



European-African Hepato-Pancreato-Biliary Association

# **E-AHPBA Webinars**

## **Robotic Liver Surgery**

**Tuesday 22nd June 2021  
1800 BST / 1900 CEST**

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# Minimal invasive ICG guided resection

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# Conflict of Interest

I declare I have no conflict of interest

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# Surgical dilemma in liver surgery

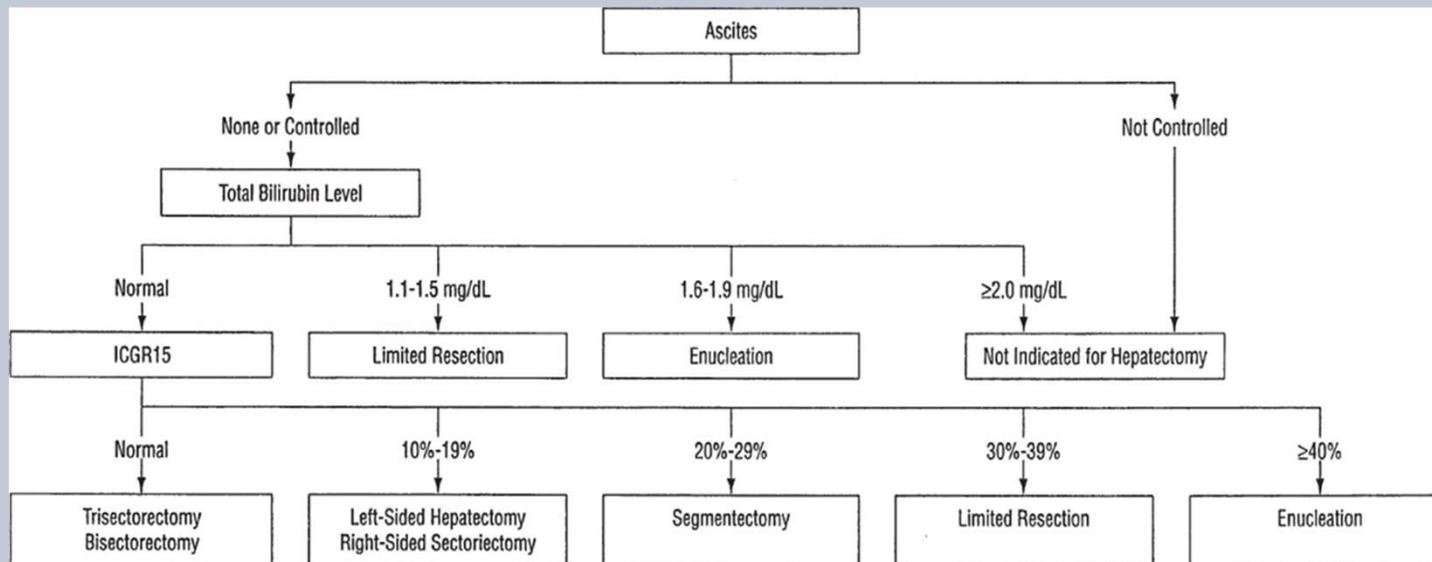
- ▶ Obtain R0 resection
- ▶ With maximal parenchym sparing
- ▶ Low complication rate
- ▶ Minimally Invasive
  
- ▶ CT/MRI/PET/IOUS/3D reconstrcution
  
- ▶ ICG firefly :created to compensate for the loss of tactile feedback



# ICG is known in HPB

- ▶ indocyanine green retention rate at 15 min (ICGR-15)

LiMON test : ICG is administered intravenously days before surgery and the blood concentration and ICG plasma disappearance rates are measured noninvasively



J Hepatobiliary Pancreat Surg. 2005;12(1):16-22.



# What is ICG?

- Indocyanine green (ICG) is a non-toxic fluorophore that appears green when stimulated by near-infrared light.
- It is approved by the Food and Drug Administration (FDA) and has been used in medicine for over 50 years
- In healthy liver tissue, ICG is fully excreted after 72 h and no remnants should be detectable

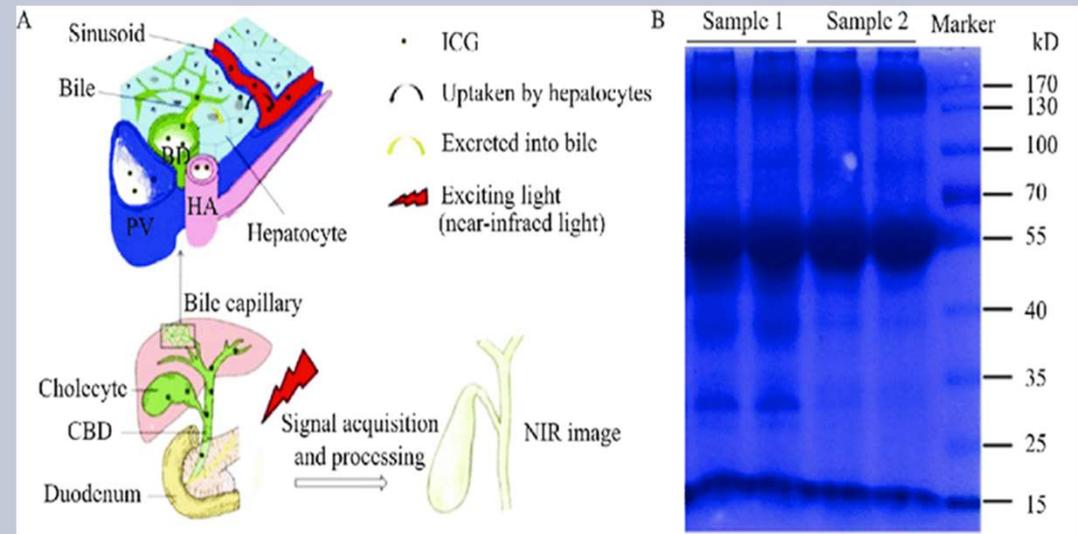
Hepatobiliary Surg Nutr. 2016 Aug; 5(4): 311–321.



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## ICG

- ▶ Hydro soluble molecule
- ▶ Binds plasma AND bile proteins
- ▶ Not metabolized
- ▶ Hepatocytes take up the ICG
- ▶ Excrete it through the bile rapidly
- ▶ Excreted from normal hepatocytes within 4 hours
- ▶ But remains fixed in tumoral and pathological hepatocytes
- ▶ And in hepatocytes around tumor lesion (underactive)
- ▶ Half life time 180 sec



