Different ways to manage indocyanine green fluorescence to different purposes in liver surgery: A systematic review

Sarah Molfino,[1] Marie Sophie Alfano,[1] Sara Benedicenti,[1] Beatrice Molteni,[1] Michele Peroni,[1] Mattia Baresi,[1] Antonio Tarasconi,[1] Fausto Catena,[2] Luigi Boni,[3] Nazario Portolani,[1] Gian Luca Baiocchi[1]

[1]Department of Clinical and Experimental Sciences, Surgical Clinic, University of Brescia; [2]Department of Emergency Surgery Unit, Ospedale Maggiore, Parma; [3]Department of General and Emergency Surgery, IRCCS Ca' Granda Policlinico Hospital University of Milan, Italy

Abstract

Fluorescent properties of indocyanine green (ICG) for hepatic tumor identification and features have been recently studied. The aim is to review the published data on the use of ICG enhanced fluorescence surgery during liver resection. A systematic search of literature was performed using MEDLINE, EMBASE, Cochrane and Web of Science libraries. For all eligible studies, the following data were extracted: study design, number of cases, management of indocyanine green (dose, time and method of administration), type of surgery, outcome variables, false positive and accuracy value, if reported. For statistical analysis, it was considered significant P<0.05, when published. 19 articles were fully analyzed and data were extracted. A total of 718 cases were globally analyzed as study group. No side effects of ICG were reported in any articles. 12 prospective observational, 1 randomized and 2 case-control studies were found. Three case reports and one experimental on animal model were also included. Detection of superficial lesions, segmental staining, biliary anatomy investigation (biliary leakage detection, biliary tree anatomy) were the main clinical application of fluorescence liver guided surgery. The overall quality of the data currently available is limited but the role of fluorescence guided liver surgery seems promising.

Correspondence: Sarah Molfino, Department of Clinical and Experimental Sciences, Surgical Clinic, University of Brescia, Via San Rocchino 199, 25123 Brescia, Italy.
E-mail: sarahmolfino@gmail.com

Key words: Liver tumor; indocyanine green; photodynamic eye; navigation in surgery; hepatectomy.

Contributions: all the Authors made substantial contributions to conception and design of the study, acquisition of data or analysis and interpretation of data, drafted the article or made critical revisions related to important intellectual content of the manuscript, and finally approved the version of the article to be published. SM and GLB conceived the study, performed Literature research and wrote the paper giving contribution in the same measurement. MSA, SB, BM and MB extracted data. MP analyzed the data. AT, FC, LB and NP reviewed the paper.

Conflict of interest: the authors declare no potential conflict of interest.

Conference presentation: this work was presented as an oral communication at the XXVIII Congress of the Italian Society of Surgical Pathophysiology (SIFIPAC), Parma 27-28 November 2017.

Received for publication: 21 February 2018.
Accepted for publication: 19 April 2018.

Journal of Peritoneum (and other serosal surfaces) 2018; 3:96
doi:10.4081/joper.2018.96

Introduction

In the recent years fluorescence-guided surgery gained interest among the scientific community and related publications are growing.[1-6] Different medical and surgical specialties (dermatology, pulmonology, urology, neurosurgery, gastro-intestinal surgery and plastic and reconstructive surgery) are currently using fluorescence imaging techniques for angyographic purpose, as well as for cancer/premalignant lesions detection, and/or lymph nodes mapping.[1-6] These fluorescence imaging techniques are based on the administration of indocyanine green (ICG), a soluble dye which emits a fluorescent light when illuminated by an infrared laser source.[7]

ICG has also been used in the last decades to evaluate hepatic function before liver surgery.[8] The application of the fluorescent properties of ICG for liver neoplasms identification and characterization was also recently investigated. The first application of this imaging technique in hepatic surgery was reported by Ishizawa *et al*. in 2009.[9] Up to date, with special reference to this possible application, clear rules for how to manage ICG (dose, time and site of administration) are lacking.

Aim of this systematic review is to collect data from current publications on the possible oncological value of indocyanine green in liver surgery for malignant diseases, and to clarify the management of ICG.

