REVIEW ARTICLE

Systematic review, meta-analysis and single-centre experience of the diagnostic accuracy of intraoperative near-infrared indocyanine green-fluorescence in detecting pancreatic tumours

Gianluca Rompianesi[1], Roberto Montalti[1], Mariano C. Giglio[1], Carlo D.L. Ceresa[2], Riccardo A. Nasto[1], Giuseppe De Simone[3] & Roberto I. Troisi[1]

[1]Division of Hepato-Bilio-Pancreatic, Minimally Invasive, Robotic and Transplant Surgery, Department of Clinical Medicine and Surgery, Federico II University Hospital, Naples, Italy, [2]Nuffield Department of Surgical Sciences, University of Oxford, UK, and [3]Division of Anaesthesia of Hepato-Bilio-Pancreatic and Liver Transplant Surgery, Department of General Surgery and Surgical Specialties, Kidney Transplantation, Intensive Care and Nephrology, Federico II University Hospital, Naples, Italy

Abstract

Background: During pancreatic resections assessing tumour boundaries and identifying the ideal resection margins can be challenging due to the associated pancreatic gland inflammation and texture. This is particularly true in the context of minimally invasive surgery, where there is a very limited or absent tactile feedback. Indocyanine green (ICG) fluorescence imaging can assist surgeons by simply providing valuable real-time intraoperative information at low cost with minimal side effects. This meta-analysis summarises the available evidence on the use of near-infrared fluorescence imaging with ICG for the intraoperative visualization of pancreatic tumours (PROSPERO ID: CRD42021247203).

Methods: MEDLINE, Embase, and Web Of Science electronic databases were searched to identify manuscripts where ICG was intravenously administered prior to or during pancreatic surgery and reporting the prevalence of pancreatic lesions visualised through fluorescence imaging.

Results: Six studies with 7 series' reporting data on 64 pancreatic lesions were included in the analysis. MINOR scores ranged from 6 to 10, with a median of 8. The most frequent indications were pancreatic adenocarcinoma and neuroendocrine tumours. In most cases (67.2%) ICG was administered during surgery. ICG fluorescence identified 48/64 lesions (75%) with 81.3% accuracy, 0.788 (95%CI 0.361–0.961) sensitivity, 1 (95%CI 0.072–1) specificity and positive predictive value of 0.982 (95%CI 0.532–1). In line with the literature, ICG fluorescence identified 5/6 (83.3%) of pancreatic lesions during robotic pancreatic resections performed at our Institution.

Conclusion: This meta-analysis is the first summarising the results of ICG immunofluorescence in detecting pancreatic tumours during surgery, showing good accuracy. Additional research is needed to define optimal ICG administration strategies and fluorescence intensity cut-offs.

Received 8 December 2021; accepted 9 May 2022

Correspondence

Gianluca Rompianesi, Division of Hepato-Bilio-Pancreatic, Minimally Invasive and Robotic Surgery, Department of Clinical Medicine and Surgery, Federico II University Hospital, Naples, Italy. E-mail: gianlucarompianesi@gmail.com

Introduction

Despite the refinement of surgical and diagnostic techniques and the development of new oncological adjuvant and neoadjuvant treatments, pancreatic tumours and in particular neuroendocrine (NET) and pancreatic ductal adenocarcinoma (PDAC) still represent a challenging entity, with no available screening protocols, rare early-stage diagnoses and frequent metastatic disease at presentation.[1,2] Moreover, prognosis of PDAC remains poor,

with an overall 5-year survival not exceeding 10%.[3,4] While gene mutations in the early stages of the onco-genetic process relating to tumour recurrence and patient survival are being investigated,[5] it is of paramount importance to minimize the already-known risk factors in order to reduce the recurrence rate and give patients the best chances of cure.

It is often challenging to assess the tumour limits and identify the ideal resection margin intra-operatively, due generalised inflammation of the pancreatic gland and a fibrotic texture that makes manual appreciation of the lesion difficult. Furthermore, the use of minimally invasive techniques provide a very limited or absent tactile feedback and a heterogenous appearance of the pancreas, even with the aid of an intraoperative ultrasound scan.[6] A thorough ultrasound examination of the pancreas requires an almost complete mobilisation of the gland and is particularly challenging and limited in the presence of adhesions due to previous surgery, inflammation, chronic pancreatitis or neoadjuvant chemotherapy. Although it does not provide useful information regarding the location of the tumour or the presence of additional nodules, an intraoperative histopathological examination of the resection margin free from malignancy may provide the surgeon some reassurance. However, its application is highly dependent on centre availability, the experience of the pathologist and may prolong the surgical time. Indocyanine green (ICG) fluorescence imaging has been increasingly adopted in various fields of surgery thanks to its low cost, simplicity and low side effect profile. It can provide the surgeon with invaluable intraoperative information such as enhanced visualization of anatomical structures and boundaries, a real-time evaluation of the organs' perfusion, the identification of tumours or the detection of non-visible metastases.[7–12]