Journal of Huazhong University of Science and Technology 2016: 37(1):44-50



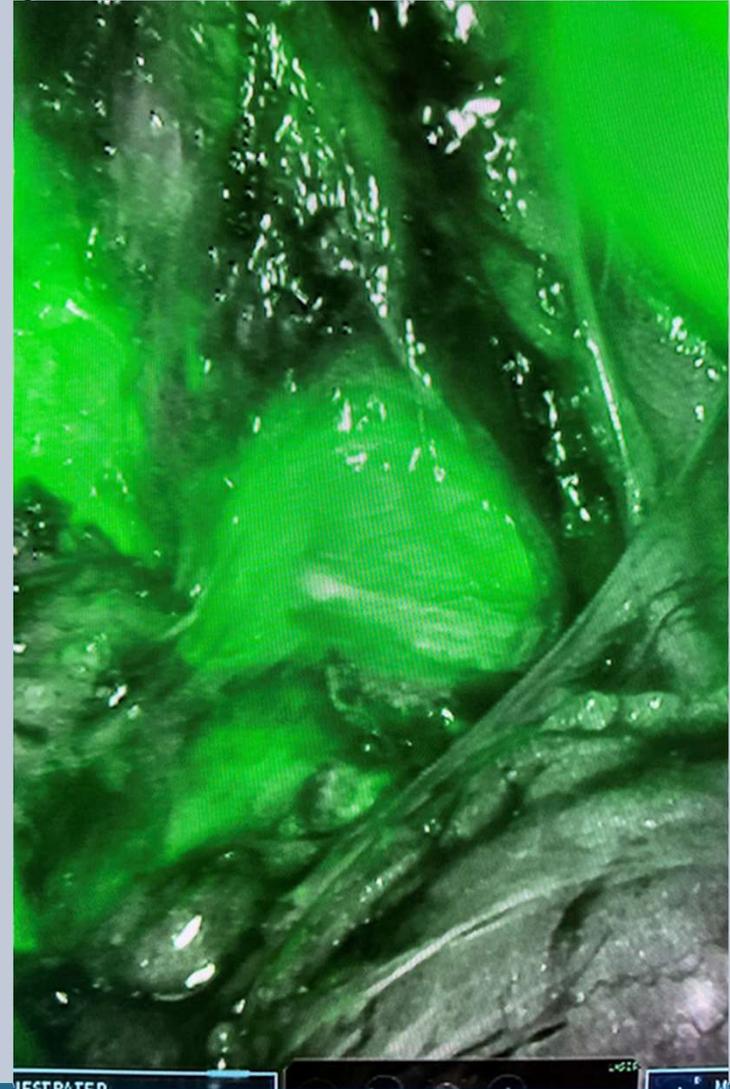
# First application

- ▶ First described in robotic surgery by Guilianotti et al. 2014: biliary imaging
- ▶ The cystic duct, the common bile duct, and the common hepatic duct were successfully visualized with ICG in 97.8%, 96.1%, and 94% of cases respectively.
- ▶ Ishizawa et al. (2009) noticed ICG accumulation in: hepatocellular carcinoma (HCC) and CRLM up to 14 days after ICG application for liver function evaluation



# European-African Hepato-Pancreato-Biliary Association Chronology

- ▶ Injection
- ▶ 5 seconds: arterial anatomy
- ▶ After 30 mins : visualisation of biliary anatomy:
- ▶ CCE + Biliary reconstructions
  
- ▶ Central liver tumors
- ▶ Hilair cholangiocarcinomas





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## Could ICG-aided robotic cholecystectomy reduce the rate of open conversion reported with laparoscopic approach? A head to head comparison of the largest single institution studies

A. Gangemi<sup>1</sup> · R. Danilkowicz<sup>1</sup> · F. E. Elli<sup>1</sup> · F. Bianco<sup>1</sup> · M. Masrur<sup>1</sup> · P. C. Giulianotti<sup>1</sup>

**Table 2** Results and *P* values

	UIC RC	UIC LC	<i>p</i> value (UIC-RC/ UIC-LC)	GHS LC	<i>p</i> value (UIC-RC/ GHS LC)	ILS LC	<i>p</i> value (UIC-RC/ ILS LC)
Number of total cases: number of acute cholecystitis or gangrenous cholecystitis cases	676:131	289:94	–	3371: –	–	13,305: –	–
# Of major biliary injuries*/percentage	0/0.0 %	1/0.34 %	0.126	4/0.12 %	0.368	20/0.15 %	0.3125
# Of minor biliary injuries**/percentage	1/0.15 %	3/1.04 %	<b>0.049</b>	–	–	32/0.24 %	0.631
# Open conversion/percentage	1/0.15 %	13/4.5 %	<b>&lt;0.001</b>	86/2.6 %	<b>&lt;0.001</b>	–	–
# Open conversions in acute cholecystitis and gangrenous cholecystitis setting/percentage	1/0.76 %	9/9.57 %	<b>0.002</b>	–	–	–	–
# Of biliary anomalies identified intraoperative/percentage	14/2.07 %	2/0.69 % <sup>^</sup>	0.170	–	–	–	–
Mean hospital stay (no complications) days (standard deviation)	1.21 (1.60)	1.20 (1.48)	0.892	–	–	2	–
Mean blood loss mL (standard deviation)	14.37 (27.26)	21.08 (72.22)	<b>&lt;.001</b>	–	–	–	–

Bold indicates a statistically significant finding

\* Injuries classified as Strasberg Types D or E

\*\* Injuries classified as Strasberg Types A, B or C

<sup>^</sup> Identified via intraoperative cholangiography



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# Dose?

- ▶ The dose used for standard diagnostic procedures lies between 0.25 and 0.5 mg/kg
- ▶ Above 0.5 mg/kg, the incidence of immediate allergic reactions increases
- ▶ 80 kg: 40 mg
  
- ▶ Peritoneal implants will not be seen



# When to inject?

- ▶ Anatomy:
- ▶ Vascular: at time you need it ( 5-60 sec)
- ▶ Biliary: at time of incision (30-45 mins)
  
- ▶ Lesions:
- ▶ ICG ineffective when < 8 hours or > 72 hours
- ▶ Ideal 24-48 hours prior to surgery ( Peyra et al.)
- ▶ Van de Vorst et al. : 72 hours to avoid fals positive resections.



# Timing ICG

Ishizawa et al

- ▶ The dose and interval between ICG injection and surgery are key determinants of the remaining background fluorescence signal in the liver and the fluorescent rim surrounding the tumor.
- ▶ In a preclinical study in rats performed, the influence of injection time prior to surgery and dose of ICG pertaining to the contrast between the fluorescent rim around the hepatic metastases and normal liver tissue (tumor-to-liver ratio) was examined.
- ▶ In this preclinical study, the highest tumor-to-liver ratio (TLR) was reached when ICG was injected 72 h prior to surgery.



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**Table 4.** Patients showing unsuccessful ICG staining.

	1	2	3	4	5	6	7
Sex	m	f	f	m	f	m	f
Age (years)	61	70	40	76	74	79	82
Comorb. (liver)	Cirrhosis (grade IV)	cirrhosis	—	fibrosis	—	—	cirrhosis (grade IV)
Dose (mg/kg)	0.23	0.50	0.28	—	0.30	—	0.32
Timediff (h:min)	—	18:25	—	15:32	7:39	12:41	17:31
IOS	df	us	ns	ns	ns	us	ns
Histopath (Resection margin)	HCC (R1)	HCC (R1)	BC	HCC	NM, initially BC	UC (R1)	NM

BC, breast cancer; Comorb., liver-associated liver comorbidities; df, diffuse staining; HCC, hepatocellular carcinoma; Histopath., final histopathological results; IOS, intraoperative staining; NM, no malignancy; ns, no staining; Timediff, time difference between application and surgery; UC, urothelial carcinoma; us, ubiquitous staining.

