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Determination of the Surgical Margin in Laparoscopic Liver Resections Using Infrared Indocyanine Green Fluorescence

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ABSTRACT

Background: The advent of minimally invasive techniques has revolutionized liver surgery, with improvement in postoperative outcomes while maintaining oncological efficacy. Achieving tumor-negative resection margins remains critical for optimal oncological outcomes. Considering the adversity of tactile feedback in minimally invasive surgery complicating margin assessment, this study evaluated the efficacy of near-infrared indocyanine green fluorescence imaging in real-time surgical margin delineation during the hepatic resection.

Methods: This is a single-centered, prospective, descriptive study conducted between 15th March 2022 and 15th March 2024 as per the revised STROBE guidelines. Patients were enrolled by convenient sampling and received 0.5 mg/kg of indocyanine green one day before surgery intravenously. During surgery, near infrared-indocyanine green imaging was recorded and utilized to assess the surgical margins along with the white light as well. The findings were compared and confirmed with the final histopathology report.

Results: A total number of 21 patients were included in this study who underwent laparoscopic liver resection. Majority of cases were of colorectal liver metastasis (90%), and most of them were located at segment 4 (80%). Participants had a normal preoperative liver status with a median tumor size of 28 mm and a median number of 1.2. Indocyanine green fluorescence successfully delineated resection margins in all cases, and final histopathological assessment confirmed R0 resection status. No adverse reactions to the indocyanine green were reported.

Conclusions: Near infrared-indocyanine green provided significant benefit regarding R0 resection in all cases confirmed with histopathology results for the intra-operative identification and demarcation of margins during laparoscopic hepatic resection.

Keywords: Colorectal liver metastasis; indocyanine green; laparoscopic liver resection.

INTRODUCTION

Laparoscopic liver resection(LLR) has expanded enormously following open surgeries since its proposition for both benign and malignant lesions with proven safety and feasibility with concordant oncological outcomes.[1] Unfortunately, both the procedures result in tumor-positive resections in 28% of cases.[2] Intraoperative ultrasonography (IOUS) has been frequently utilized for tumor assessment; however, chances of microscopic margin positivity (R1) and challenging access to right posterior lesions are the shortcomings of its isolated use.[3,4] Near-infrared fluorescence (NIRF) imaging, utilizing the contrast indocyanine green (ICG), has been validated for its numerous advantages, especially, when administered in a relatively low dose, one day before surgery with acquisition of the surgical margins of more than one millimeter (mm), which has significantly improved the postoperative outcomes.[5,6]

This study aims to determine the surgical resection margin of liver lesions using near-infrared fluorescence imaging to assess tumor margins in vivo in patients undergoing LLR and evaluate the perioperative outcomes.

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METHODS

This is a prospective descriptive observational study conducted in the Department of GI and General Surgery, Kathmandu Medical College Teaching Hospital from 15th March 2022 to 15th March 2024.

Inclusion criteria Colorectal liver metastasis (CRLM): solitary or multiple. Hepatocellular cancer(HCC) of liver who were planned for anatomical liver resection.

Exclusion criteria patient with allergic to contrast iodine dye. Patients who were diagnosed with CRLM and HCC amenable to liver resection were included in the two years study. All patients underwent Contrast Enhanced Computed Tomography (CECT) abdomen and pelvis with chest before surgery, thus, patients with known allergy to iodine substances were excluded from the study.

This hospital-based prospective descriptive observational study was conducted per the revised Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

All patients received a test dose of 1ml followed by the weight-based dosage of ICG mixture prepared with 25mg of ICG powder in 10ml of Normal saline. 0.5mg/kg of patient weight. The lower doses of ICG were administered considering the impaired biliary excretion to retain ICG longer and avoiding excessive background fluorescence of the liver hindering the optimal tumor to liver differentiation. The dose was also planned in view of minimizing the potential toxicity and side effects of the contrast. At least 24 hours before surgery. As ICG is selectively taken up by the hepatocytes and excreted in bile, tumors with poor biliary excretion retain ICG longer, avoiding rapid clearance from the bloodstream and thus preventing suboptimal imaging contrast.