This systematic review and meta-analysis is aimed at summarizing all the available evidence and published data on the use of near-infrared (NIR) fluorescence imaging with ICG for the intraoperative visualization of pancreatic tumours. Furthermore, we report our experience with intraoperative ICG administration in patients undergoing pancreatic surgery.

Methods

The present systematic review and meta-analysis has been conducted in accordance with the Preferred reporting items for systematic reviews and metanalyses (PRISMA)[13] and has been recorded on PROSPERO (ID: CRD42021247203).

Search strategy

MEDLINE, Embase, and Web Of Science electronic databases were searched using the following terms: "pancrea*" AND "indocyanine green*". The last search was run on June 30, 2021 with no language or publication status restriction. Additional potentially relevant studies were identified from the reference list of selected studies.

Study selection

To be included studies had to[1]: Include patients undergoing any pancreatic surgery for any disease,[2] Have ICG intravenously administered prior to or during surgery,[3] Report the prevalence of pancreatic lesions visualised through fluorescence imaging. Case reports, reviews, communications, as well as non-human studies, were excluded. Two reviewers (GR and RM) independently screened the results of the electronic search at the title and abstract levels. The full texts of the selected references were also retrieved for further analysis and data extraction. When duplicate reports from the same study were identified, only the most recent and complete publication was included.

Data extraction and quality assessment

Two reviewers (GR and RN) extracted data from each selected study regarding the first author, publication year, country of origin, study design, number of patients undergoing pancreatic resections (PR), patients characteristics (age, sex), underlying disease requiring PR, surgical technique (open, laparoscopic, robotic), timing and dose of intravenous ICG administration, visualisation of pancreatic nodules through ICG fluorescence, tumour-to-background fluorescence ratio, length of surgery, prevalence of R0 resections. The quality of each included study was evaluated independently by two reviewers (GR and RN) according to the methodological index for non-randomised studies (MINORS) criteria.[14] Any disagreement was resolved through discussion and reaching consensus of the study team.

Statistical analysis and data synthesis

The primary outcome was the prevalence of pancreatic lesions visualised with intraoperative ICG fluorescence imaging. Secondary outcomes were the sensitivity and specificity, positive predictive value (PPV) and negative predictive value (NPV) of intraoperative ICG fluorescence imaging in detecting pancreatic tumours.

Statistical analyses were performed using R, version 4.0.3 (2020, The R Foundation for Statistical Computing). The prevalence of each event has been calculated for every study included in the analysis and expressed as a percentage. The Freeman-Tukey double arcsine transformation of the prevalence was used in order to incorporate in the pooled analysis studies with the prevalence of 0%.[15] The presence of heterogeneity among the studies was assessed by the Cochran's Q test and quantified with the I^2 inconsistency index, with 25, 50 and 75th percentiles considered as thresholds for low, moderate and high statistical heterogeneity.[16,17]

Results

Six studies[18–23] met the inclusion criteria and were included in the systematic review and meta-analysis (Fig. 1). One study[19] presented data of two independent groups of patients receiving