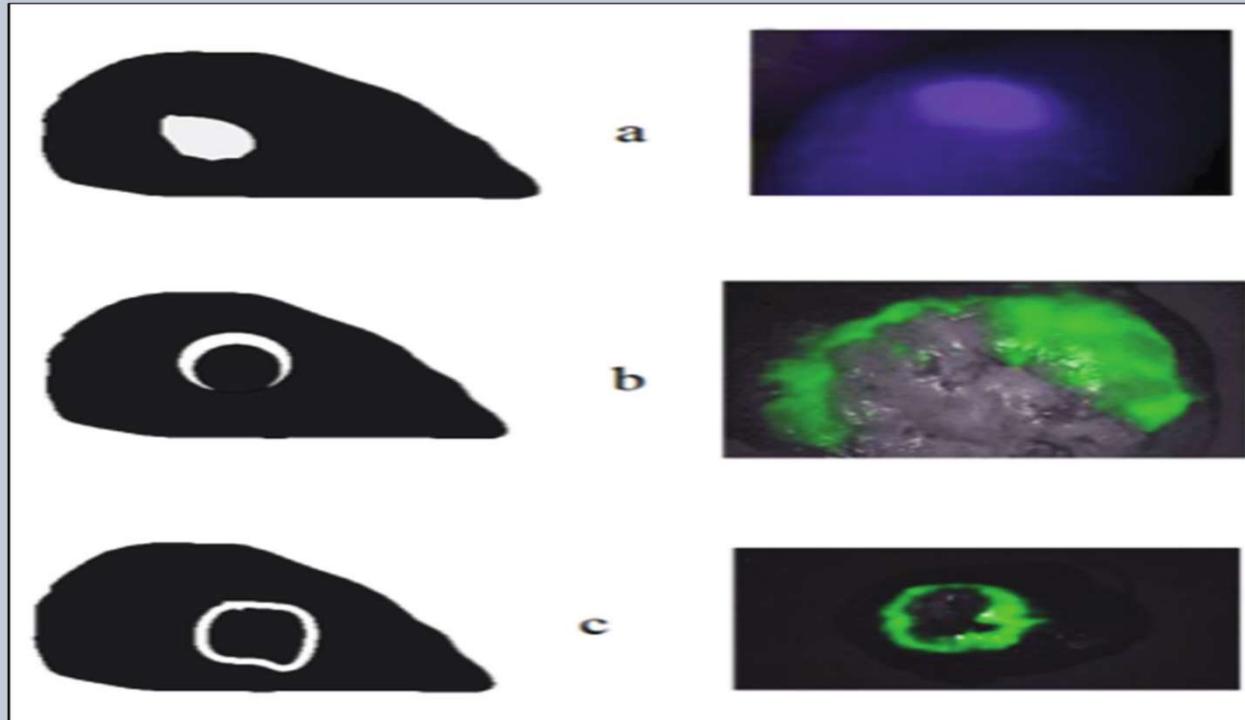


# What do you see?

- ▶ Fluorescence pattern is related to type of malignancy and the grade of differentiation/ the vascular pattern/tumor biology
- ▶ Well differentiated HCC; strong fluorescence pattern
- ▶ Poorly differentiated HCC : rim of fluorescence or no fluorescence
- ▶ CRLM: rim of fluorescence

Hepatobiliary Surg Nutr. 2016 Aug; 5(4): 311–321

# What do you see?



**Figure 2.** Schematic visualization of liver lesions by FIS. A - homogeneous fluorescence (typical aspect of well differentiated HCC); B - partial fluorescence (visualized in moderately differentiated HCC); C - peri-tumoral fluorescence (fluorescent ring in poorly differentiated HCC, colorectal liver metastasis, cholangiocarcinomas)

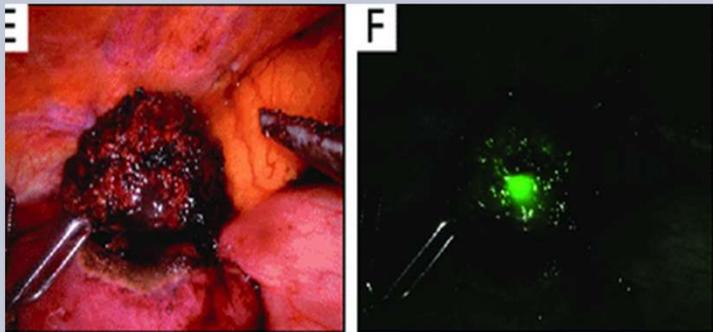


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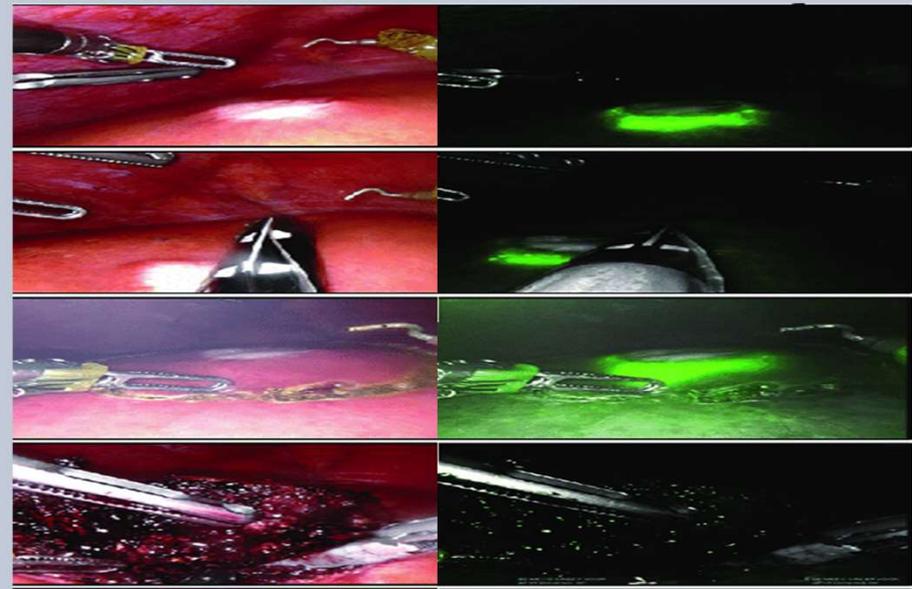
# Indicator of the surgical margin during liver resection

## Real time margin check

- ▶ Tumor fluorescence + Peri tumoral fluorescence
- ▶ absence of fluorescent signals on the resected surface indicates a secure surgical margin
- ▶ Margin : 0.8 mm
- ▶ NO green = 0.8mm R0



Langenbecks Arch Surg 2018 Aug;403(5):671-680.



# How it helps for R0

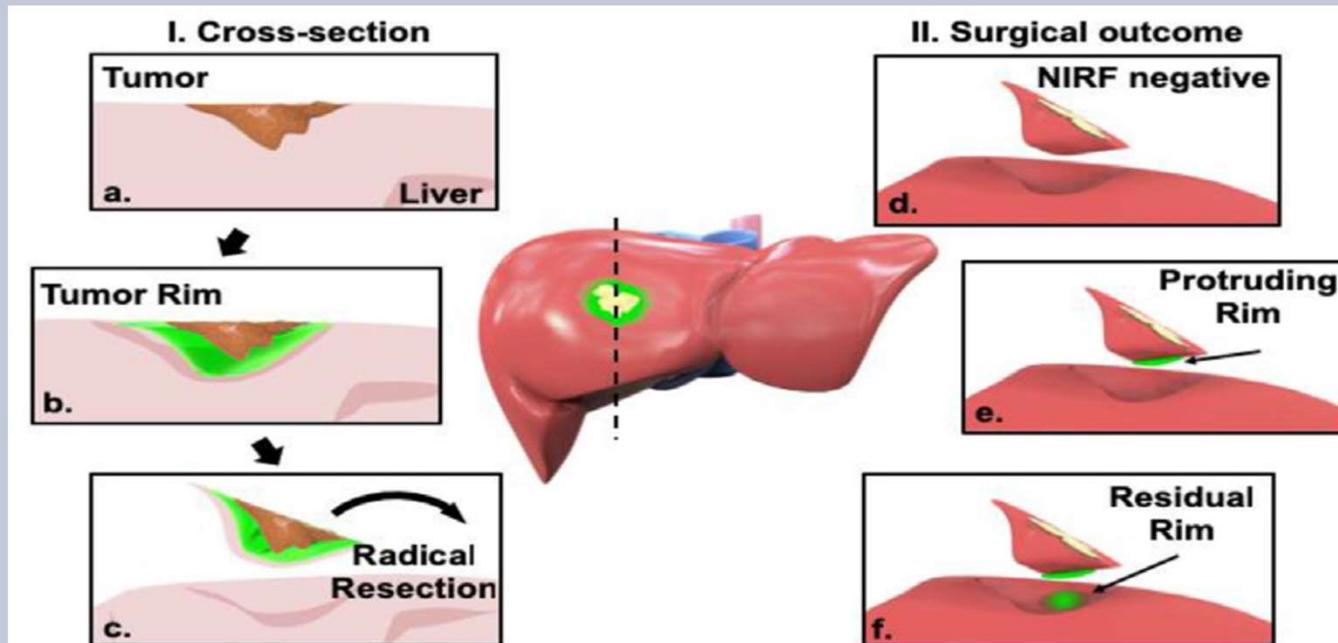


Fig. 1: 3D model of the liver with a CRLM in segment V/VIII showcasing the technique's Background (a-c) and possible surgical outcomes (d-f).