The Monitor of Karl Storz TM343 model¤ was utilized with 4k + NIR/ICG compatibility. The patient was placed in the supine or left semi-lateral decubitus position using 3-4 ports of variable size (5-12mm) placed at variable positions as per the location of the tumor. Diagnostic laparoscopy was performed to confirmed the uptake of ICG by hepatic lesion and number of lesion and anatomical location of lesion were confirmed and correlated with CECT findings.

The target lesion was visualized using the NIRF (green or blue color) just before, during, and after the resection along with the white light giving real time assessment of lesion. For colorectal liver metastasis, parenchymal sparing liver resection principle was followed which included 2cm circumferential margin from the lesion and for hepatocellular carcinoma, anatomical segmental resection was performed. The fluorescence area around the tumor was observed and marked and was matched along with pathological report for R0 resection or nearest circumferential margin. The negative margin was defined as more than 1mm from the tumour margin.

The ethical approval was taken from the institutional review committee of Kathmandu Medical College and Teaching Hospital (KMC-IRC No 1102202203). Informed consent was obtained from all patients.

All collected data were entered into a secure electronic database. Key outcomes measured included the number of complete tumor negative surgical margins and the perioperative complications after LLR guided by ICG fluorescence. Appropriate statistical methods were employed to evaluate these outcomes and determine their significance. The study population included all the cases of CRLM and HCC who underwent LLR. Data was collected with the help of a proforma and entered in SPSS version 26. Categorical variables were presented as absolute or relative frequencies with percentages, while continuous variables were demonstrated as mean ± SD.

RESULTS

In two years periods, total 21 patients underwent laparoscopic liver resection for various indication as in Table:1. Among them,14 were male, and seven were female, with a male-female ratio of 2:1. The median age was 57 years (38-75). Among histology, the majority of cases were colorectal liver metastasis (n=13,61.90 %), and most of them were located at segment four (n=5,23.80 %). Most of the patients had normal liver status preoperatively with a median tumor size of 28 mm and a median number of 1.2. **(Table:1)**

Table 1. Patient demographics and lesion characteristics.

Variables	Number (n=21) (Percentage %)
Median Age (years)	57 (38-75)
Sex	
Male	14 (66.67)
Female	07 (33.33)
Histology	
CRLM	13
HCC	8
Tumor location	
S2/S3/S4/S5/S6/S7/S8	1/3/5/3/4/3/2
Liver background	
Normal/Chronic Hepatitis/Cirrhosis	19/2/0
Tumor size (mean)	28 mm
Tumor Number (mean)	1.2

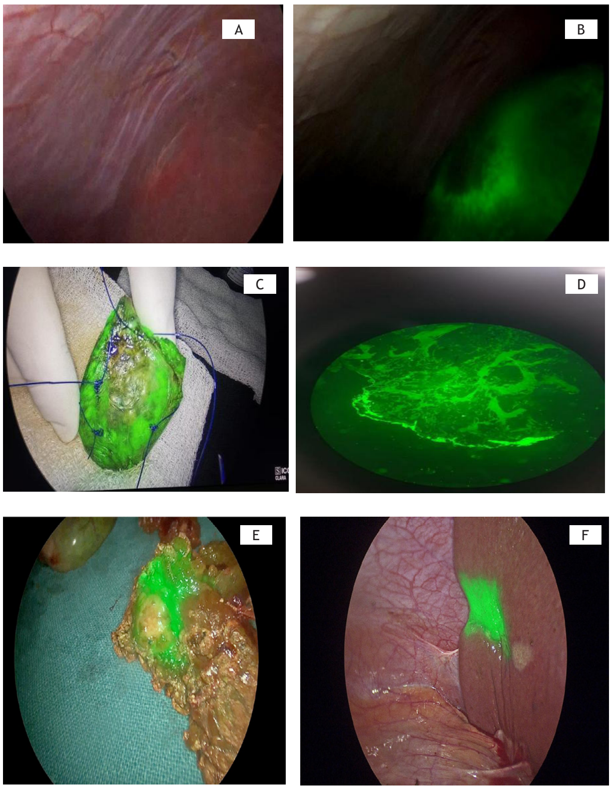

Figure 1. Intraoperative NIR fluorescence imaging and HPE. A 45-year-old female with colorectal liver metastasis in white light (A) and ICG overlay (B). Resected specimen (C) and HPE slide (D) A 65 year old male with colorectal liver metastasis in ICG overlay: Specimen after laparoscopic resection of segment 7 (E), Intraoperative localization of the CRLM of segment 7 (F)

