Researchers have also studied its use in evaluating intraoperative perfusion of the remnant stomach or tumor localization [26]. In the present study, we generally found ICG fluorescence easy to discern under NIRFI during both laparoscopic and robotic gastrectomy. The Color Segmented Fluorescence mode, which depicted blood perfusion on a gradient color scale, was particularly useful, relative to black and white or green overlay fluorescence images. However, at times, fluorescent areas were not always clearly defined along the anatomic segments of the liver. Sometimes, spotty or merely weak fluorescence was encountered in parts of the liver: for instance, the fluorescence defects in segment 3 in Patient No. 17 and in segments 3 and 4 in Patient No. 9. These instances may reflect specific segments of the liver fed by multiple blood supplies from various collateral arteries, which would be difficult, if not impossible, to detect by conventional radiologic examination [14, 27].

In most cases, discontinuation of blood flow through an ALHA upon ligation of the LGA has only a minor clinical adverse impact, albeit with transient and slight elevations in liver enzymes [14, 28]. This is because the lobar

Table 4 Comparison of surgical outcomes and complications according to ligation or preservation of an aberrant left hepatic artery

Variables		ALHA ligated ($n=20$)	*ALHA preserved ($n=10$)	*P*
Operation time, minutes		192.80 ± 49.91	201.80 ± 18.07	0.479
Fluorescent activation time, seconds		43.75 ± 11.30	42.40 ± 13.80	0.777
Number of retrieved lymph nodes		37.35 (23–73)	41.2 (20–59)	0.439
Number of metastatic lymph nodes		0	1.2 (0–11)	0.301
Blood loss, ml		77.55 ± 73.51	80.10 ± 52.37	0.923
Hospital stay, POD, days		7.15 ± 3.56	7.90 ± 4.80	0.632
Clavien–Dindo classification†				0.958
	Grade 1	4	2	
	Grade 2	9	5	
	> Grade 3	0	0	
Readmission < 6 months		0	0	NA
Reoperation < 6 months		0	0	NA
Aspartate transaminase (AST), IU/L				
	Operation day	32.40 ± 7.93	38.10 ± 9.36	0.091
	POD 1	31.15 ± 12.24	30.80 ± 7.45	0.935
	POD 2	31.90 ± 21.68	23.50 ± 5.13	0.241
	POD 3	21.50 ± 8.38	19.00 ± 4.29	0.385
	POD 5	17.50 ± 5.98	17.20 ± 3.29	0.884
Alanine transaminase (ALT), IU/L				
	Operation day	27.60 ± 10.03	31.20 ± 9.31	0.343
	POD 1	29.55 ± 16.62	28.30 ± 8.33	0.825
	POD 2	33.05 ± 30.24	22.60 ± 6.50	0.293
	POD 3	26.05 ± 22.61	17.80 ± 4.13	0.266
	POD 5	18.75 ± 12.60	14.90 ± 3.67	0.356

ALHA aberrant left hepatic artery, *POD* postoperative day

*One person who failed ALHA preservation is excluded

†Thirty-day postoperative complication

hepatic arteries usually have collateral vessels that stem from other hepatic or phrenic arteries, and these are known to begin to work at no later than 10 h after ligation of the artery [29, 30]. However, lethal complications associated with ligation of ALHAs, such as necrosis or abscess of the liver, cholangitis, and liver failure, have been reported in the literature [8, 13, 28, 31–33]. When performing some upper gastrointestinal surgeries, such as esophagectomy or bariatric/metabolic surgery, awareness of the presence of an ALHA and its significance regarding blood supply to the liver is relatively more crucial than when performing gastrectomy [7, 33–35]: liver dysfunction is known to be more common in esophagectomy, which requires more extensive lymph node dissection that is more likely to eliminate the collateral arterial supply to the left lobe of the liver from the retroperitoneum and the mediastinum [35]. In one report, severe liver abscess after esophagectomy was recorded in 6% of patients with an ALHA [35]. Meanwhile, in liver transplantation, whether this artery should be reconstructed during implantation to prevent hepatic necrosis is also a critical issue [36].