Materials and Methods

Search methods

A systematic search of literature was performed using MEDLINE, EMBASE, Cochrane and Web-of-Science libraries.

Publications were considered from the beginning of 2008 to the end of 2016. Keywords for search item were: liver tumor, indocyanine green, photodynamic eye, navigation in surgery, hepatectomy. MeSH terms were: indocyanine green/liver surgery, idocyanine green/navigation, indocyanine green/cholangiography. Preference has been given to English publications. All references in selected articles were further screened for additional publications. Articles were retrieved according to the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses guidelines (Figure 1).

Study selection

Articles were selected if their abstract showed a clinical usefulness of application of indocyanine green in hepatic surgery. Papers reporting use of indocyanine green in other surgical areas, as well as the preoperative setting for hepatic function evaluation, or explaining characteristics of indocyanine green itself, were excluded.

Data extraction

For all eligible studies, a standard Excel data form was filled in and the following data were extracted: study design, number of cases, management of indocyanine green (dose, time and method of administration), type of surgery, outcome variables, false positive and accuracy value, if reported. For statistical analysis, $P<0.05$ was considered significant, when available.

Methodological quality assessment

Two reviewers (SM and GLB) independently assessed the study quality according to the Newcastle-Ottawa scale, including the selection of patients, the reproducibility of the procedure, comparability of groups, and ascertainment of outcome of interest (being most of the analyzed studies a monocentric single series, without control group). The high-quality study was defined as a study with ≥6 awarded stars.

Results

Titles and abstracts of a total of 1331 articles were screened separately by 2 authors for eligibility.

Among those, 1296 were excluded, either for having abstract unavailable (n=25), or for describing other possible application of indocyanine green (*i.e.* for hepatic function or for not-hepatic surgery (n=750), or being irrelevant to our topic (n=371).Congress presentation and letters to the editor (150) were excluded from the analysis. Of the remaning 35 articles, 16 of which were excluded after full text examination, either for being narrative review (n=4, these have been cited in *Discussion* section [29, 31, 32, 33]), or being irrelevant as comments to other papers (n=7), or only available in abstract form (n=5).

The remaining 19 articles were fully analyzed and data were extracted as summarized in Tables 1-4.[9-27]

A total of 718 cases were globally analyzed as study group. No side effects of ICG were reported in any articles.

The majority of studies are prospective observational (n=12) and one only randomized prospective study was found. Two case-control study, three case reports and one experimental on animal model study were also included. Considering similar outcome variables, as defined in each articles, it appears reasonable to identify three different fields of application of indocyanine green in hepatic surgery: detection of surface lesions, segmental staining, biliary anatomy investigation (for biliary leakage detection and for staining of biliary tree, the so-called fluorescence cholangiography).

Detection and characterization of surface liver lesions

Articles and data regarding this topic and relative managing of indocyanine green are summarized in Table 2.