The median operative time taken for resection was 185 minutes (125-270) with a median estimated blood loss of 375 ml (250-1000). The warm ischemia time was 25(0-60) minutes in the median with all cases acquiring negative margins of a median of 3.2 mm (1-20) providing 100 % results. **(Table:2)**

Table 2. Intraoperative variables.

Variables	Number (Range)
Operative time (min) Mean	185 (125-270)
Estimated blood loss(ml) Mean	375(250-1000)
Warm ischemia time(min) Mean	25 (0-60)
Surgical margin(mm) Positive/Negative	3.12 (0-20) 3/21

In terms of postoperative morbidities, there was one (4.7%) case of infected subhepatic collection, which was drained using a pigtail catheter, and one (4.7 %) case each of postoperative ileus and biliary fistula managed conservatively. However, there were no mortalities during our study among resected cases up to 90 days with a mean hospital stay of 5.6 days. (Table:3)

Table 3. Post operative morbidities and mortality.

Outcome	Number (Percentage %)	Clavien-Dindo Classification
Postoperative bleeding	0	0
Biliary fistula	1 (4.7 %)	0
Infected collection	1 (4.7%)	IIIa
Ascites	0	0
Post-operative Ileus	1(4.7%)	II
Liver failure	0	0
Mortality (30/90 days)	0	0
Hospital stay	5.6 days	

Table 4. Tumor margin assessment with NIRF.

Lesion No.	Tumor margin		Tumor margin (mm)
	NIRF	Histopathology	
1	Negative	Negative	3
2	Negative	Negative	6
3	Negative	Negative	20
4	Negative	Negative	5
5	Positive	Positive	0.5
6,1	Negative	Negative	2,2
7	Negative	Negative	3
8	Negative	Negative	3
9	Negative	Negative	2
10	Negative	Negative	2
11,1,2	Positive	Positive	0,1,1
12	Negative	Negative	4
13	Negative	Negative	2
14,1	Negative	Negative	2
15	Negative	Negative	3
16	Negative	Negative	4
17	Negative	Negative	5
18	Negative	Negative	3
19,1	Negative	Negative	2,3
20	Positive	Positive	0
21	Negative	Negative	3

DISCUSSION

Our study showed that the use of ICG for delineating the hepatic lesion, either primary like HCC or metastasis from colorectal cancer, in addition to identifying unidentified lesions which were not documented in the preoperative CECT scan of abdomen and pelvis, was possible. Among 21 patients, three patients had positive ICG margins, which had positive R1 resection in pathology. Among them, two patients had anatomical segmental resection for HCC , whereas one patient had undergone parenchymal sparing liver resection for CRLM.

The surgical removal of the entire fluorescent rim, guided by NIRF imaging, can greatly improve tumor-negative resection rates during minimally invasive procedures. Improving these rates could potentially lead to prolonged disease-free and overall survival as the NIRF signal has a penetration depth of around 8 mm. The absence of the NIRF signal in the resection plane should, therefore, indicate a tumor-negative or radical resection.[7]

Identifying the hepatic segments and intersegmental planes during hepatic resection is crucial, and ICG plays a significant role in accomplishing this by guiding the demarcation line after the portal staining or the control of the inflow to the required segment or section of the liver, which is also termed as positive and negative staining, respectively. This has been a well-established approach for parenchymal preservation and oncological radicality in open hepatic resections.[8]

There are numerous methods or approaches to hepatic resections; parenchymal resection first, vein guided, and inflow control approaches. Couinaud demonstrated three main approaches to the inflow at the hepatic hilum; the intrafascial, the extrafascial, and the extrafascial and transfissural approach. The benefit of using ICG as an adjunct to these approaches needs more emphasis especially on complex liver resection cases like segmentectomies. Even though, the complete transection on the basis of segmental planes is highly challenging, ICG allows surgeons to distinguish the course and directs the transection of the hepatic parenchyma. There have been several novel applications of ICG, one of such as described by Ueno et al. where the author states the use of interventional radiology-assisted direct perfusion method using ICG to detect a liver segment during hepatic resection. This technique, although time-consuming and cost drawbacks, poses potential during complex segmentectomies of the right side of the liver.[9]