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## Usability of Indocyanine Green in Robot-Assisted Hepatic Surgery

Anne-Sophie Mehdorn <sup>1b</sup>, Jan Henrik Beckmann <sup>1b</sup>, Felix Braun, Thomas Becker and Jan-Hendrik Egberts \*

**Table 3.** Intraoperative indocyanine green (ICG) use (according to surgeon's perception).

	(n = 20)
Dose of ICG applied (mg/kg) mean ± SD (range)	0.32 ± 0.08 (0.22–0.50)
Duration between ICG application and surgery (h:min) mean ± SD (range)	21:24 ± 4:52 (7:39–47:05)
Intraoperative ICG signal <sup>a</sup>	2.4 ± 1.4 (1–6)
The intraoperative ICG signal helped during surgery (yes), % (n)	60.0 (12)
ICGA was clear and unequivocal (yes), % (n)	60.0 (12)
IOUS was used (yes), % (n)	100 (20)
Did IOUS and ICGA correlate? (yes), % (n)	75.0 (15)
Which intraoperative support helped the most? n	
ICGA	3
IOUS	4
Combination	8
None	4
None necessary because of macroscopic detection	1

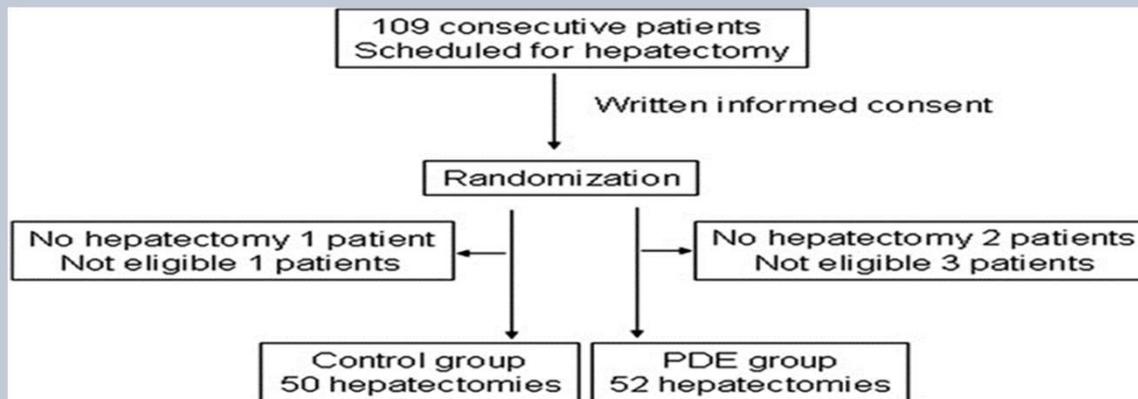
ICG, indocyanine green; ICGA, ICG accumulation; IOUS, intraoperative ultrasound; n, number of patients.

<sup>a</sup> 1 = excellent signal, 2 = good signal, 3 = moderate signal, 4 = sufficient, 5 = insufficient signal, 6 = no signal at all.



# Bile leakage after hepatectomy

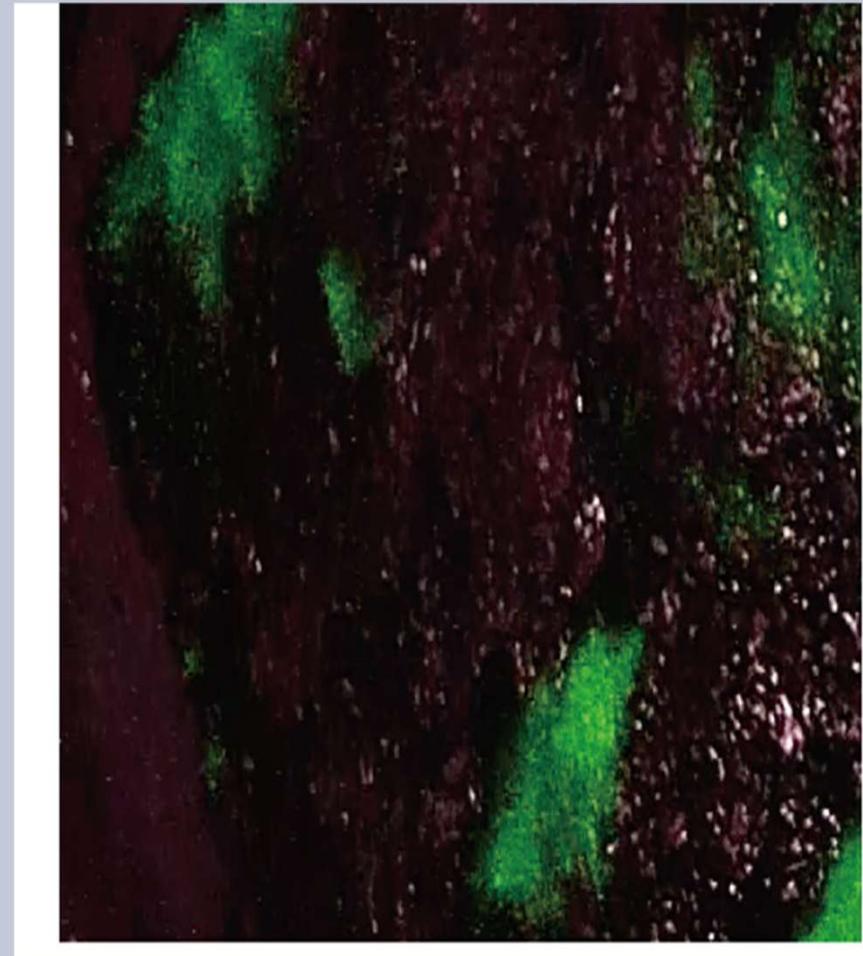
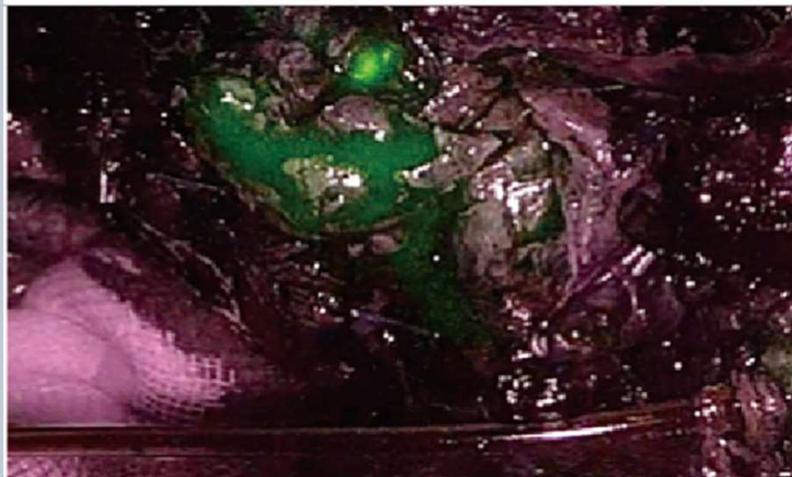
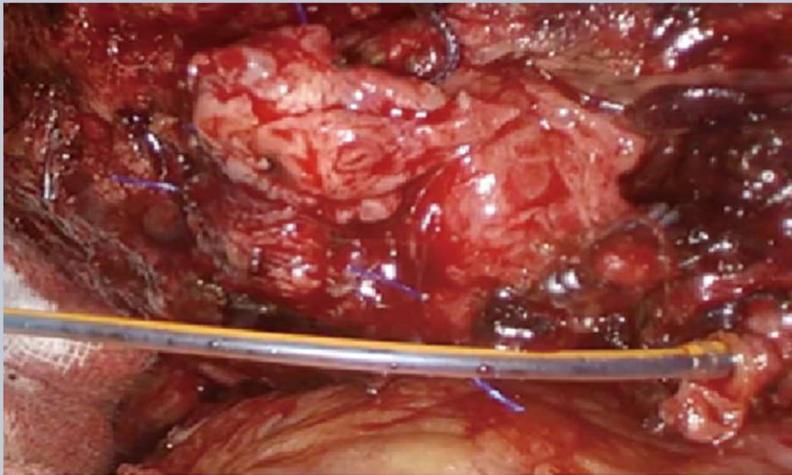
- ▶ Keiburi et al. : RCT 102 patients
- ▶ Five patients developed postoperative bile leakage among the 50 patients in the control group versus no bile leakage among the 52 patients in the PDE group.



