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Role of Indocyanine Green in Diagnostic Staging Laparoscopy in Intra-Abdominal Malignancy

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ABSTRACT

Background: Patients with abdominal cancers may present with advanced disease either locally or metastatic and so, accurate staging help in selection of the appropriate treatment plan (curative or palliative). Up to 50% of patients diagnosed with colorectal cancers (CRC) and 40% of patients diagnosed with pancreatic cancers will have metastatic hepatic lesions during the course of the disease, where 7% of patents with CRC and 14% of patients with advanced gastric cancers will develop peritoneal metastases. Despite advances in pre-operative imaging used for diagnosis and staging as CT, MRI and PET-CT many patients are diagnosed either intra-operative or in early post-operative period with distant metastases. *Aim of the work:* The study aim is to assess and provide precise data for the efficacy and added value of using Indocyanine Green (ICG) in diagnostic staging laparoscopy in intra-abdominal malignancy, especially in the identification of hepatic malignancies or liver and peritoneal metastases.
Patients and Methods: This is a cross-sectional prospective study which was conducted on thirty patients with operable intra-abdominal malignancy presented to Theodor Bilhariz research institute from February 2022 to July 2023.
Results: In our study, total number was 12 hepatic lesions, 8 lesions were discovered during routine pre-operative investigation and 11 lesions were identified by intra-operative ICG florescence with histopathological confirmation of metastasis in 57%.
Conclusion: ICG is a safe and applicable tool for intra-operative assessment and detection of liver lesions with high sensitivity. It is not specific for malignant lesions rather than hypervascular lesions, affecting its specificity. Another study with larger sample size and dedicated post-operative follow up may be needed for more precise data.
Key words: indocyanine green, near infra-red, florescence maging, staging laparoscopy, intra-abdominal malignancy, liver metastasis, peritoneal carcinomatosis

Abbreviations:
ICG: Indocyanine Green;
CRC: colorectal cancers;
PC: peritoneal carcinomatosis;
SL: staging laparoscopy;
FIGS: Florescence imaging guided surgery;
NIR: near-infrared;
CBC: complete blood count;
EUS: endoluminal ultrasound;
ERCP: endoscopic retrograde cholangio-pancreaticography;

INTRODUCTION

Patients with abdominal cancers may present with advanced disease either locally or metastatic and so, accurate staging help in selection of the appropriate treatment plan (curative or palliative). Although advanced pre-

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operative imaging as (trans-abdominal and endoscopic ultrasound, CT scan, MRI, and PET scan), many patients may have unexpected, unresectable disease at exploration (1).

Despite presence of advanced imaging modalities, the sensitivity of radiological evaluation in identifying metastatic liver and peritoneal lesions is limited. The accuracy of ultrasound was 76% and 79% for CT in detecting metastatic hepatic lesions (2).

US, CT scan and MRI are the cornerstones of detecting and staging of hepatic malignancies with high degree of accuracy and their preoperative use of them is helpful in a hepatic resection.

But one of their limitations is that they may miss focal lesions less than 0.5 cm and they provide still pictures only with a limited value as a diagnostic and guidance (3).

Peritoneal carcinomatosis (PC) is a challenge. Detection of peritoneal involvement at an early stage may help improving treatment response and final results (4). Present pre-operative diagnostic and staging techniques and imaging modalities have low sensitivity for PC less than 0.5 cm (5).

Staging laparoscopy (SL) is a safe and available tool that may help to increase accuracy of staging of abdominal malignancies by direct visualization of abdominal organs, take tissue biopsy and aspiration cytology, assist in appropriate treatment plan selection and decrease unnecessary laparotomies form 40% to 17% with less morbidity and mortality (6).

However, even with direct inspection during SL or laparotomy some small lesions could be missed, especially in if bowel mobilization is needed as in the pelvis (7).

Florescence imaging guided surgery (FIGS) and near-infrared (NIR) fluorescence is a newly developed technique that could be used to detect and visualize structures in real time intraoperative. ICG is tri-carbocyanine dye that has a molecular weight of 775 Da, a negatively charged, amphiphilic, water-soluble but relatively hydrophobic (8).

Advantages include high tissue penetration and low auto-fluorescence where the human eye is insensitive to its excitation light wavelength (doesn`t alter the surgical field). It binds to plasma protein , circulating in the blood then uptake occur by hepatocytes with rapid biliary excretion, with a high favorable safety and a lack of ionizing-radiation exposure (9).