464 patients were included in these studies; dose, site and time

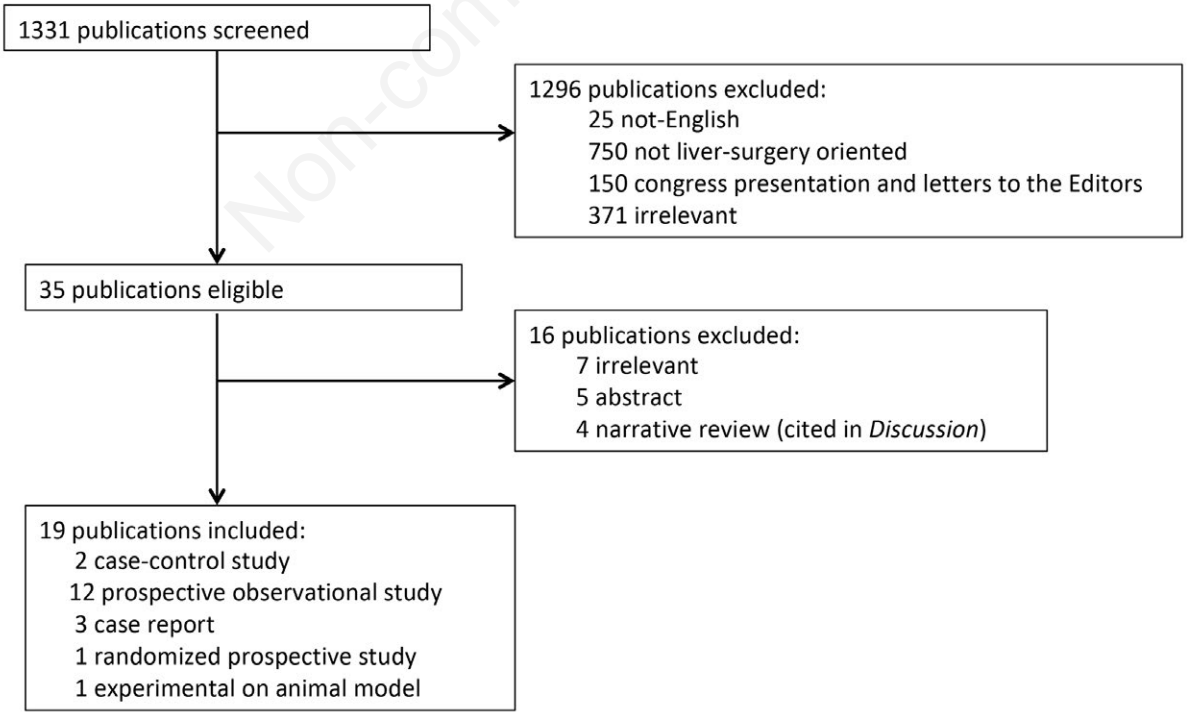

Figure 1. FArticles retrieval strategy, according to the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses guidelines.

of injection of ICG were reported in each article. The dose ranged from 0.25 mg/kg to 2.5 mg/kg; the site of injection of ICG was always intravenous; time of iv injection ranged from one to fourteen days before surgery.

Accuracy and false positive value, when reported, range from 50% to 100% and from 0% to 50% respectively. If published, P value was <0.05 comparing ICG to intra-operative ultra-sound in detection of other lesions, unknown before surgery (*missed lesions*), in favor of ICG fluorescence.

All the articles agree in recognizing that this technique is of limited value in detection of deep nodules (>10 mm from the surface) and has a high rate of false positive results in cirrhotic liver.

Segmental staining

Articles and data regarding this topic and relative managing of ICG are summarized in Table 3. A total of 64 patients were included in the analysis. ICG dose ranges from 0.25 mg/kg to 2.5 mg/kg while site of injection was always intra-portal branch of liver segment involved in hepatic resection and time was always intra-operative. All the 3 articles showed a 100% accuracy in segmental staining.

Table 1. Studies reporting feasibility and surgical usefulness of ICG in liver surgery.