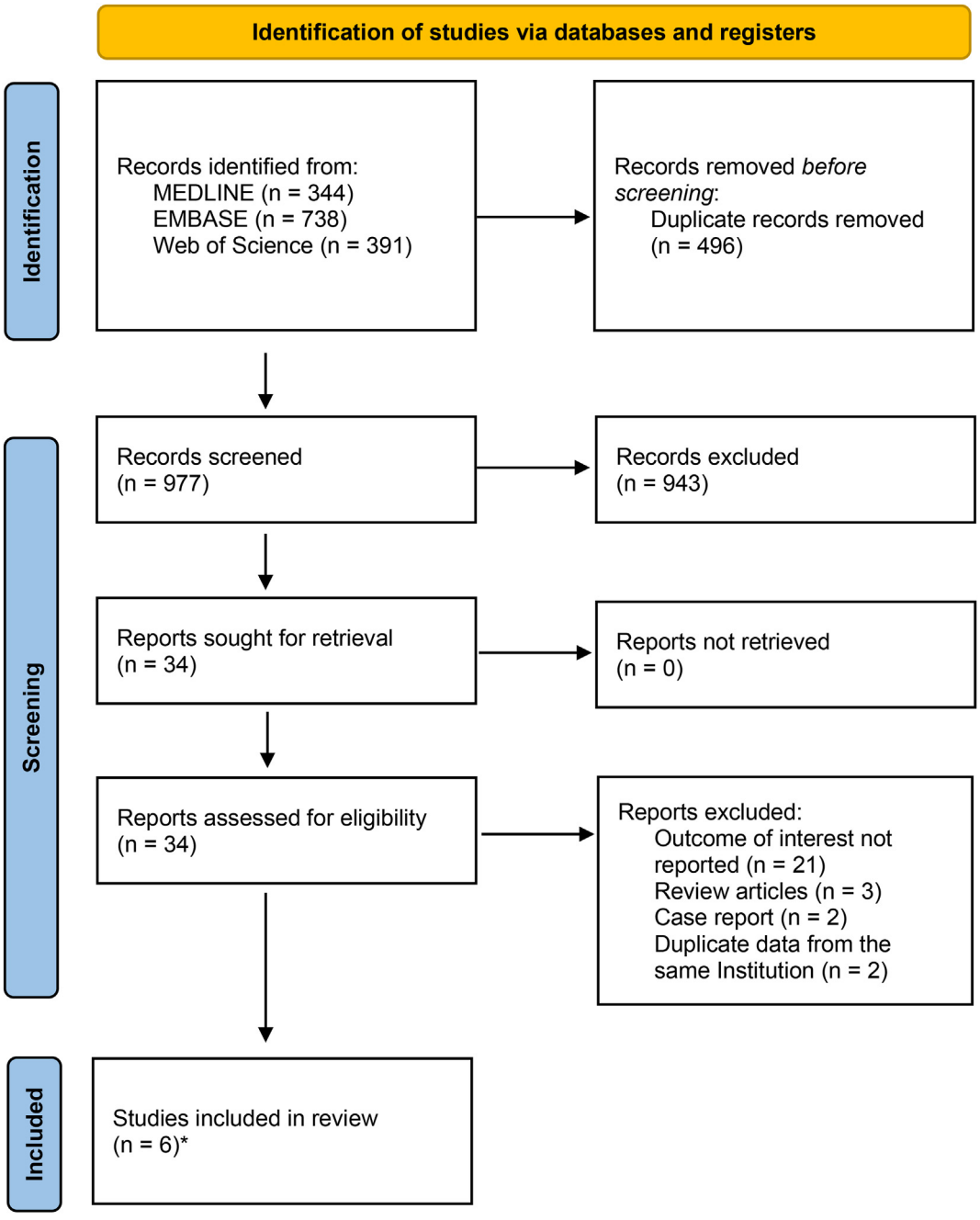

Figure 1 PRISMA flow diagram. *one study (Hutteman et al., 2011) presents data of two independent groups of patients receiving different indocyanine green doses that have been included and analysed separately

different indocyanine green doses that have therefore been included and analysed separately. The characteristics of the included studies are reported in Table 1. A total of 64 pancreatic lesions in 61 patients undergoing pancreatic surgery and ICG intravenous administration have been included in this analysis. All included series were retrospective cohort studies. The most frequent indications were NET and PDAC, both in 24 patients from 6[18–23] and 4 series[19,20,22] respectively, followed by intraductal papillary mucinous neoplasm (IPMN) in 7 patients from 2 series.[20,22] ICG fluorescence identified 48 out of the 64 pancreatic lesions (75%).

Quality assessment and publication bias

The results of the quality assessment of the 13 included studies according to MINORS criteria are summarised in Table 1. The scores ranged from 6 to 10, with a median of 8.

Table 1 Summary of the included studies with patients' characteristics and quality assessment (MINORS criteria)

Author and year	N	Age	Sex F, N (%)	Lesion size (mm)	Indication (PDAC-NET-other)	Technique (open-laparoscopic)	Tumour site (HOP-body/tail)	MINORS score
Alle et al., 2017	3				0-3-0	0–3		7
Francescato et al., 2020	2	47 ± 33.3	1 (50)	13.5 ± 0.7	0-2-0	0–2	0–2	10
Hutteman et al., 2011/1[a]	3	73 ± 14.7	11 (33.3)	43.5 ± 4.9	3-0-0	3–0	3–0	10
Hutteman et al., 2011/2[a]	3	79 ± 8.7	2 (66.6)	31.7 ± 24.5	2-1-0	3–0	3–0	10
Newton et al., 2019	21	65 ± 15.2	10 (47.6)		12-2-7	18–3	10–11	8
Paiella et al., 2017	10	49 ± 9.3	5 (50)	23 ± 9.5	0-10-0	0–10	0–10	8
Shirata et al., 2018	22	58 ± 17.2	9 (40.9)	27.8 ± 13.4	7-6-9	19–3	12–10	6

N, number of pancreatic lesions; F, female; PDAC, pancreatic ductal adenocarcinoma; NET, neuroendocrine tumour; HOP, head of pancreas.
[a] Included as two separate populations as reported in the original manuscript.