Aim of the work

The study aim is to assess and provide precise data for the efficacy and added value of using ICG in diagnostic staging laparoscopy in intra-abdominal malignancy, especially in the identification of hepatic malignancies or liver and peritoneal metastases. Whether or not the ICG laparoscopic staging will alter the management plan, is yet to be seen?

PATIENTS AND METHODS

This is a cross-sectional prospective study which was conducted on thirty patients with operable intra-abdominal malignancy presented to Theodor Bilhariz research institute from February 2022 to July 2023.

Population of study and disease condition: 30 patients who were diagnosed with operable intra-abdominal malignancy presented to surgery department at Theodor Bilhriz Research Institute.

Inclusion criteria

Adult Patients (males or females) with operable intra-abdominal malignancy and fit for laparoscopic procedure.

Exclusion criteria

Age below 18 years, Inoperable malignancy or unfit for laparoscopic surgery, pregnancy or lactation, mentally disabled patients, renal failure and allergy to iodine, urografin or ICG.

Methodology in details

History: Detailed history including Age, Sex, presence of co-morbidities, Family history and specific history related to the complaint e.g. onset, course, duration, associations as weight loss, loss of appetite.

Examination: General: Cachexia, Jaundice.

Abdominal: inspection, palpation, percussion, auscultation.

Investigations

Laboratory

Routine pre-operative labs e.g. Complete blood count (CBC), Liver functions (AST, ALT, Albumin, Bilirubin), coagulation profile (PT, INR), Kidney functions (urea, creatinine, electrolytes), Virology (HBsAg, HCV Ab, HIV Ab), Random Blood glucose level.

Tumor markers e.g.: AFP, CEA, CA 19-9, CA 125.

Imaging

For diagnosis: according to site of primary tumor: Pelvi-abdominal ultra-sound, CT scan on abdomen and pelvis with intravenous contrast ± oral, enemal contrast, MRI study for abdomen and pelvis.

For staging: Ct abdomen, chest, brain + bone Scan, or PET CT.

Endoscopic

According to the primary disease: upper GI endoscopy, colonoscopy, endoluminal ultrasound (EUS), and endoscopic retrograde cholangio-pancreaticography (ERCP).

Pre-operative preparation

Consent: 30 patients will participate in this study. Nature and merit of the research will be explained to patients only those will accept and provide an informed written consent will be included.

In addition to standard-of-care, patients will receive an IV injection of 0.25- 0.5 mg/kg ICG 24-72 hours prior to surgery.

Intra-operative: All patients will be under general anesthesia, supine position. During surgery, patients undergo a staging laparoscopy, whereupon inspection then NIR fluorescence imaging will be performed searching for hepatic focal lesions or peritoneal nodules. The NIR system includes light source with double filter (white and 760 nm light) and a 30° laparoscopic lens that have optical filters. The operator can easily use foot pedal to switch between usual white light and near infra-red. 10 mm trocar inserted through umbilicus and other two ports at least for allowing good exposure and completing the exploration.

The whole abdomen is visualized and inspected for suspected lesions, including the liver (right and left lobe), the parietal and visceral peritoneum, greater omentum, transverse mesocolon and the pelvis. Any suspected lesions are sampled and sent to histopathological assessment.

If no metastases are identified, the procedure will continue as planned. If metastases are suspected, the decision to resume primary cancer resection or convert to palliative or abort is up to the surgeon.

Statistical analysis

The data will be analyzed using Microsoft Excel 2016 and statistical package for social science 'IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA)'. Continuous normally distributed variables will be represented as mean ±SD. with 95% confidence interval, while non-normal variables will be summarized as median with 25 and 75 percentiles and using the frequencies and percentage for categorical variables; a p value < 0.05 will be considered statistically significant. To compare the means of normally distributed variables between groups, the Student's t test will be performing, and Mann-whitney U test will be used in non-normal variables. χ^2 test or Fisher's exact test will be used to determine the distribution of categorical variables between groups. Spearman's rank correlation coefficient (r) will be done to show the correlation between different parameters in this study, in addition to regression analysis to evaluate the risk assessment (33).