Ref.	Year	Study design	N (cases)	Surgery	Outcome variables	False positive	Accuracy	P value
Abo *et al.*[10]	2014	Case-control	117	Liver resection	Diagnosis of lesion compared to IOUS	24%	94%	
			28	Liver resection	Segmental staining	0%	100%	
Aoki *et al.*[11]	2008	Prospective observational	35	Liver resection	Segmental staining	0%	100%	
Ashitate *et al.*[12]	2011	Experimental on animal model	10	Cholecystectomy	Detection biliary duct and artery	0%	100%	
Gotoh *et al.*[13]	2009	Prospective observational	10	Liver resection	Evidence of *missed* lesion[1]	NR	100%	
Harada *et al.*[14]	2009	Case report	3	Liver resection	Evidence of liver cholestasis[2]	NR	100%	
Ishizawa *et al.*[15]	2010	Prospective observational	52	Cholecystectomy	Evidence of biliary tree	0%	100%	
Ishizawa *et al.*[16]	2008	Prospective observational	13	Liver resection	Evidence right and left hepatic ducts	0%	100%	
			10	Cholecystectomy	Evidence of biliary tree	0%	100%	
Ishizawa *et al.*[17]	2012	Case report	1	Liver resection	Segmental negative-staining[3]	0%	100%	
Ishizawa *et al.*[9]	2009	Prospective observational	49	Liver resection	Grade of differentiation (HCC)	NR	NR	<0.001
Kaibori *et al.*[18]	2011	Randomized prospective	50 (control group[4]) 52 (study group[5])	Liver resection	Post-operative bile leakage	NR	NR	<0.001
Kaibori *et al.*[19]	2013	Prospective observational	48	Liver resection	Evidence of *missed* lesion[1]	50%	94%	
Kawaguchi *et al.*[20]	2011	Case report	2	Liver resection Liver resection	Detection of lesion Detection of biliary duct	0% 0%	100% 100%	
Kokudo *et al.*[21]	2012	Prospective observational	49	Liver resection	Diagnosis of lesion	NR	NR	
Peloso *et al.*[22]	2012	Prospective observational	25	Liver resection	Evidence of *missed* lesion[1]	NR	NR	0.007
Satou *et al.*[23]	2013	Prospective observational	17	Liver resection	Detection of extrahepatic metastases of HCC	NR	100%	
Takahashi *et al.*[24]	2016	Prospective observational	15	Liver resection	Detection of small lesion compared to IOUS	NR	50%	
Van der Vorst *et al.*[25]	2013	Case-control	40	Liver resection	Optimization of ICG dose and timing	NR	NR	NS
Yokoyama *et al.*[26]	2012	Prospective observational	42	Liver resection	Evidence of *missed* lesion[1] (*pancreatic metastases*)	0%	100%	
Zhang *et al.*[27]	2016	Prospective observational	50	Liver resection	Detection of small lesion and detection of margin of lesion	34%	100%	

[1]*missed* lesions are nodules not detected at the preoperative imaging. [2]Intraoperatively, fluorescent imaging clearly identified the subsegment of segment VII with cholestasis caused by bile duct invasion. [3]Citation from the article: *Negative-Staining Technique. To estimate the liver volume of segment II during resection of a hepatic tumor located in segment III, we found that the root of the portal pedicle for segment III had to be temporarily clamped and that the ICG dye (2.5 mg in 1 mL of normal saline) had to be intravenously injected. All hepatic segments, except segment III, were clearly fluorescent 1 minute after injection.* [4]The control group underwent a leak test after hepatic resection with ICG dye alone. [5]The experimental group underwent a leak test with ICG dye, followed by ICG fluorescent cholangiography using the Photodynamic Eye. NR, not reported; NS, not significant; HCC, hepatocellular carcinoma; IOUS, intra-operative ultra-sound.

Evidence of biliary tree and/or bile leakage during hepatectomy

Articles and data regarding this topic and relative managing of ICG are summarized in Table 4.

192 patients were analized with ICG dose that ranges from 0.025 mg/kg to 2.5 mg/kg. Site of injection was either intravenous or intra-biliary (most frequently, the cystic duct was cannulated). Time of injection ranges from intra-operative to 2-4 days before surgery. Each article publishes an accuracy of 100% in detection biliary tree during liver resection. One randomized prospective study[19] demonstrates a statistically significant difference ($P<0.05$) in post-operative biliary leakage comparing control group (patients underwent a leak test after hepatic resection with ICG dye alone injected via biliary duct) to experimental group (patients underwent a leak test with ICG dye, followed by ICG fluorescent cholangiography using the Photodynamic Eye).

Discussion

Interest to ICG-guided surgery is growing in the liver surgery community. ICG is already used by surgeons since many years to put indications for liver resection as described by Makuuchi *et al.*[28] The test is generally performed three days before surgery on average (1 to 7 days for HCC and 1 to 14 days for metastases).[9] Trading on the administration of ICG to test the liver function, many teams described the potentially intraoperative usefulness of this technique for surgical and for oncological purposes.