As far as we know, only a few studies have described strategies for preserving ALHAs during gastrectomy. One reported that it was necessary to concurrently resect the left lobe of the liver in 0.91% of the patients in the study when the diameter of an ALHA, which the authors suggested should be divided, was wider than 1.5 mm [8]. Okano et al. suggested that ALHAs with a large diameter should be preserved to achieve postoperative liver function similar to that observed in patients without an ALHA, although a cut-off value was not proposed [28]. Meanwhile, in an attempt to specify patients in whom an ALHA should be preserved, Shinohara et al. noted that routine preservation of ALHAs may be able to maintain oncologic safety. Interestingly, in their study, there were no significant differences in the numbers of total/metastatic lymph nodes, postoperative morbidity/mortality, and overall survival between patients whose ALHAs were preserved and those whose were divided [6]. Obviously, preserving all detected ALHAs would be desirable; however, doing so requires complicated dissection that poses a potentially higher risk of perioperative bleeding. Thus, it would be

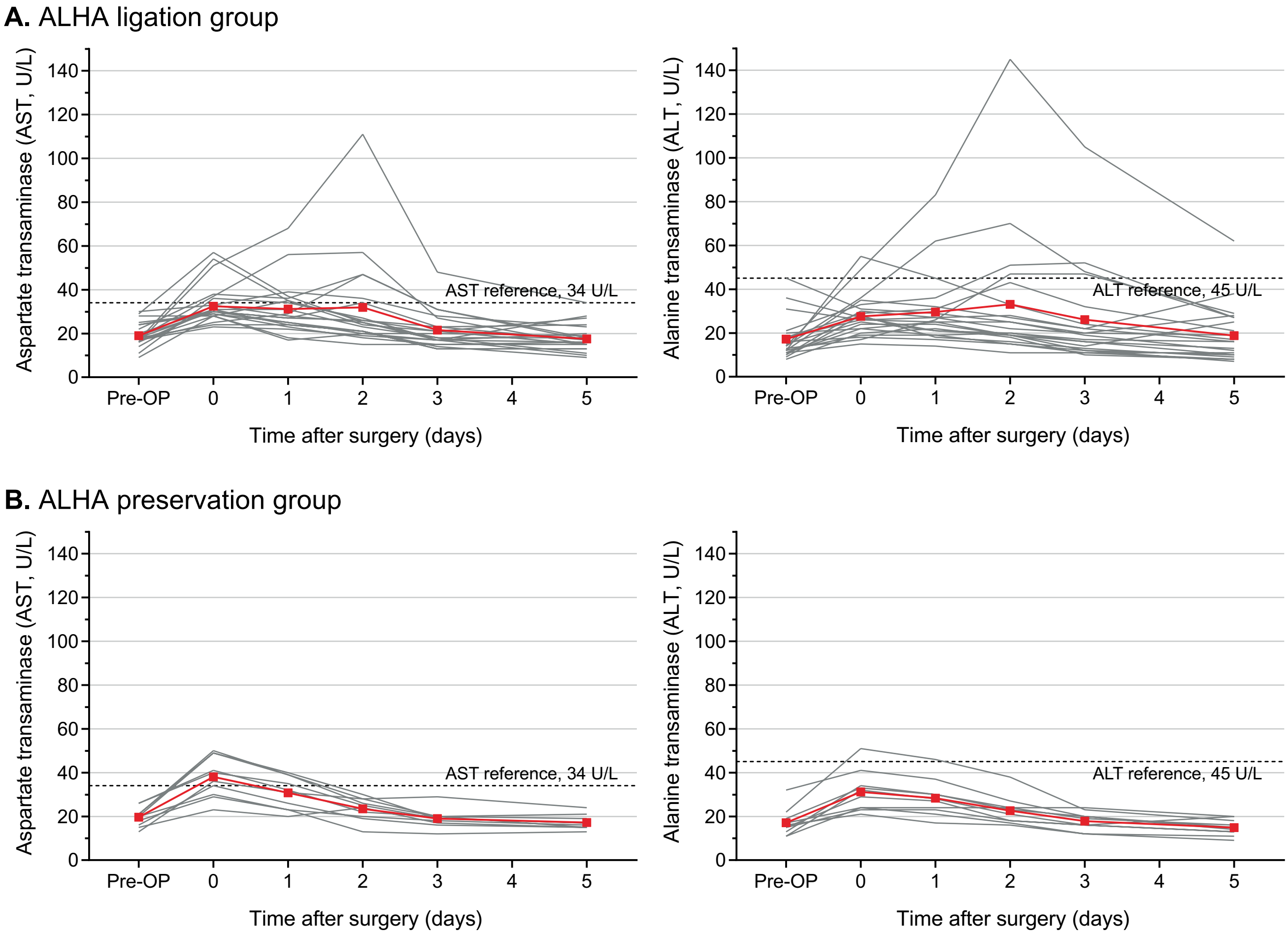

Fig. 3 Perioperative changes in liver function test results according to management of an aberrant left hepatic artery (ALHA). The liver function results (AST and ALT levels) for each patient are superimposed on the graphs as gray lines. Mean values are indicated by solid red lines. The dashed lines indicate the upper limits of reference values. **A** ALHA ligation group ($n=20$), **B** ALHA preservation group ($n=10$) (Color figure online)

less reproducible, especially for non-expert surgeons. In our study, an attempt to preserve the ALHA in one of the 11 patients in whom we sought to do so failed, and in the 10 patients in whom preservation was successful, the dissection took a mean of 13 min. In a more recent study, Kim et al. reported that if the internal diameter of the LGA is larger than 5 mm, preservation of an ALHA from the LGA ought to be considered [10]. If so, the likely elevation in liver enzymes would be within twice the upper limit of normal. However, in a recent study evaluating esophagectomy cases, liver infarction occurred even when the diameter of the LGA was less than 5 mm [35]. Also, to perform the assessment proposed in Kim et al.'s study, a complicated CT protocol, such as three-dimensional CT angiography may be needed, although even these advanced imaging modalities show rates of detecting arterial variations lower than their actual reported incidences [2, 7, 35, 37–40].