RESULTS

Table 1 - Demographic distribution of the studied cases according to patient data (n = 30)

	No.	%
Sex		
Male	17	56.7
Female	13	43.3
Age		
Min. – Max.	36.0 – 76.0	
Mean ± SD.	53.70 ± 10.0	
Median (IQR)	56.0 (46.0 – 62.0)	

IQR: Inter quartile range; SD: Standard deviation

Table 2 - Distribution of the studied cases according to past history (n = 30)

	No.	%
Medical		
No	18	60.0
Liver Cirrhosis	0	0
DM	3	10.0
HTN	5	16.7
IHD	1	3.3
Stroke	1	3.3
CCC	1	3.3
DM - IHD	1	3.3
Surgical		
No	20	66.7
Cholecystectomy	4	13.3
Hysterectomy	2	6.7
CS	2	6.7
OIH mesh repair	1	3.3
PUH mesh repair	1	3.3

Table 3 - Distribution of the studied cases according to Dx Site (n = 30)

	No.	%
Dx Site		
Colon	18	60.0
• Ascending	8	26.6
• Transvers	2	6.6
• Descending	2	6.6
• Sigmoid	6	20
Pancreas	5	16.7
Rectum	1	3.3
Stomach	5	16.7
Duodenum	1	3.3

Table 4 - Findings for preoperative radiological investigations

CT findings	No.	%
Colo-rectal mass with regional lymphadenopathy	16	53.3
• Cecum	2	6.6
• Ascending	4	13.3
• Hepatic flexure	1	3.3
• Transverse	2	6.6
• Descending	1	3.3
• Sigmoid	5	16.6
• Rectum	1	3.3
Colon mass + regional lymphadenopathy and lung nodule	2	6.6
• Ascending	1	3.3
• Sigmoid	1	3.3
Splenic flexure mass + regional lymphadenopathy and hepatic focal lesion likely hemangioma	1	3.3
Gastric lesions	5	16.6
• Fundus	1	3.3
• Greater curvature at body	1	3.3
• Antrum	2	6.6
• Pyloric canal	1	3.3
Duodenum “Hypervascular lesion at 3rd part”	1	3.3
Pancreatic lesions	5	16.6
• Regional lymphadenopathy	3	10
• Regional lymphadenopathy + hepatic focal lesions likely metastases.	1	3.3
• Regional lymphadenopathy + hepatic focal fatty infiltration (segment IVb).	1	3.3

Table 5 - Distribution of the studied cases according to other radiological imaging (n=30)

	No.	%
MRI		
Not requested	29	96.7
Mass with regional lymphadenopathy	1	3.3
PET-Ct		
Not requested	26	86.7%
No mets	3	10.0
Mets	1	3.3

Table 6 - Hepatic focal lesions demonstration (n=12)

	No.	%
Pre-operative	8	67%
Intraoperative - ICG	11	92%

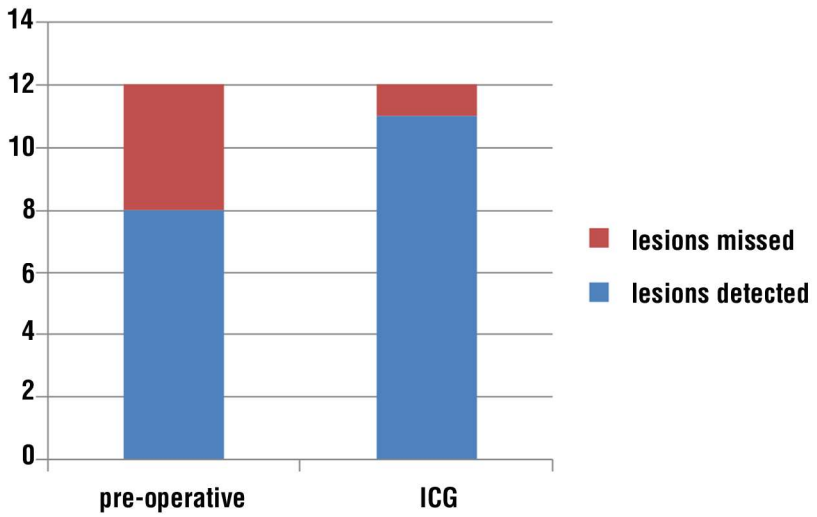

Figure 1 - Hepatic focal lesions (n = 12)