While the development and adaptation of these technologies in surgery provide an immense amount of information, interpretation of these fluorescent images and mastering the technique of using fluorescence in the operating room requires training and experience. Fundamentals and developments in fluorescence-guided cancer surgery have been discussed by Mieog et al. in their review. We highlight the advantages of this technique in properly assessing tumor margins in vivo using ICG as a contrast agent. [9-10]

The assessment and outcome of surgical margins in open liver resection have been discussed in different literature.[9-11] There are differences between conventional and LLR in achieving tumor-free margins.[12] The caudal-cranial angle of parenchymal transection and extent of liver exposure and mobilization are difficult in LLR along with difficulties in interpreting intraoperative ultrasound images due to spatial orientation and tissue manipulation compounded by two-dimensional visual feedback. The evolvement of a novel innovative method using ICG fluorescence imaging with NIR light during laparoscopic hepatectomy aims to enhance precision by providing a clearer visualization of anatomical details, potentially facilitating the attainment of R0 margins—a crucial standard in tumor resection. With the aid of ICG, the visualization of hepatic lesions, anatomy of the biliary tract, and both arterial and venous blood flows have been better understood along with better delineation of segmental and sectional anatomy of the liver.[12,13] In our study, all the tumors were identified by ICG, however, reports are suggesting the ability of ICG fluorescence to identify liver tumors from 85-100 %.[14-16] The background liver status is an important factor in this regard, and the absence of liver cirrhosis in our patients probably resulted in better outcomes.

Manen et al. have discussed a practical guide for the use of ICG and methylene blue in fluorescence-guided abdominal surgery where they conclude liver tumors could be easily detected with ICG due to clearance through the liver and being nonspecific for other solid abdominal tumors like pancreatic and renal tumors. Similarly, a study by van der Vorst et al. discussed the changes in architecture of the liver parenchyma by the presence of hepatic metastases leading to hepatic parenchyma compression, infiltrations of inflammatory cells, transformation of the ducts, and high immature hepatocytes, thus explaining the rim fluorescence of the ICG and impaired biliary clearance.

A prospective multicenter MIMIC trial was conducted between 2018 and 2021, which concluded an increase in the R0 resection rates to 92.4% utilizing ICG fluorescence during minimally invasive resection of CRLM, and almost a third of the procedures (27.9%) were altered intraoperatively secondary to the findings of the ICG fluorescence. The trial administered 10mg of ICG a day before the surgery which was similar to our study, but with even lower dosage. The highlight of the trial was they stated five percentage increase in the R0 rates after the re-resection of ICG fluorescent tissue in the resected cavity of the liver.

The applicability of fluorescence in guiding the parenchymal transection line after the identification of the tumor and associated liver anatomy makes segmentectomies and sectionectomies more specific and anatomical. The provision of overlay over white light also added the advantage of real-time confirmation of the location of the tumor and surgical margin using a switch on the camera setting.[17]

Implementing the diagnostic benefit of ICG at centers with less expertise and generalizing it as a standard intraoperative adjunct is the topic of discussion. Studies have shown variable false positive results of additional lesions identified during surgery. In view of the safety of the patient, unnecessary additional interventions, and overall complete radicality of the tumor, training surgical personnel and following proper ICG protocol or guidelines seem imperative. The judicious use of ICG regarding its dosage and timing is equally essential for its applicability for future interventions.

The limitations of this study include a relatively small sample size within a single center with no cases selected from cirrhotic patients during convenient sampling.

CONCLUSIONS

The intraoperative identification and demarcation of liver lesions using NIRF is an effective tool and provides adequate intraoperative assessment of the surgical margin, holding a beneficial role in addressing the postoperative complications and associated morbidities.

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CONFLICT OF INTEREST

We declare that there is no conflict of interest regarding this article.

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