PPV, NPV, sensitivity and specificity of ICG in detecting pancreatic lesions

Forty-eight out of 64 pancreatic lesions were visualised intraoperatively through ICG fluorescence, with a PPV of 0.982 (95% CI 0.532–1) and a NPV of 0.2 (95%CI 0.077–428). ICG fluorescence sensitivity in detecting pancreatic lesions was 0.788 (95%CI 0.361–0.961), and the specificity was 1 (95%CI 0.072–1), as reported in Fig. 2.

NPV, sensitivity and specificity of ICG in detecting PDAC

Sixteen out of 24 PDAC were visualised intraoperatively through ICG fluorescence, with a NPV of 0.333 (95%CI 0.131–0.624). ICG fluorescence sensitivity in detecting pancreatic lesions was 0.562 (95%CI 0.159–0.897), and the specificity was 1 (95%CI 1-1), as reported in Fig. 3.

PPV and sensitivity of ICG in detecting pancreatic NETs

Twenty-one out of 24 NETs were visualised intraoperatively through ICG fluorescence, with a PPV of 0.913 (95%CI 0.711–0.978). ICG fluorescence's sensitivity in detecting pancreatic NETs was 1.000 (95%CI 0.930–1), without a calculable specificity, as reported in Fig. 3.

ICG administration and operative details

Six authors[18,19,21–23] reported the ICG to have been administered intravenously to the patients during the surgical procedure and in only 21 patients (32.8%) from 1 series(20) was given 1 day prior to the pancreatic resection. The included studies reported highly variable ICG doses, ranging from 2.5 mg in a single administration[22], to 5 mg/kg(20) or 5 boluses of 5 mg each[21,23].

In 43 patients (67.2%) from 5 series[19,20,22,23], the surgical procedure was performed via open surgery, and in 21 patients (32.8%) from 5 series[18,20–23] it was performed laparoscopically. Patients' median body mass index (BMI) was 26.26 (range 22.8–27) as reported in 4 series[19,21,22]. The most frequently performed surgery was distal pancreatectomy in 32 patients (50%) from 4 series(20–23), followed by pancreaticoduodenectomy in 27 patients (42.2%) from 4 series(19, 20, 22). The median tumour-to-background fluorescence ratio, as described in 5 series[19–22], was 1.22 (range 0.89–7.7), with only Paiella[21] reporting the latency time of 79 ± 18 s and a visibility time of 221 ± 18 s. No patient was reported to experience any ICG administration-related adverse event[20,21,23]. Out of the 64 pancreatic tumours, 8 (12.5%) presented positive margins (R1) at the histopathological examination, and 4 of them were reported to show intraoperative visible ICG fluorescence on the surgical margin.

Our experience with ICG fluorescence in pancreatic surgery

From March to October 2021, 6 patients underwent pancreatic resection with the aid of ICG fluorescence to assist the intraoperative identification of pancreatic lesions. All cases were performed robotically with the utilisation of the Firefly™ fluorescence imaging for the DaVinci Xi™ system, and all patients received 5 mg of ICG intravenously during the procedure. Patients and tumours characteristics are reported in Table 2. ICG fluorescence facilitated the intraoperative identification of the pancreatic lesion in 5 out of 6 cases (83.3%) and the surgical specimens were also re-evaluated with the Firefly™ fluorescence imaging ex situ after the specimen extraction (Fig. 4). In all cases a R0 resection was achieved.

Discussion

This systematic review summarises all the current evidence on the role of ICG immunofluorescence in detecting pancreatic tumours during surgery.