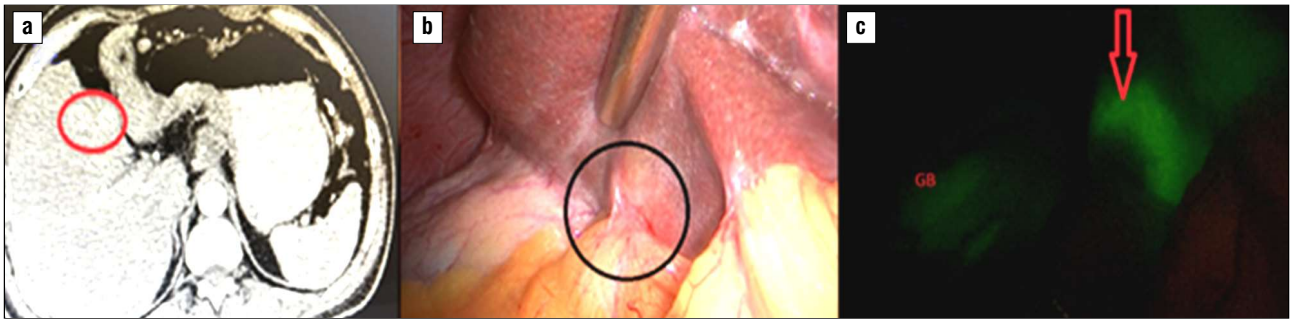

Figure 2 - Photo shows hepatic focal lesions (segment IVb) as seen in (a) CT image, (b) naked eye during staging laparoscopy and by (c) ICG auto-fluorescence

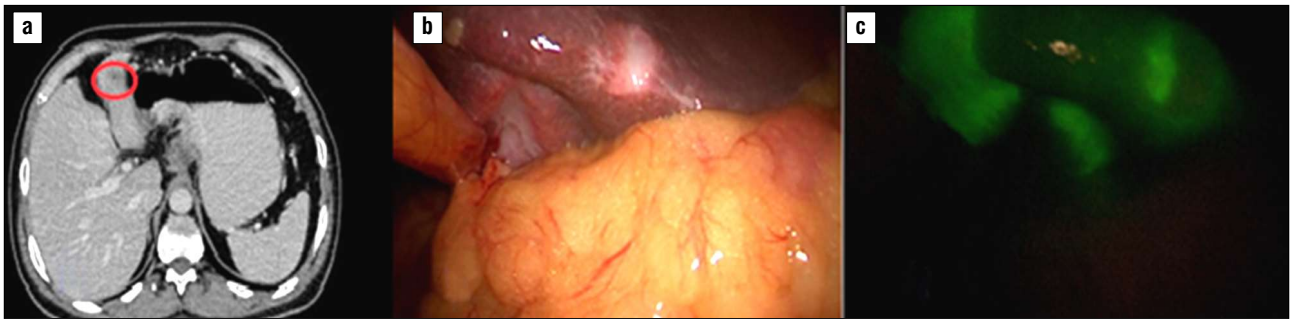

Figure 3 - Photo show segment III in (A) CT image shows only one focal lesion, while (B) naked eye during staging laparoscopy shows two focal lesions and in (C) ICG auto-fluorescence shows two hepatic focal lesions