During the intervention, the investigation is performed by placing the infrared camera above the liver. The light in the operation room should be decreased as much as possible to improve the contrast of images seen on the screen. In some cases, ICG may be retained by cancer cells, due to reduced biliary delivery; however, more frequently, the same happens in a parenchymal ring surrounding the tumor, which is compressed and do not work as the normal tissue. The contrast between fluorescent and non-fluorescent areas closely depends on the interval between the time of ICG injection and the timing of fluorescence measurement, as well as on the liver function. On the other side, visualization of liver segmentation is closely related to the ability of selectively inject ICG in portal branches, usually under US guidance. Finally, the presence of fluorescence in bile structures depends upon the hepatic metabolism, thus it is related to the timing of iv injection. The exact optimal dosage and timing still remains to be defined.[7,29]

Technical aspects and historical context of ICG fluorescence

Table 2. Studies reporting use of ICG to detect hepatic lesions: management of ICG.

Ref.	Year	Study design	N (cases)	ICG dose	Site of injection ICG	Timing of ICG	False positive	Accuracy	P value
Abo *et al.*[10]	2014	Case-control	117	0.5 mg/kg	Intravenous	Day before surgery	24%	94%	
Gotoh *et al.*[13]	2009	Prospective observational	10	0.5 mg/kg	Intravenous	1-8 days before surgery	NR	100%	
Ishizawa *et al.*[9]	2009	Prospective observational	49	0.5 mg/kg	Intravenous	1-7 days before surgery	NR	NR	<0.001
Kaibori *et al.*[19]	2013	Prospective observational	48	0.5 mg/kg	Intravenous	14 days before surgery	50%	94%	
Kawaguchi *et al.*[20]	2011	Case report	2	0.5 mg/kg	Intravenous	2-3 days before surgery	0%	100%	
Kokudo *et al.*[21]	2012	Prospective observational	49	0.5 mg/kg	Intravenous	14 days before surgery	NR	NR	
Peloso *et al.*[22]	2012	Prospective observational	25	0.5 mg/kg	Intravenous	Day before surgery	NR	NR	0.007
Satou *et al.*[23]	2013	Prospective observational	17	0.5 mg/kg	Intravenous	1-5 days before surgery	NR	100%	
Takahashi *et al.*[24]	2016	Prospective observational	5 OR	2.5 mg/kg 7.5 mg	Intravenous Intravenous	2 days before surgery Day before surgery	NR	50%	
Van der Vorst *et al.*[25]	2013	Case-control	40	10 mg 20 mg 10 mg 20 mg 10 mg	Intravenous Intravenous Intravenous Intravenous Intravenous	Day before surgery Day before surgery 2 days before surgery 2 days before surgery Day before surgery	NR 0%	NR 100%	NS
Yokoyama *et al.*[26]	2012	Prospective observational	42	25 mg	Intravenous	Day before surgery	0%	100%	
Zhang *et al.*[27]	2016	Prospective observational	50	0.25 mg/kg	Intravenous Portal vein	Intraoperative	34%	100%	

Table 3. Studies reporting use of ICG to detect segmental staining: management of ICG.

Ref.	Year	Study design	N (cases)	ICG dose	Site of injection ICG	Timing of ICG	False positive	Accuracy
Abo *et al.*[10]	2014	Case-control	28	0.25 mg/kg	Portal vein	Intraoperative	0%	100%
Aoki *et al.*[11]	2008	Prospective observational	35	5 mg/kg	Portal vein	Intraoperative	0%	100%
Ishizawa *et al.*[17]	2012	Case report	1	2.5 mg/kg	Intravenous	Intraoperative	0%	100%

are well reported in the review by Reinhart *et al*.,[30] but pathophysiological mechanisms of ICG secretion are not totally elucidated.[31] Possible uses in oncological surgery are summarized in two reviews.[32,33] Many articles has been published about the staining of biliary tree during cholecystectomy as described by Boni *et al*.[34] but it was not the goal of our review.

Detection and characterization of surface liver lesions

Clearly, the most important limitation of this technique in detecting tumoral nodules is the lack of evidence of deep lesions.[7,29] On the other side, many advantages are described in detection of small nodules unknown before surgery with a statistical significant difference compared to intra-operative ultrasound.[9,13,19,21] Ishizawa *et al*.[9] showed in their report that 13% of lesions were not evident unless observed by ICG fluorescent imaging. Gotoh *et al.*[13] found 40% of new HCC nodules that were not detected by any preoperative and intraoperative examination, including IOUS.