The precise identification of all possible malignant lesions and their extension and limits represents one of the key steps of successful pancreatic surgery. Various adjuncts to the surgeon's visual and tactile assessment have been developed to improve the intraoperative accuracy in detecting and defining tumours and their role has become essential, especially when these senses are

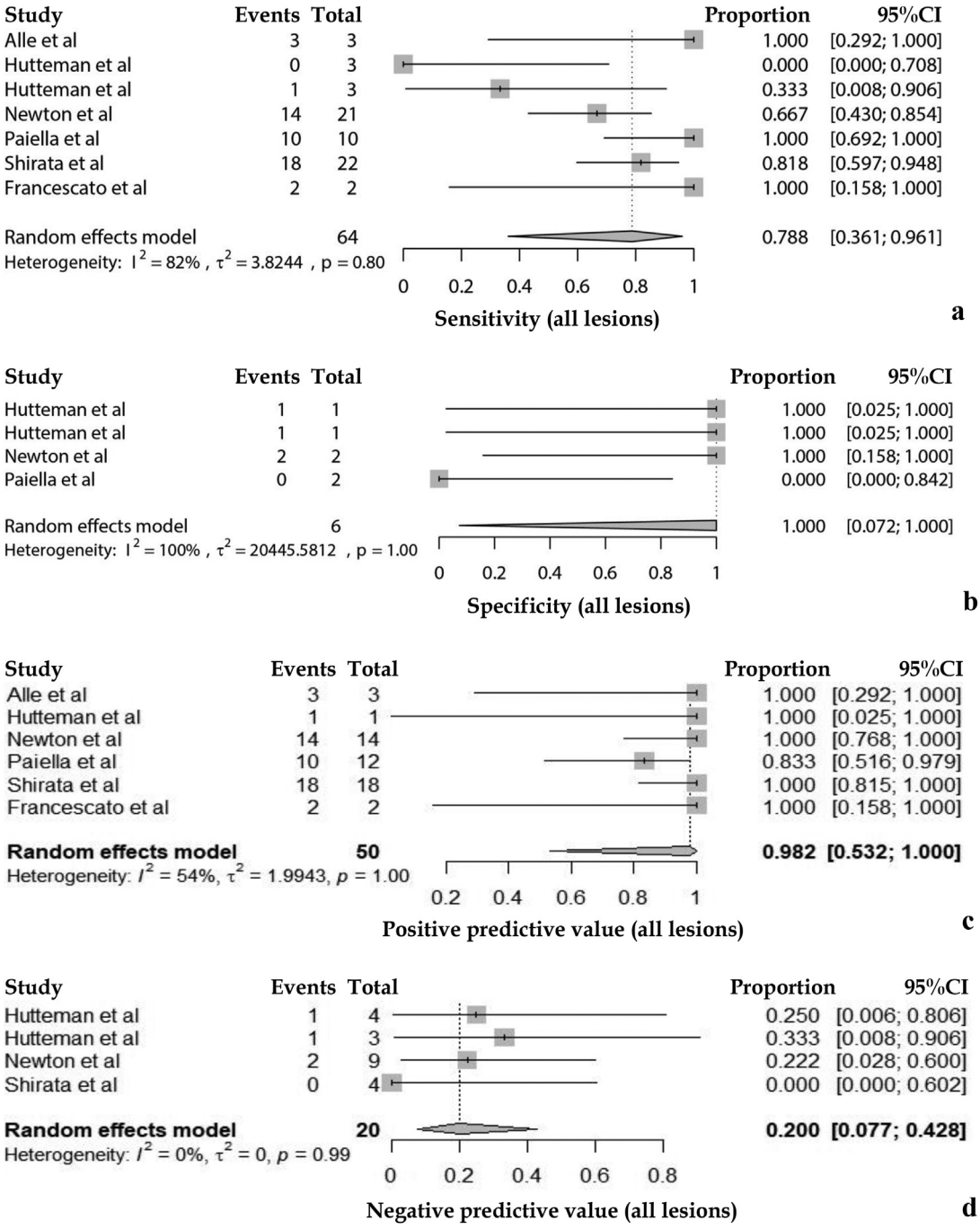

Figure 2 Sensitivity (a), specificity (b), positive (c) and negative (d) predictive values of indocyanine green fluorescence in detecting pancreatic lesions

limited or absent, such as in case of surgery performed via laparoscopic or robotic techniques[24–26].

ICG is a cyanide dye which has been widely used for decades in various medical fields, including surgery, and has an absorption and fluorescence spectrum in the NIR region. It binds with plasma proteins and therefore remains confined to the intravascular system[27,28] before being cleared from the plasma by the hepatocytes and exclusively secreted into the bile after a half-life of 2.5–3 min[29]. As it operates in the tissue optical window, its fluorescence can be detected with a NIR camera and thanks to its low toxicity and rapid excretion it can be safely administered repeatedly at reduced costs[30]. Multiple applications of ICG fluorescence in hepato-bilio-pancreatic surgery have been described including the visualisation of structures such as blood