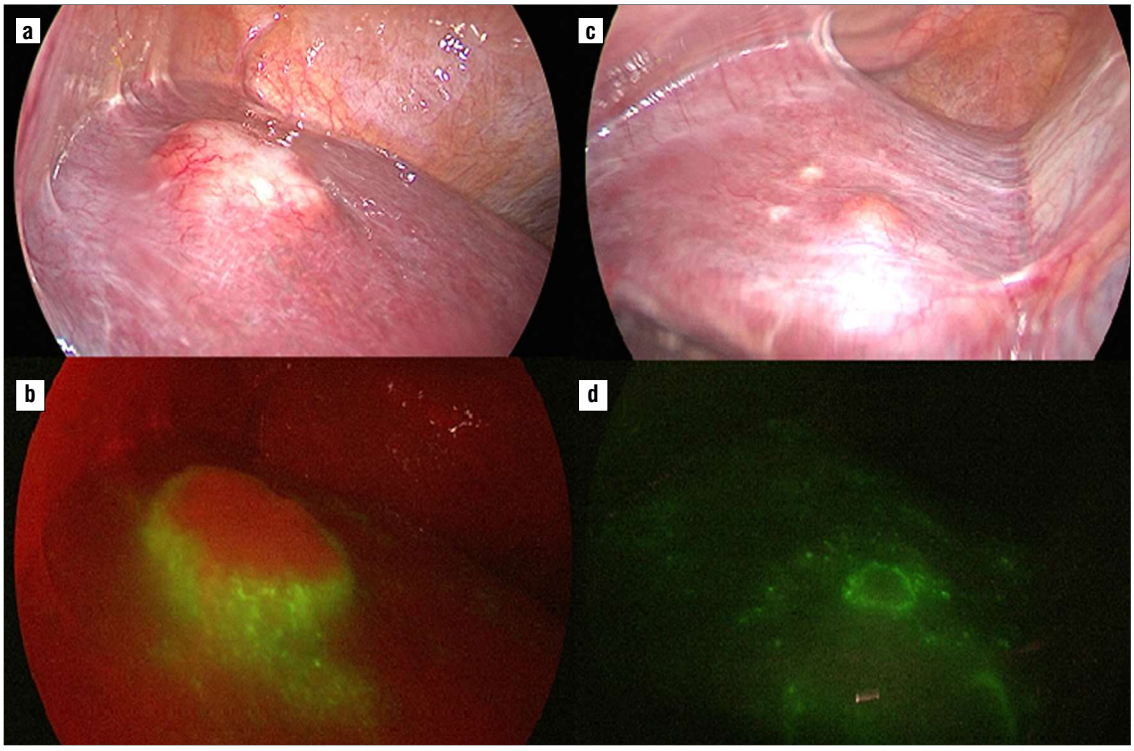

Figure 4 - Photo shows (a) segment III focal lesion by naked eye and (b) by ICG (c) segment IVb focal lesions by naked eye and (d) by ICG

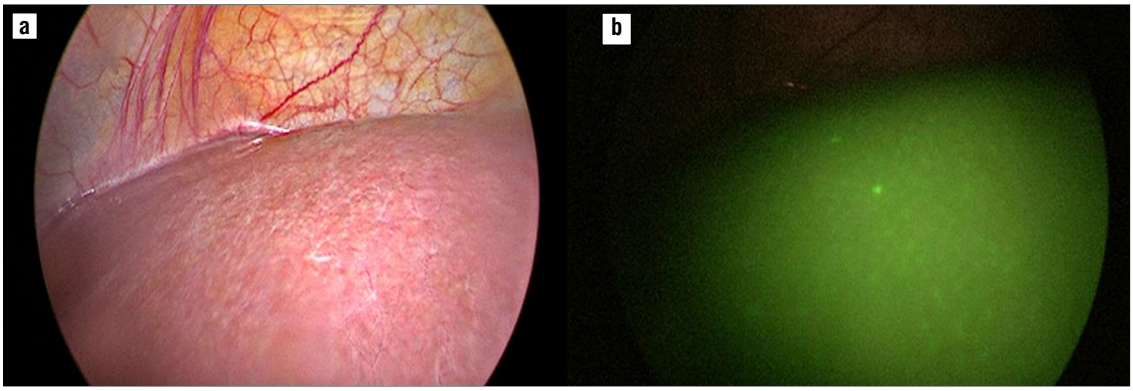

Figure 5 - Photo show (A) left liver lobe with no obvious lesions (B) left lobe of liver with no micro-lesions

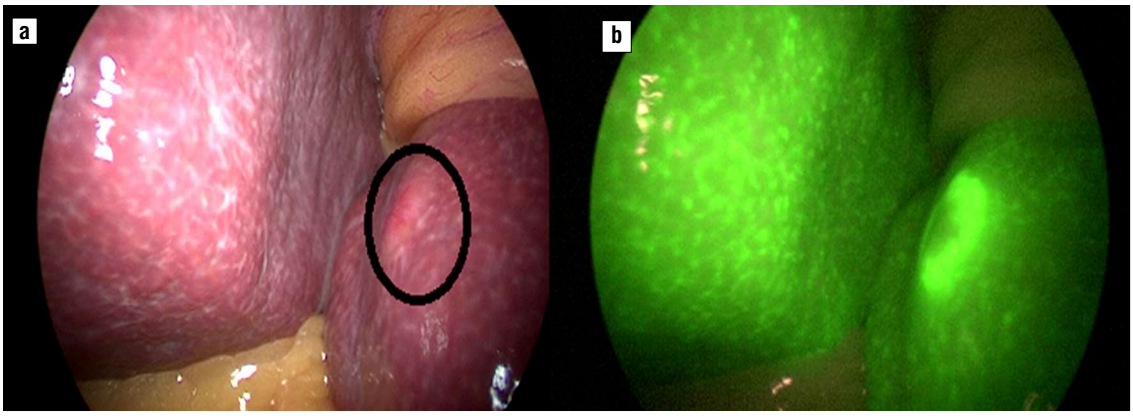

Figure 6 - Photo show (a) segment III with hepatic focal lesion and (b) the same lesion by ICG autoflorescence