Furthermore, ICG could be useful in tumor characterization: several Authors describe different grade of staining of fluorescent view related to type of lesion (HCC *vs* metastases *vs* cholangiocarcinoma)[9,10,22,25] or to grade of differentiation.[13] Ishizawa *et al.*[9] defined, as a pattern of staining, that well- differentiated HCCs appeared as uniformly fluorescing lesions with higher lesion-to-liver contrast than that of moderately or poorly differentiated HCCs (P<0.001), while metastases were delineated as rim- fluorescing lesions. However, there are not at the moment sufficient data to address this issue. Other fields of interest would be the final check of a free margin, as mentioned by Zhang *et al*.,[27] and the detection of extra-hepatic (*i.e.* hepatic pedicle nodes) metastases, as described by Takahashi *et al.*[24]

With reference to the management of ICG administration, the majority of the Authors used a standard dose of 0.5 mg/kg injected during the pre-operative test aimed at liver function evaluation, as described in Table 2. The only published case-control study[25] suggests injecting 10 mg of ICG intravenously the day before surgery, which guarantees a high accuracy rate. Thus, this dose may be suggested as a standard dose for hepatic lesions detections; further confirmation studies are needed, with special reference to the relationship with hepatic function.

Segmental staining

Since Torzilli & Makuuchi[35] described intraoperative ultrasonography during liver resection, this technique is the goal standard to guide hepatic surgeons. A possible easy alternative way to perform segmental resection has been described by some Authors, as shown in Table 3[10,11,17] based on segmental fluorescent staining with ICG, injected during the intervention in the intrahepatic portal branches, with a dose ranging from 0.25 mg/kg to 5 mg/kg. However, only small series and anecdotal data are available by now to confirm the usefulness of this technique.

Evidence of biliary tree and/or bile leakage during hepatectomy

A full agreement seems to be evident in the Literature, either in managing of ICG and in possible fields of application for biliary anatomy and biliary leakage detection during surgery, as demonstrated in Table 4. The accuracy of biliary tree staining is 100% in all the reported series, either during cholecystectomy[15,16,34] and during hepatic resection (for example to detect left or right hepatic ducts involved by neoplasm[14,16,20]). ICG search may prove useful for intraoperative bile leakage detection after liver resection; the only available prospective randomized study shows a statistically significant advantage in the ICG fluorescent staining arm.[18]

The dosage proposed to this intent ranged from 0.025 mg/kg to 0.25 mg/kg when direct injection of ICG in bile duct is provided, and 2.5 mg/kg when intravenous injection is performed, some variable time before the surgical intervention or following intubation as shown in Table 4.

Two recent studies of our Institution have shown the optimal dosage and timing of administration of ICG to give a good visualization of hepatic lesion.[36,37]

Conclusions

In conclusion, our review suggests different fields of application of ICG fluorescence detection in hepatic surgery and, with limitations due to relative few data available, different ways to manage of ICG to different purposes are reported. Future studies about relationship between managing of ICG and liver function are needed.

Table 4. Studies reporting use of ICG to detect biliary tree and bile leakage: management of ICG.

Ref.	Year	Study design	N (cases)	ICG dose	Site of injection ICG	Timing of ICG	False positive	Accuracy	P value
Ashitate *et al.*[12]	2011	Experimental on animal model	10	0.04 mg/kg	Intravenous	Intraoperative	0%	100%	
Harada *et al.*[14]	2009	Case report	3	0.5 mg/kg	Intravenous	2-4 days before surgery	NR	100%	
Ishizawa *et al.*[15]	2010	Prospective observational	52	2.5 mg/kg	Intravenous	Following intubation	0%	100%	
Ishizawa *et al.*[16]	2008	Prospective observational	13 10	0.025 mg/kg 2.5 mg/kg	Transcystic tube Intravenous	Intraoperative 1 hour before surgery	0% 0%	100% 100%	
Kaibori *et al.*[18]	2011	Randomized prospective	50 (control group*) 52 (study group°)	2.5 mg/kg	Intra bile duct	Intraoperative	NR	NR	<0.001
Kawaguchi *et al.*[20]	2011	Case report	2 OR	2.5 mg/kg 0.025 mg/kg	Intravenous Intra bile duct	Followin intubation Intraoperative	0%	100%	

*The control group underwent a leak test after hepatic resection with ICG dye alone. °The experimental group underwent a leak test with ICG dye, followed by ICG fluorescent cholangiography using the Photodynamic Eye.