- ▶ ICG cholangiography : detection of leakage at bile ducts on the cutting surface (deep 8-10 mm), not detected by classic leakage test



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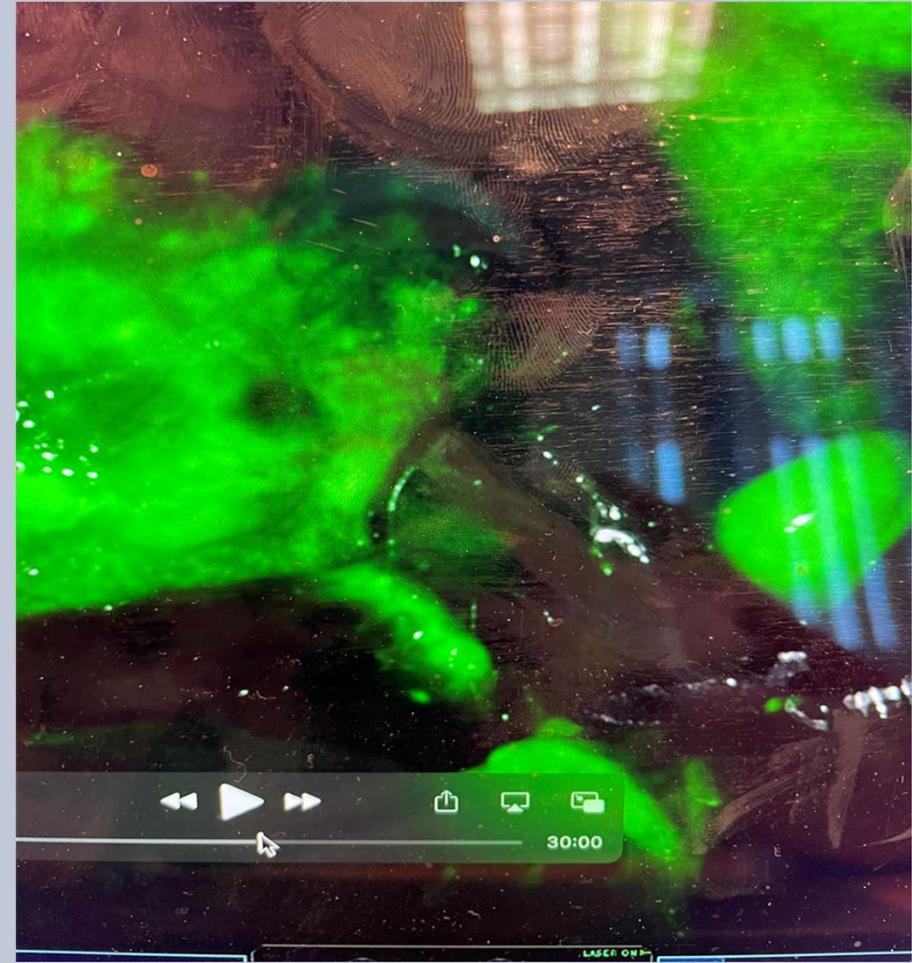
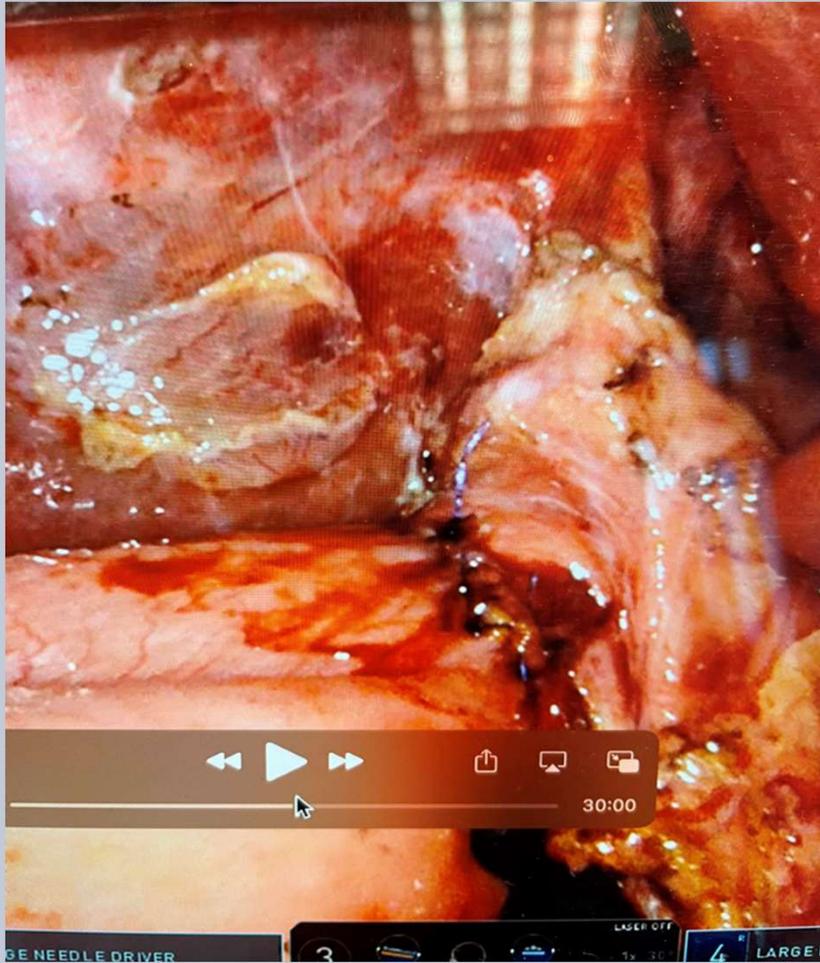


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## Long-term follow-up after near-infrared fluorescence-guided resection of colorectal liver metastases: a retrospective multicenter analysis