Table 7 - Patients with peritoneal nodules demonstration (n = 30)

	No.	%
Pre-operative		
No	30	100
Yes	0	0
Intraoperative - Naked Eye		
No	28	93.3
Yes	2	6.7
Intraoperative - ICG		
No	29	96.7
Yes	1	3.3

Table 8 - Histopathological results for ICG detected liver lesions

Pathology of hepatic lesion	No.	% Out of 7
Metastatic	4	57.2
Non specific	2	28.5
Hemangioma	1	14.3

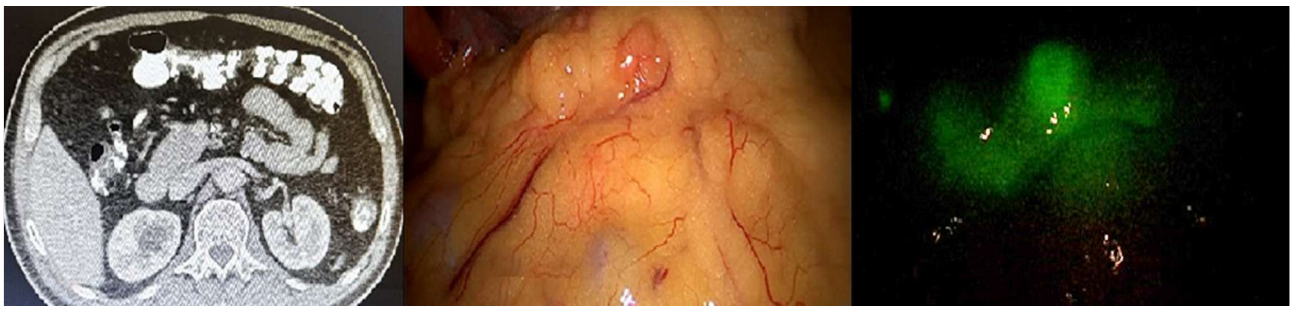

Figure 7 - Photo shows peritoneal (Omentum) nodules as seen in (a) CT image,(b) naked eye during staging laparoscopy and (c) by ICG auto-fluorescence

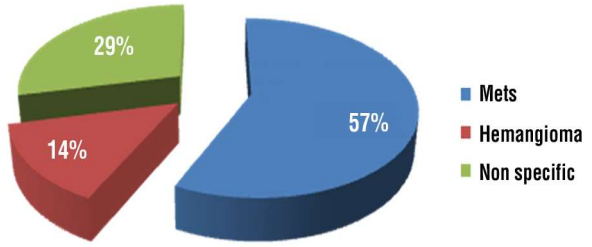

Figure 8 - Histopathological results for ICG detected liver lesions

Table 9 - Demonstration of histopathological results for detected peritoneal lesions

Pathology of peritoneal nodules	No.	% Out of 4
Metastatic	4	100

Table 10 - Distribution of the studied cases according to decision changed (n = 30)

Decision changed	No.	%
No	29	93.3
Yes	2	6.7

DISCUSSION

Patients with abdominal cancers may present with advanced disease either locally or metastatic and so, accurate staging help in selection of the appropriate treatment plan (curative or palliative) (1). Metastatic spread is the most common cause of morbidity and mortality in malignant patient, resemble about 90% (10). According to seed and soil theory liver is the commonest site for metastatic spread especially from gastrointestinal tumors up to about 30-50% of patients with CRC will have metastatic hepatic lesions during the course of the disease and about 35% in patients with pancreatic cancers (11).