This study has several limitations. First, the results were based on a small number of cases. Also, the assessment of liver perfusion with ICG fluorescence may have varied between surgeons and vision systems, because the assessment was qualitative, not quantitative, and depended on the surgeon's perception. Second, although 1 patient in the ALHA ligation group experienced an elevation in liver enzymes three times higher than the upper limit of normal, the exact reason thereof was not easily discernible, as various potential causes were not properly controlled: for instance, use of antibiotics, antipyretics, and pain medicine. Third, the impact of portal flow could not be clearly explained because interruption of portal flow by clamping of the portal vein was not attempted. We assumed that the difference in fluorescence excitation on the liver was primarily derived from the difference in the amounts of ICG from the arteries. Lastly, because of safety reasons, we attempted to ligate ALHAs in only 65% of the enrolled patients who had strong, uniform fluorescence on the left lobe of the liver. Future study to broaden the indications for ligation of an ALHA should be followed for patients with focal or limited fluorescence. Despite these limitations, we believe that the results of this study may benefit surgeons seeking guidance on when to preserve or ligate ALHAs and raise caution against simply ligating ALHAs without concern for any serious hepatic damage. This technique should be evaluated and may prove helpful in other gastrointestinal surgeries or in treating patients with combined liver diseases.

Conclusions

In this study, we have described a novel and simple technique for visualizing areas of blood supply from ALHAs on the liver in real time. This method could be beneficial to limiting potential liver-related complications in minimally invasive surgeries.

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Compliance with ethical standards

Disclosures Drs. Hyoung-Il Kim, In Gyu Kwon, Joong Ho Lee, Minah Cho, Taeil Son, Woo Jin Hyung, Yong Eun Chung, and Yoo Min Kim have no conflicts of interest or financial ties to disclose.

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