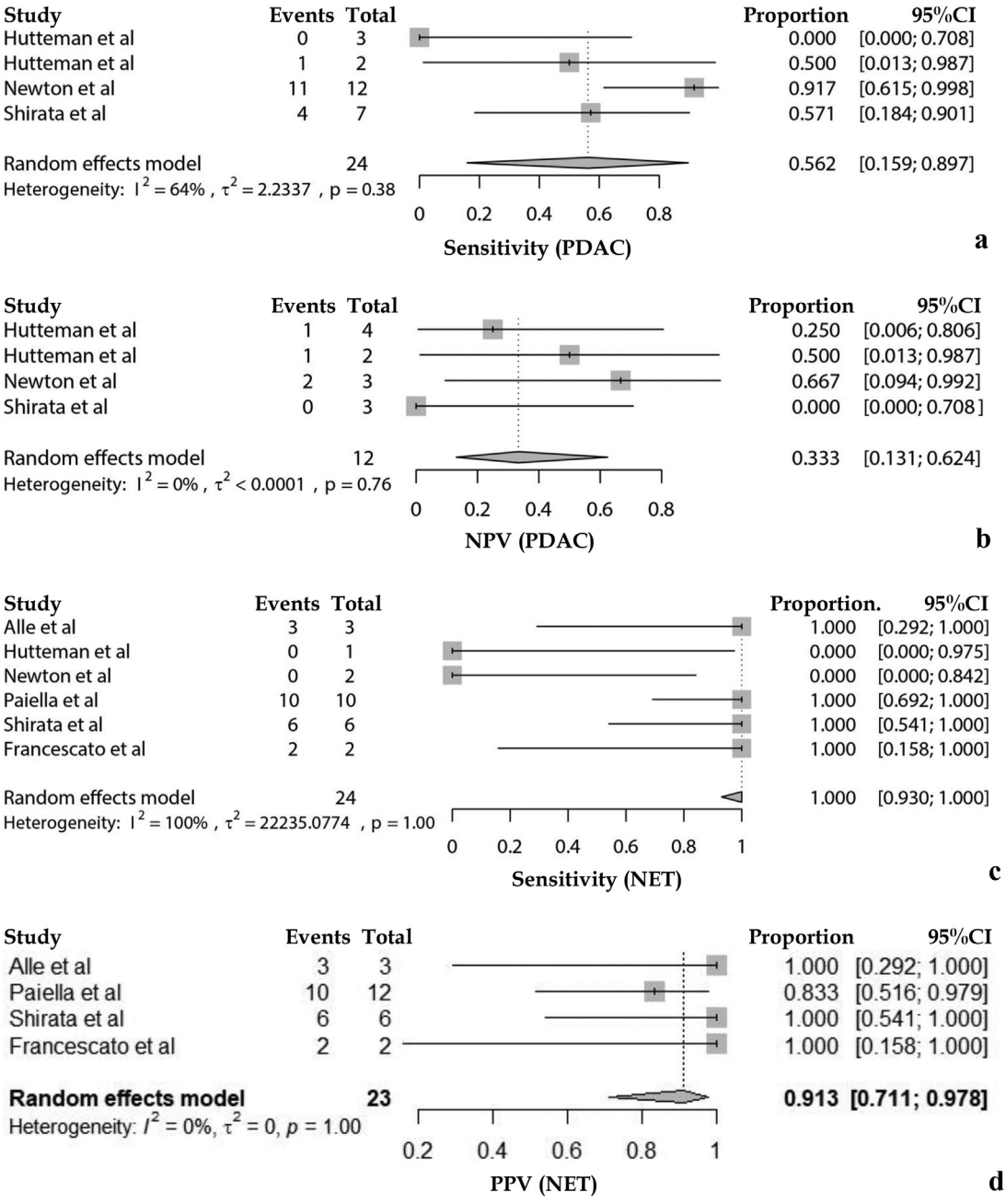

Figure 3 Sensitivity and negative predictive value (NPV) in detecting pancreatic adenocarcinoma (PDAC; figures a and b) and sensitivity and positive predictive value (PPV) in detecting neuroendocrine tumours (NET; c, d) of indocyanine green fluorescence

vessels, bile ducts the anatomical limits of liver segments, the evaluation of organs' perfusion and the identification of tumours, lymph nodes and metastatic deposits[31]. Currently, the evidence from studies analysing the role of ICG fluorescence in the identification of pancreatic tumours is limited to case series or relatively small, single-centre cohort studies. Our systematic review and meta-analysis has shown how intraoperative ICG fluorescence can guide surgeons in identifying pancreatic lesions with a high accuracy of 81.3% (0.788 sensitivity and 1 specificity, Fig. 2. These results are affected by limited data on observed true and false negatives, and the possible different ICG fluorescence detection ability depending on the depth of the nodule location in the pancreatic parenchyma. Furthermore, it is not known whether neoadjuvant chemotherapy could affect ICG clearance or tissue absorption.