Transcoelomic mechanism through shedding of malignant cells is the theory suggested for peritoneal carcinomatosis and metastatic nodules, where 7% of patents with CRC and 14% of patients with advanced gastric cancers will develop peritoneal metastases (12). Despite advances in preoperative imaging used for diagnosis and staging as U/S, CT scan, MRI, and PET-CT scan, many patients are diagnosed either intra-operative or in early post-operative period with distant metastases (2).

Diagnostic laparoscopy (DL) is a less invasive technique help in intra-abdominal lesions diagnosis. It enables visualization and examination of large surface areas of intraabdominal organs and deep parts that cannot be easily reached by laparotomies. Facilitate biopsy specimen taking, use laparoscopic ultrasound, fluorescence imaging and may be therapeutic. It's associated with less post-operative pain, less morbidity and decreases the need of unnecessary laparotomy from 40 to 17% (13). However, even with direct inspection during SL or laparotomy some small lesions could be missed, especially in if bowel mobilization is needed as in the pelvis (7).

Fluorescence image is used as a color code for delineation of malignant tissues, confirm sentinel lymph nodes, detecting early peritoneal disease and metastasis, decrease recurrence rate (14). ICG is a negatively charged tri-carbocyanine dye which has a high safety profile, with very low risk for anaphylaxis and cross-reactions with iodine sensitivity (1:10000). It is excreted unchanged in bile and not absorbed by intestinal mucosa diminishing risk of toxicity (15).

ICG binds to plasma proteins which extravasate through vascular neogenesis and hyper permeability of malignant vasculature and then illuminate by a light with an excitation wavelength range from 750 to 800 nm with high tissue penetration (millimeters to centimeters) where the human eye cannot detect so, it does not alter the surgical field. ICG device need a couple of filters, a special camera and a light source. The pattern of ICG florescence of tumors is classified into three types: total, partial and rim fluorescence (16).

This study was conducted in order to assess and provide precise data for the efficacy and added value of using ICG in diagnostic staging laparoscopy in intra-abdominal malignancy, especially in the identification of hepatic malignancies or liver and peritoneal metastases. Thirty patients with operable intra-abdominal malignancy presented to Theodor Bilhariz research institute from February 2022 to July 2023 were included in this study. In addition to standard of care, patients received an intravenous injection of 0.25-0.5 mg/kg ICG 24-72 hours prior to surgery. During surgery, patients underwent a staging laparoscopy; where upon inspection then near infra-red (NIR) fluorescence imaging was performed searching for hepatic focal lesions or peritoneal nodules.

In our study, the primary cancer was in the colon in 18 patients (60%), pancreas in 5 patients (16.7%), rectum in 1 patient (3.3%), stomach in 5 patients (16.7%) and duodenum in 1 patient (3.3%). In another study conducted by Lim, et al., ICG ability to localize liver tumor (17). Shirakawa, et al., and Handgraaf, et al.,

used indocyanine green to detect hepatic micro-metastases in patients with pancreatic cancer (13,18).

In another studies conducted by Filippello et al., and Barabino et al., assessed the affinity of Indocyanine green in the detection of peritoneal carcinomatosis (PC) in colorectal cancers (19,20). Satou et al., study search for PC in hepato-cellular carcinoma (HCC) patients Satou et al. (21), Ikoma et al., search for PC in gastric cancers Ikoma et al. (22) and Shirakawa, et al., search for PC in pancreatic cancers (18).

In our study, 0.25-0.5 mg/kg of ICG 24-72 hours pre-operative was injected. Kose, et al., inject ICG 24-48 hours pre-operative (23). Yokoyama, et al., inject 25 mg IV 24 hour before surgery (24).

No adverse reactions were recorded in any of our patients. This is concomitant to the results reported by Lim et al. (17) and Kose et al. (23).

In our study, total numbers of patients who had hepatic focal lesions were 6 patients, one patient had fatty infiltration, so, he was excluded (n=5). 4 patients (80%) discovered with contrast computed tomography (CT) which was concomitant with the study conducted by Shah et al. (25), 4 patients (80%) were discovered by near infra-red indocyanine green auto-florescence. Total numbers of hepatic focal lesions were 12 lesions (n=12); 8 lesions (67%) were detected by contrast computed tomography (CT), while 11 lesions (92%) were detected by near infra-red indocyanine green auto-florescence, (p value) this is almost similar to the result conducted by Piccolo, et al., reported sensitivity up to (100%) in detection of liver metastasis by ICG (26). Lim et al., reported (82.7%) successful ICG detection (17). Boogerd reported experience in a series of patients with multiple hepatic tumors where ICG allowed detection of 3 other lesions with overall sensitivity (94%) Boogerd et al. (27), but these were not concomitant with the results reported by Kose et al., who reported only (43%) accuracy in detection of liver lesions by ICG versus (74%) for pre-operative imaging (23).