References

1. Morton CA, Brown SB, Collins S, et al. Guidelines for topical photodynamic therapy: report of a workshop of the British Photodermatology Group. Br J Dermatol 2002;146:552-67.
2. Lam B, Wong MP, Fung SL, et al. The clinical value of autofluorescence bronchoscopy for the diagnosis of lung cancer. Eur Respir J 2006;28:915-9.
3. Tobis S, Knopf JK, Silvers CR, et al. Near infrared fluorescence imaging after intravenous indocyanine green: initial clinical experience with open partial nephrectomy for renal cortical tumors. Urology 2012;79:958-64.
4. Stummer W, Stocker S, Wagner S, et al. Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. Neurosurgery 1998;42:518-25.
5. Kusano M, Tajima Y, Yamazaki K, et al. Sentinel node mapping guided by indocyanine green fluorescence imaging: a new method for sentinel node navigation surgery in gastrointestinal cancer. Dig Surg 2008;25:103-8.
6. Ogata F, Narushima M, Mihara M, et al. Intraoperative lymphography using indocyanine green dye for near-infrared fluorescence labeling in lymphedema. Ann Plast Surg 2007;59:180-4.
7. Lim C, Vibert E, Azoulaya D, et al. Indocyanine green fluorescence imaging in the surgical management of liver cancers: Current facts and future implications. J Visceral Surg 2014;151:117-24.
8. Lau H, Man K, Fan ST, et al. Evaluation of preoperative hepatic function in patients with hepatocellular carcinoma undergoing hepatectomy. Br J Surg 1997;84:1255.
9. Ishizawa T, Fukushima N, Shibahara J, et al. Real-Time Identification of Liver Cancers by Using Indocyanine Green Fluorescent Imaging. Cancer 2009;115:2491-504.
10. Abo T, Nanashima A, Tobinaga S, et al. Usefulness of intraoperative diagnosis of hepatic tumors located at the liver surface and hepatic segmental visualization using indocyanine green-photodynamic eye imaging. Eur J Surg Oncol 2015;41:257-64.
11. Aoki T, Yasuda D, Shimizu Y, et al. Image-Guided Liver Mapping Using Fluorescence Navigation System with Indocyanine Green for Anatomical Hepatic Resection. World J Surg 2008;32:1763-7.
12. Ashitate Y, Stockdale A, Choi HS, et al. Real-Time Simultaneous Near-Infrared Fluorescence Imagingof Bile Duct and Arterial Anatomy. J Surg Res 2012;176:7-13.
13. Gotoh K, Yamada T, Ishikawa O, et al. A Novel Image-Guided Surgery of Hepatocellular Carcinoma by Indocyanine Green Fluorescence Imaging Navigation. J Surg Oncol 2009;100:75-9.
14. Harada N, Ishizawa T, Muraoka A, et al. Fluorescence Navigation Hepatectomy by Visualization of Localized Cholestasis from Bile Duct Tumor Infiltration. J Am Coll Surg 2010;210:6.
15. Ishizawa T, Bandai Y, Ijichi M, et al. Fluorescent cholangiography illuminating the biliary tree during laparoscopic cholecystectomy. Br J Surg 2010;97:1369-77.
16. Ishizawa T, Tamura S, Masuda K, et al. Intraoperative Fluorescent Cholangiography Using Indocyanine Green: A Biliary Road Map for Safe Surgery. J Am Coll Surg 2009;208:e1-4.
17. Ishizawa T, Zuker NB, Kokudo N, et al. Positive and Negative Staining of Hepatic Segments by Use of Fluorescent Imaging Techniques During Laparoscopic Hepatectomy. Arch Surg 2012;147:393-4.
18. Kaibori M, Ishizaki M, Matsui K, et al. Intraoperative indocyanine green fluorescent imaging for prevention of bile leakage after hepatic resection. Surgery 2011;150:91-8.