Henricus J.M. Handgraaf, MD<sup>1</sup>, Leonora S.F. Boogerd, MD<sup>1</sup>, Diederik J. Höppener, BSc<sup>1</sup>, Peloso Andrea, MD, PhD<sup>2</sup>, Babs G. Sibinga Mulder, BSc<sup>1</sup>, Charlotte E.S. Hoogstins, MD<sup>1</sup>, Henk H. Hartgrink, MD, PhD<sup>1</sup>, Cornelis J.H. van de Velde, MD, PhD<sup>1</sup>, J. Sven D. Mieog, MD, PhD<sup>1</sup>, Rutger-Jan Swijnenburg, MD, PhD<sup>1</sup>, Hein Putter, PhD<sup>3</sup>, Marcello Maestri, MD, PhD<sup>2</sup>, Andries E. Braat, MD, PhD<sup>1</sup>, John V. Frangioni, MD, PhD<sup>4</sup>, and Alexander L. Vahrmeijer, MD, PhD<sup>1,\*</sup>

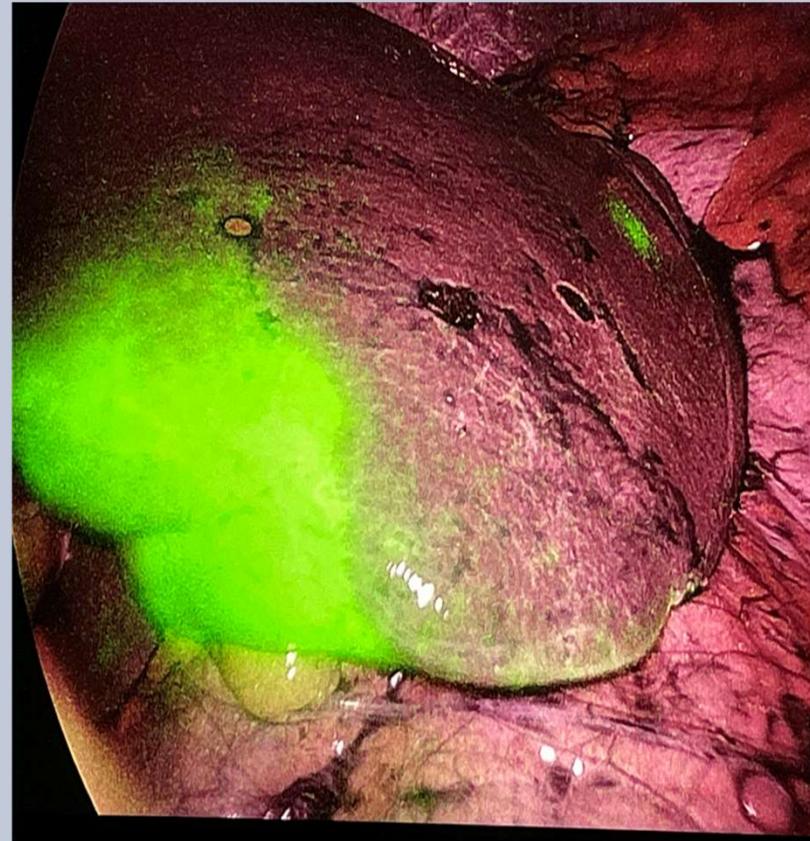
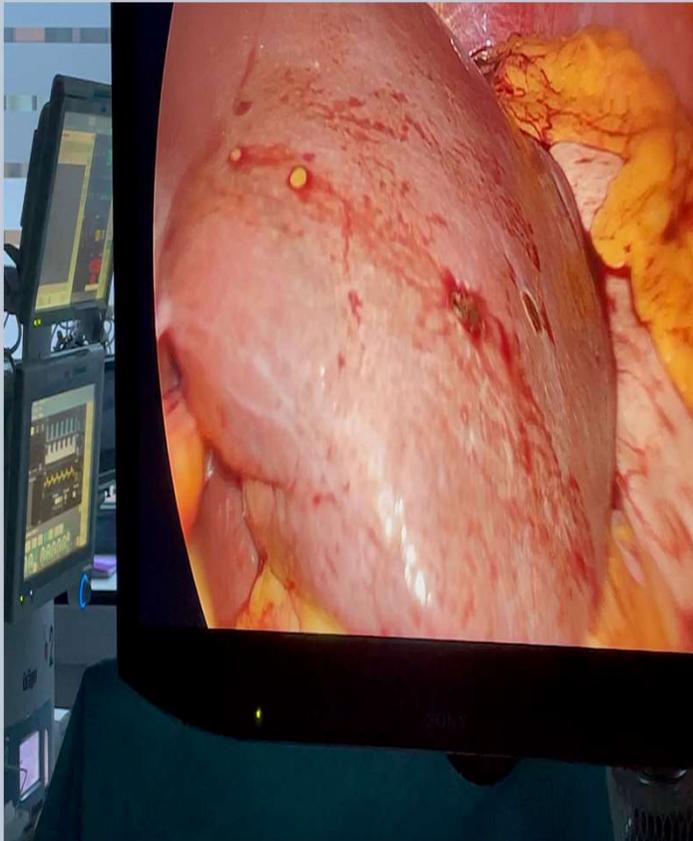
### ► Recurrence rate FLARE resection vs classical resection

**RESULTS**—Eighty-six patients underwent resection with NIRF imaging and 87 without. In significantly more patients of the NIRF imaging cohort additional metastases were identified during surgery (25% vs. 13%,  $p=0.04$ ). Tumors identified solely by NIRF imaging were significantly smaller compared to additional metastases identified also by inspection, palpation or intraoperative ultrasound ( $3.2 \pm 1.8$  mm vs.  $7.4 \pm 2.6$  mm,  $p<0.001$ ). Liver-specific recurrence-free survival at 4 years was 47% with NIRF imaging and 39% without (hazard ratio at multivariate analysis 0.73, 95%CI 0.42–1.28,  $p=0.28$ ). Overall survival at 4 years was 62% and 59%, respectively ( $p=0.79$ ). No liver recurrences occurred within 3 years follow-up in 52% of patients in whom additional metastases were resected based on only NIRF imaging.

better survival due to resection of additional lesions missed on preoperative imaging



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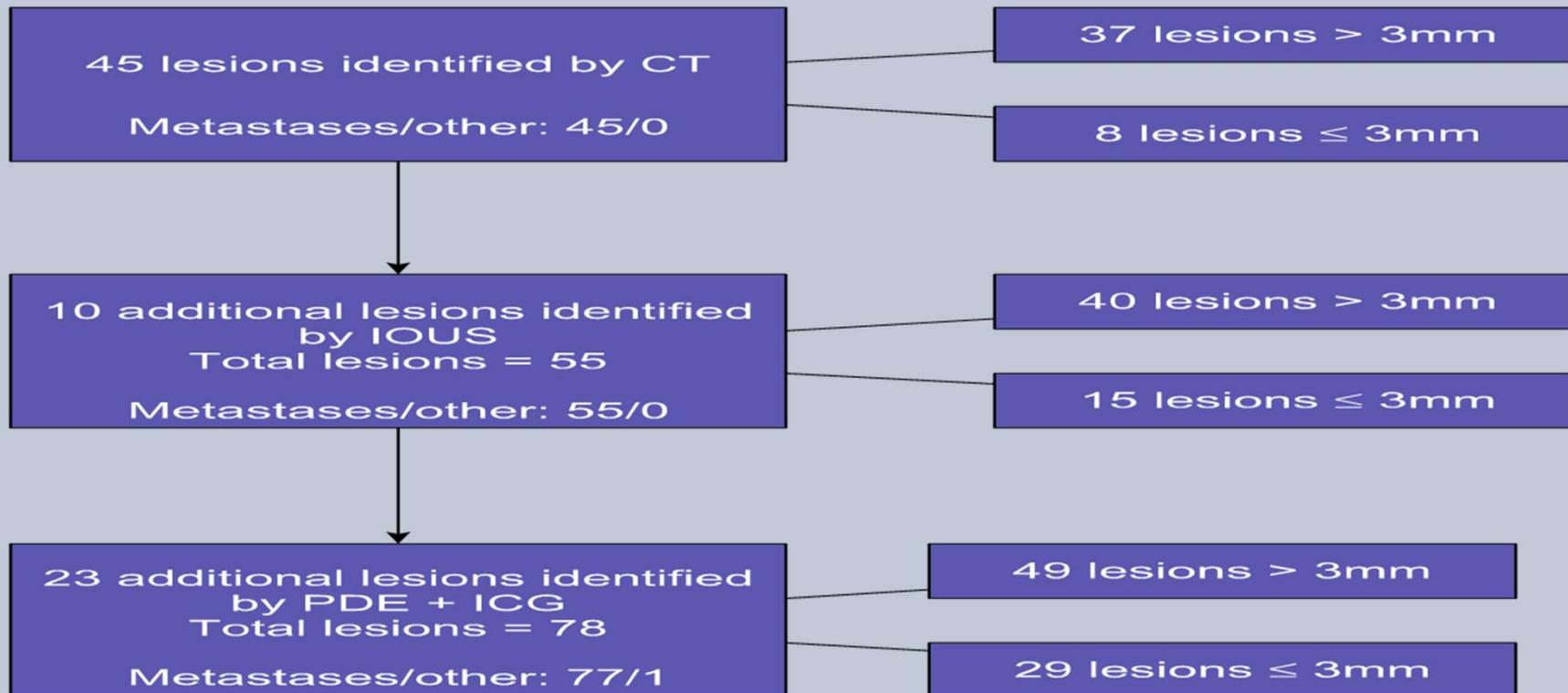