In our study, hepatic focal lesions which were positive for metastases were seen intraoperative by near infra-red technique as a rim of florescence with dark center. The area for florescence was larger than the actual size of the metastatic lesion (margins were pathologically negative) and this was concomitant with the study conducted by Naoyuki, et al., who said the area of the fluorescence was larger than the actual tumor size, indicating that the metastatic cells themselves did not fluorescence (28).

All of other lesions detected by indocyanine green auto-florescence were superficial "< 1cm in depth" and the one missed by ICG was a hemangioma as it was impeded in liver parenchyma. These are concomitant with the study conducted by Lim et al., reported accuracy (84.1%) for lesions at depth <1cm and less than (50%) for lesions at depth >1cm from liver surface Lim et al. (17) and Kose et al., study findings accuracy of ICG were (95%) for superficial lesions and (4%) for deep lesions (23). Ishizawa et al., and Boogerd et al., studies found limited of depth of detection (8 mm) from the surface (27,29).

One out of five of patients presented with pancreatic malignancy (20%) had 2 micro-lesions not seen in triphasic CT imaging or during diagnostic staging laparoscopy, which are concomitant with the study done by Piccolo et al. Indocyanine green allow detection of hidden micro lesions that were missed by pre-operative imaging (26). Yokoyama et al. demonstrated that ICG is able to detect additional micro nodules in the liver in (16%) of the patients with pancreatic cancer (24). Yokoyama and Otani in another study reported presence of liver micro-metastases by ICG in 4 out of 26 patients (15.4%) who previously diagnosed with liver metastases in colorectal cancer (CRCLM) (24).

In our study, 7 hepatic lesions were biopsied for histopathological assessment, 4 lesions were positive for metastasis (57.2%) and one was identified as hemangioma (14.3%) and the last 2 lesions (micro-lesions) showed non specific findings (28.5%). In the study conducted by Yokoyama et al., 31 liver biopsy had been taken and 17 (55%) were positive for malignancy and the rest of specimens were false positive and in CT examination follow up 6 months post-operative, the patients with liver micro metastatic nodules developed liver metastases more than the patients without micro metatatic nodules(24).

In our study, by conventional preoperative investigations no peritoneal nodules were identified, while two patients were discovered to have multiple peritoneal nodules during diagnostic laparoscopy. ICG auto-florescence imaging helped in identification of peritoneal nodules in one patient only (over all sensitivity 50%). Lieto, et al., study reported that the ICG florescence allowed identifying of 16 nodules undiagnosed from conventional procedures, adding a 25% diagnostic improvement (30). In contrast to Kose, et al., study reported that peritoneal (omental and diaphragmatic) metastatic nodules did not show fluorescence (23).

In our study, all histopathological assessment of peritoneal (omentum and diaphragmatic) nodules are positive for malignancy.

In our study, the surgical decision had been changed

in 2 out of 30 patient (6.7%) and this is concomitant with the study conducted by Uchiyama et al. who used contrast enhanced intra-operative ultrasound plus ICG and they changed the surgical strategy in 6% of patients (31). Liberale et al. study results showed that intra-operative ICG florescence is helpful in the detection of peritoneal metastases of (CRC), resulting in surgery modifications in 38% of patients (32).

Limitation

The main limitation for the usage of indocyanine green is the cost and availability of laparoscopic near infra-red auto-florescence system. A major drawback of ICG in detection of hepatic lesions is the limited penetration power; hence, only superficial lesions could be seen.

CONCLUSION

ICG is a safe and applicable tool for intra-operative assessment and detection of liver lesions with high sensitivity. It is not specific for malignant lesions rather than hyper-vascular lesions, affecting its specificity. There is a discrepancy between sensitivity of ICG for detection of liver lesions and detection of peritoneal nodules, which may be affected by dose or time of pre-operative injection. Another study with larger sample size and dedicated post-operative follow up may be needed for more precise data.

Conflicts of interest and source of funding

No conflicts of interest, no source of funding.

Ethics approval

The procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Committee for Human Rights.

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