19. Kaibori M, Matsui K, Ishizaki M, et al. Intraoperative Detection of Superficial Liver Tumors by Fluorescence Imaging Using Indocyanine Green and 5-aminolevulinic. Acid Anticanc Res 2016;36:1841-50.
20. Kawaguchi Y, Ishizawa T, Masuda K, et al. Hepatobiliary Surgery Guided by a Novel Fluorescent Imaging Technique for Visualizing Hepatic Arteries, Bile Ducts, and Liver Cancers on Color Images. J Am Coll Surg 2011;212:e33-9.
21. Kokudo N, Ishizawa T. Clinical Application of Fluorescence Imaging of Liver Cancer Using Indocyanine Green. Liver Cancer 2012;1:15-21.
22. Peloso A, Franchi E, Canepa MC, et al. Combined use of intraoperative ultrasound and indocyanine green fluorescence imaging to detect liver metastases from colorectal cancer. HPB 2013;15:928-34.
23. Satou S, Ishizawa T, Masuda K, et al. Indocyanine green fluorescent imaging for detecting extrahepatic metastasis of hepatocellular carcinoma. J Gastroenterol 2013;48:1136-43.
24. Takahashi H, Zaidi N, Berber E. An Initial Report on the Intraoperative Use of Indocyanine Green Fluorescence Imaging in the Surgical Management of Liver Tumors. J Surg Oncol 2016;114:625-9.
25. van der Vorst JR, Schaafsma BE, Hutteman M, et al. Near-Infrared Fluorescence- Guided Resection of Colorectal Liver Metastases. Cancer 2013;119:3411-8.
26. Yokoyama N, Otani T, Hashidate H, et al. Real-Time Detection of Hepatic Micrometastases From Pancreatic Cancer by Intraoperative Fluorescence Imaging. Cancer 2012;118:2813-9.
27. Zhang Y-M, Shi R, Hou J-C, et al. Liver tumor boundaries identified intraoperatively using real-time indocyanine green fluorescence imaging. J Cancer Res Clin Oncol 2017;143:51-8.
28. Makuuchi M, Kosuge T, Takayama T, et al. Surgery for small liver cancers. Semin Surg Oncol 1993;9:298-304.
29. Ishizawa T, Saiura A, Kokudo N. Clinical application of indocyanine green-fluorescence imaging during hepatectomy. HepatoBiliary Surg Nutr 2016;5:322-8.
30. Reinhart MB, Huntington CR, Blair LJ, et al. Indocyanine Green: Historical Context, Current Applications, and Future Considerations. Surg Innovat 2016;23:166-75.
31. Kawaguchi Y, Ishizawa T, Miyata Y, et al. Portal uptake function in veno-occlusive regions evaluated by real-time fluorescent imaging using indocyanine green. J Hepatol 2012;58:247-53.
32. Polom K, Murawa D, Rho Y-S, et al. Current Trends and Emerging Future of Indocyanine Green Usage in Surgery and Oncology. Cancer 2011 [epub ahead of print].
33. Zelken JA, Tufaro AP. Current Trends and Emerging Future of Indocyanine Green Usage in Surgery and Oncology: An Update. Ann Surg Oncol 2015;22:S1271-83.
34. Boni L, David G, Mangano A, et al. Clinical applications of indocyanine green (ICG) enhanced fluorescence in laparoscopic surgery. Surg Endosc 2015;29:2046-55.
35. Torzilli G, Makuuchi M. Intraoperative ultrasonography in liver cancer. Surg Oncol Clin N Am 2003;12:91-103.
36. Benedicenti S, Molfino S, Alfano MS, et al. Indocyanine-Green Fluorescence-GUIDED Liver Resection of Metastasis from Squamous Cell Carcinoma Invading the Biliary Tree. Case Rep Gastrointest Med 2018;2018:5849816.
37. Alfano MS, Molfino S, Benedicenti S, et al. Intraoperative ICG-based imaging of liver neoplasms: a simple yet powerful tool. Preliminary results. Surg Endos. 2018 [epub ahead of print].