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## Combined use of intraoperative ultrasound and indocyanine green fluorescence imaging to detect liver metastases from colorectal cancer

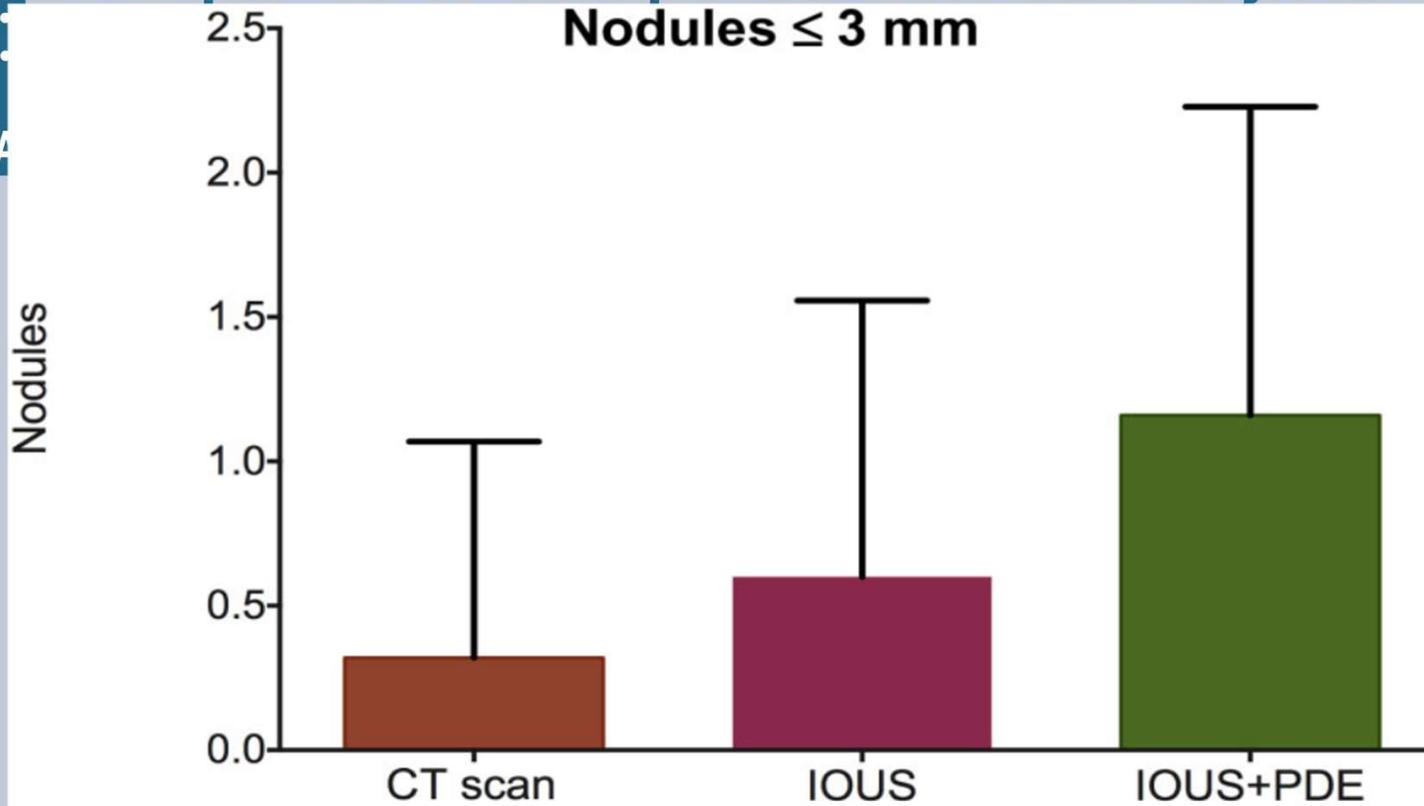
Andrea Peloso<sup>1</sup>, Eloisa Franchi<sup>1</sup>, Maria C. Canepa<sup>1</sup>, Letizia Barbieri<sup>1</sup>, Laura Briani<sup>1</sup>, Jacopo Ferrario<sup>1</sup>, Carolina Bianco<sup>1</sup>, Pietro Quaretti<sup>2</sup>, Silvia Brugnatelli<sup>3</sup>, Paolo Dionigi<sup>1</sup> & Marcello Maestri<sup>1</sup>





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## Nodules $\leq 3$ mm



Kruskal-Wallis test,  $P < 0.0001$

Dunn's multiple comparisons test	Mean rank diff.	Summary	Adjusted $P$ -value
CT scan versus IOUS	-11.88	NS	0.0708
CT scan versus IOUS+PDE	-24.48		$< 0.0001$
IOUS versus IOUS+PDE	-12.61		0.0328

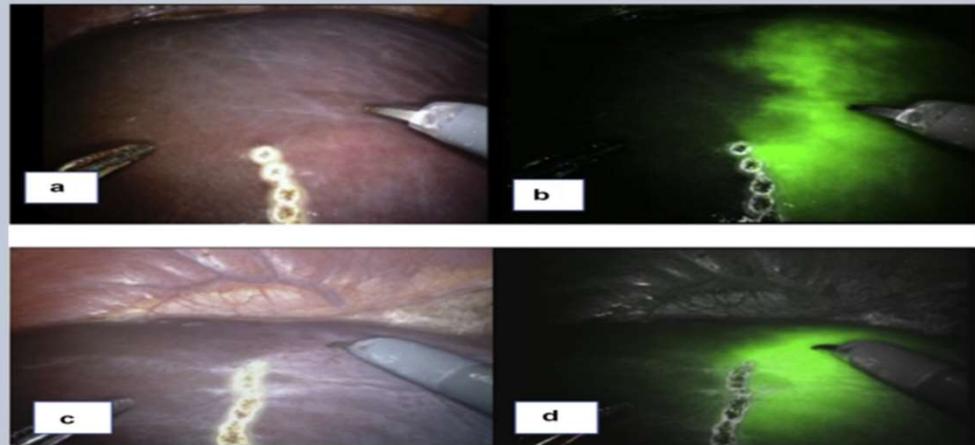


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### Robotic ICG guided anatomical liver resection in a multi-centre cohort: an evolution from “positive staining” into “negative staining” method