PDAC and NET comprised the two most frequent indications in the included series, contributing for 48 out of the 64 total pancreatic lesions (75%). ICG fluorescence remains

Table 2 Characteristics of patients undergoing surgery for pancreatic lesions where ICG fluorescence has been utilised at our Institution

PATIENT	AGE (years)	SEX	INDICATION	LESION DIAMETER (mm)	SURGERY	TECHNIQUE	Dose (mg)	ICG Visualisation	Staining
#1	46	M	pNET	26	Distal pancreatectomy and splenectomy	Robotic	5	Yes	Positive
#2	35	F	PPT	69	Spleen Preserving Distal pancreatectomy	Robotic	5	Yes	Negative
#3	53	M	SCA	80	Spleen Preserving Distal pancreatectomy	Robotic	5	Yes	Negative
#4	82	M	IPMN	37	Spleen Preserving Distal pancreatectomy	Robotic	5	Yes	Positive
#5	74	F	PDAC	25	Anterior RAMPS	Robotic	5	No	
#6	47	F	IPMN	34	Pancreaticoduodenectomy	Robotic	5	Yes	Positive

ICG, indocyanine green; pNET, pancreatic neuroendocrine tumour; PPT, pseudopapillary tumour; SCA, serous cystadenoma; IPMN, intraductal papillary mucinous neoplasm; PDAC, pancreatic adenocarcinoma.