Adrian K H Chiow<sup>1,\*</sup>, Seoung Yoon Rho<sup>2,\*</sup>, Ian J.Y. Wee<sup>3</sup>, Lip Seng Lee<sup>1</sup> & Gi Hong Choi<sup>2</sup>

- ▶ by injecting ICG dye into the segmental portal branch<sup>6</sup> (positive staining) or by intravenously administering ICG dye after clamping the segmental portal pedicle (negative staining).
- ▶ Multicenter study evaluating added value of ICG in anatomical robotic resections
- ▶ Compared ICG demarkation line versus ischaemic demarkation line
- ▶ Compared positive and negative staining technique





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**Table 2** Intra-operative parameters

Intra-operative parameters and findings	Value
Negative staining technique (n/%)	40/52 (76.9)
Positive staining technique (n/%)	12/52 (23.1)
ICG dose (mg) <sup>a</sup>	5.0 (2.0–5.0)
Ability to show ICG demarcation line clearly (n/%)	43/52 (82.7)
Clear ICG demarcation line with positive staining (n/%)	6/12
Clear ICG demarcation line with negative staining (n/%)	37/40
ICG demarcation line as clear as ischaemic demarcation line (n)	14/43
ICG demarcation line clearer than ischaemic demarcation line at superior liver surface (n)	19/43
ICG demarcation line clearer than ischaemic demarcation line at the whole liver surface (n)	10/43
ICG demarcation line not well seen (n/%)	9/52 (13.5)
Operative time (min) <sup>a</sup>	472.0 (355.5–532.0)
Conversion (n/%)	0/52 (0.0)
Complication from ICG usage (n/%)	0/52 (0.0)

Continuous outcomes are reported as median (interquartile range); n, number of patients as a fraction.

<sup>a</sup> Reported as median (range).



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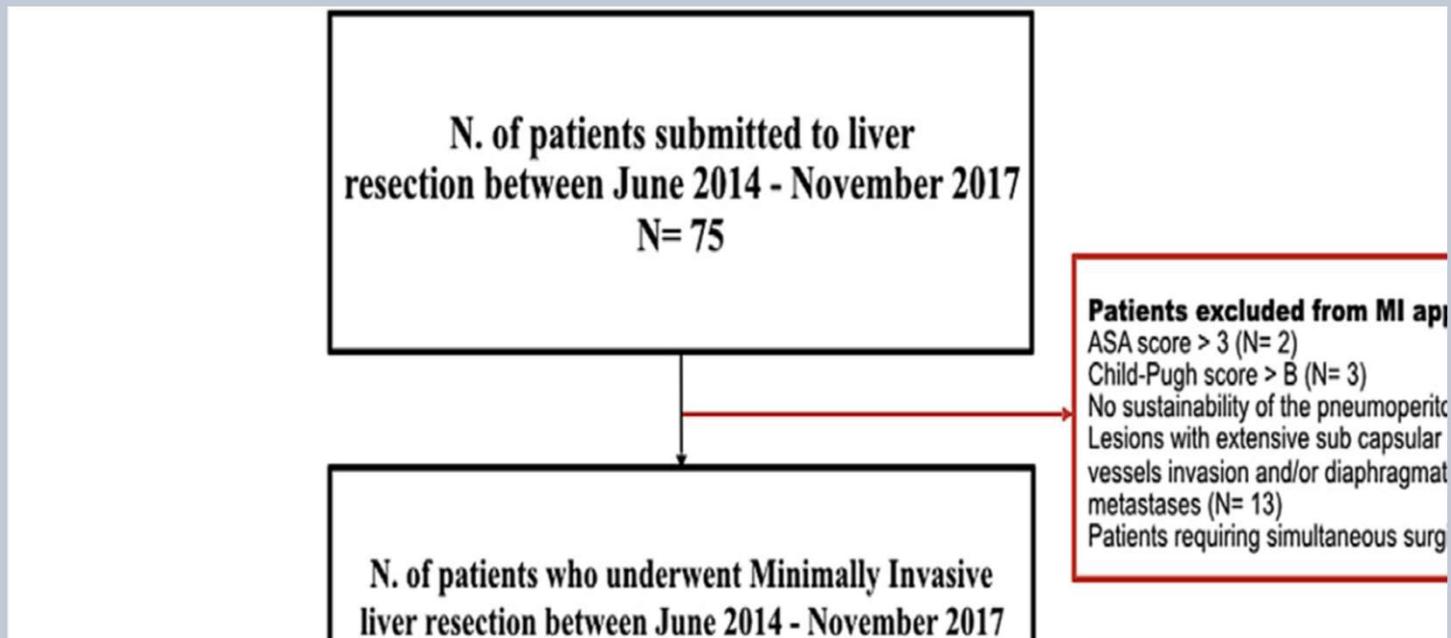
- ▶ ICG guided resection improves visualisation of the demarkation line
- ▶ Negative staining technique more easy



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## The application of indocyanine green-fluorescence imaging during robotic-assisted liver resection for malignant tumors: a single-arm feasibility cohort study

Marco Vito Marino<sup>1,2,\*</sup>, Mauro Podda<sup>3</sup>, Carmen C. Fernandez<sup>1</sup>, Marcos G. Ruiz<sup>1</sup> & Manuel G. Fleitas<sup>4</sup>



dv flow diagram



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Resection margin, mm	12 (5–22)
R1	0
R0	40
Pattern of recurrence, n (%)	8 (20%)
Intrahepatic recurrence	6
Extrahepatic recurrence	2
Mortality, n (%)	1 (2.5%)

PHLF: Posthepatectomy liver failure.



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**Table 4** Results of the staining methods applied

Staining Method	Positive	Negative
Number	20	20
Number of injections, n	26	20
Total amount of ICG injected, ml (range)	0.28 (0.25–2)	2.9 (2.2–6)
Time to territory visualization, sec (range)	90 (65–145)	375 (315–400)
Demarcation rate of liver segment boundaries, n (%)	16 (80%)	19 (95%)
Clarity and duration of image, ratio	59/80	65/80
Satisfaction and comfort of the surgeon, ratio	42/60	51/60



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# HCC: Fals positive

- ▶ Liver cirrhosis: dysplastic nodules vs HCC
- ▶ Ishizawa et al: 40 % fals positive
- ▶ ICG 6 days prior to surgery



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	HCC	CRC metastases	CCC
Dose	0.5 mg/kg KG	0.5 mg/kg KG	0.5 mg/kg KG
Timepoint of intravenous injection	2–14 days preoperative	2–14 days preoperative	2–14 days preoperative
Limitations	Depths of visualization, False-positive signals due to bad liver function, depending on studies 8–40% false-positive results	Depths of visualization, false-positive signals due to bad liver function, Limited assessability of bad-differentiated HCCs and metastases	Depths of visualization, false-positive signals due to bad liver function, indirect visualization by surrounding cholestasis
Detection rate	70–100%	69–100%	100% (less data)

**Tumor visualization and fluorescence angiography with indocyanine green (ICG) in laparoscopic and robotic hepatobiliary surgery – valuation of early adopters from Germany**



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## Conclusion

- ▶ Recognition of vascular and biliary anatomy :helps decrease intraoperative complications, especially in the presence of anatomical variations.
- ▶ 0.50 mg/kg IV
- ▶ 24-72 hours prior to surgery
- ▶ Additional small and subcapsular lesions detected
- ▶ Improves R0 ratio
- ▶ Cheap / no radiation/ not time consuming
  
- ▶ Should be part of robotic HPB surgeon's arsenal