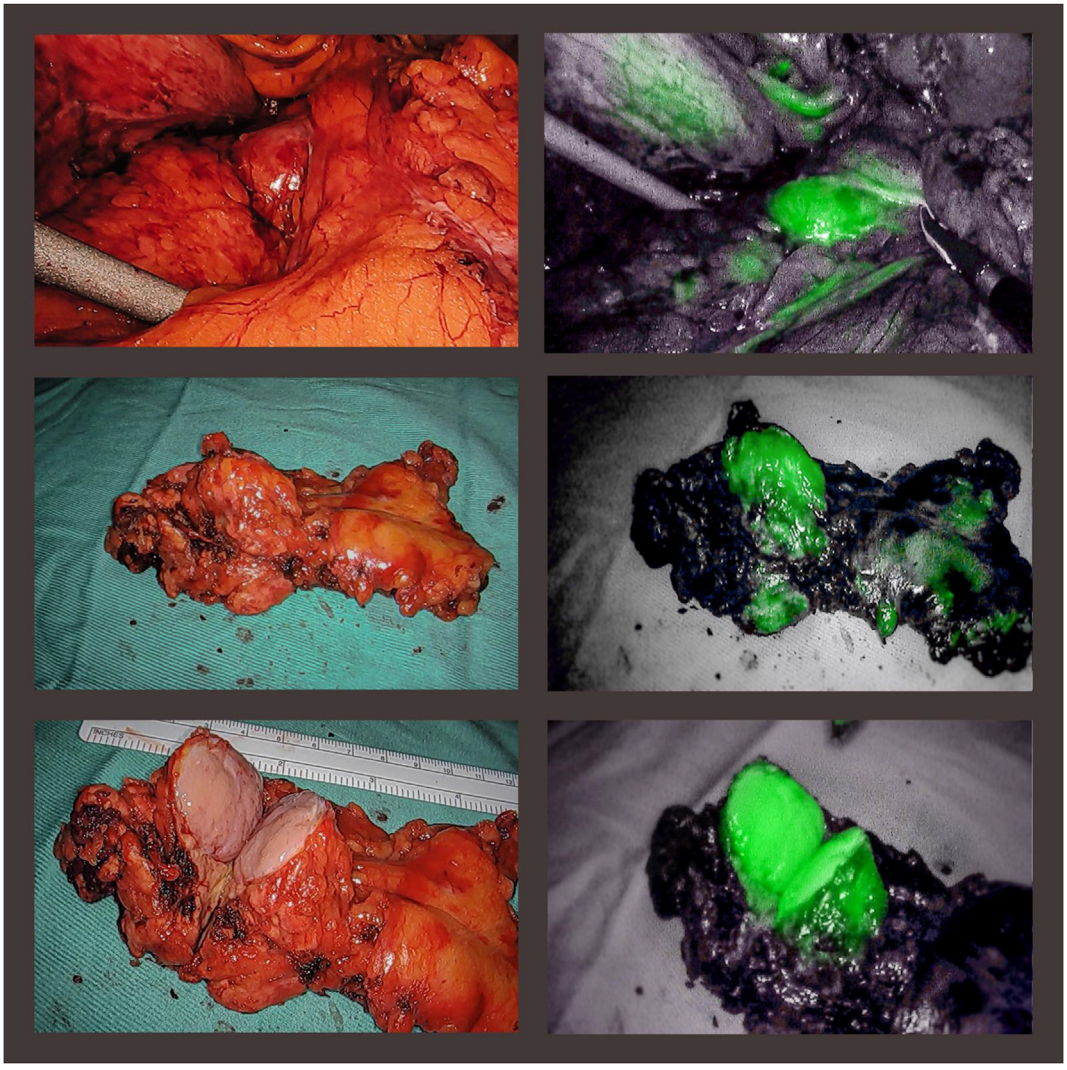

Figure 4 Indocyanine green fluorescence of a pancreatic neuroendocrine tumour (Case #1). A1-2: intraoperative visualisation (without and with Firefly™ imaging for the DaVinci Xi™ system), B1-2: ex situ visualisation after specimen extraction, C1-2: sectioned tumour inspected without and with ICG fluorescence

advantageous as it is easily performed, reproducible, has limited costs and minimal side-effects. In addition to potentially detecting pancreatic lesions, ICG evaluation of the pancreatic cut surface has shown the ability of predicting the margin status on the pathological examination with 83.3% PPV and 100% NPV(20). In the meta-analysis and our own small series, a high R0 resection rate has been observed; 87.5% and 100%, respectively. As there is some evidence to suggest that an R1 resection is linked to an earlier recurrence and an inferior 5-year survival when compared to an R0 resection,[32–35] this might be an interesting avenue to explore further when considering the potential benefits of ICG. It is also important to consider not only resection margins, but also any impact on recurrence-free and overall survival which are arguably more relevant outcomes. This could be tested in a randomised setting with a standardised pathology reporting protocol. Nevertheless, a reliable real-time evaluation of surgical margins would have the advantage of reducing the risk of residual disease and reduce operative timings when compared to an extension of the resection performed only after the intraoperative frozen section result is available. It can also provide invaluable information about biliary and vascular anatomy, especially in complex cases or in patients with anatomical variations[36,37]. Another possible future fascinating application of ICG has been evaluated by Aung et al.[38] In their pancreatic cancer model, they observed evidence of necrotic cell death-associated features following the near-infrared photoimmunotherapeutic effect mediated by an anti-tissue factor antibody conjugated to indocyanine green. Finally, the use of intra-operative ICG could also provide an effective assessment of the resection margin perfusion, avoiding ischaemia and the consequent necrosis and increased risk of pancreatitis and fistula formation.

In our unit, ICG fluorescence is routinely utilised in open, laparoscopic and robotic hepato-bilio-pancreatic surgery for the identification of vascular and biliary structures, the evaluation of liver vascular anatomical limits, the assessment of the perfusion of the transection margins, the presence of residual disease, and the identification of liver and pancreatic tumours. In line with the results of this meta-analysis, our case series confirms that the majority of pancreatic lesions can be positively or negatively visualised through intraoperative ICG fluorescence, providing valuable assistance to the surgeon especially when an accurate and reliable ultrasound examination of the pancreas is difficult to achieve, and the tactile feedback is lacking. Our hypothesis is that PDAC can be identified less frequently by ICG fluorescence both because of a deep location within the pancreatic parenchyma, and because the tumour is characterised by the presence of dense fibrotic stroma or desmoplasia, that can possibly limit ICG absorption[39]. This could be particularly evident in patients that received neoadjuvant chemotherapy, which is often associated with encapsulating fibrosis[40], like in the case of the PDAC patient reported in our series.

The results of this meta-analysis are limited by the sample size, the lack of randomised controlled trials, and the paucity of consistent information about the quantification of the tumour glow or the tumour-to-background ratio. We also observed a high heterogeneity among the included studies, also regarding dose and timing of ICG administration, that could have had an impact on the detection. Intraoperative ICG fluorescence pancreatic evaluation represents a useful adjunct that provides valuable pieces of information to assist surgeons in defining the optimal resection site, but additional research is needed to define best ICG administration strategies and fluorescence intensity cut-offs. This meta-analysis is aimed at setting the ground for further studies that should evaluate the role of ICG fluorescence in detecting pancreatic lesions in prospective, controlled, and rigorous settings.

Conflicts of interest

None to declare.

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