Indocyanine Green Fluorescence-Guided Intraoperative Detection of Peritoneal Carcinomatosis: Systematic Review.

Gian Luca Baiocchi (gianluca.baiocchi@unibs.it)
https://orcid.org/0000-0003-2402-2178

Federico Gheza
Brescia University

Sarah Molfino
Azienda Socio Sanitaria Territoriale degli Spedali Civili di Brescia

Luca Arru
Centre Hospitalier de Luxembourg

Marco Vaira
Istituto per la Ricerca e la Cura del Cancro di Candiolo

Simone Giacopuzzi
Universita degli Studi di Verona

Research article

Keywords: indocyanine green, fluorescence, peritoneal carcinomatosis, colorectal cancer, ovarian cancer, gastric cancer

Posted Date: May 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-26024/v1

Version of Record: A version of this preprint was published on July 17th, 2020. See the published version at https://doi.org/10.1186/s12893-020-00821-9.

Abstract

BACKGROUND. To review the available clinical data about the value of Indocyanine Green (ICG) fluorescence imaging for intraoperative detection of peritoneal carcinomatosis.

METHODS. We conducted a systematic review, according to the PRISMA guidelines, for clinical series investigating the possible role of ICG fluorescence imaging in detecting peritoneal carcinomatosis during surgical treatment of abdominal malignancies. Key words for search were "*indocyanine green", "carcinomatosis", "peritoneum", "fluorescence"*. Papers including trials with fluorophores other than ICG were excluded. Papers including in vitro and experimental animals series were also excluded. We extracted data on patients and cancer features, timing, dose and modality of ICG administration, sensitivity, specificity and accuracy of fluorescence diagnosis of peritoneal nodules.

RESULTS. Out of 192 screened papers, we finally retrieved 7 series reporting ICG-guided detection of peritoneal carcinomatosis. Two papers reported the same cases, thus only 6 series were analyzed, for a total of 71 patients. The investigated tumors were colorectal carcinomas in 28 cases, hepatocellular carcinoma in 16 cases, ovarian cancer in 26 cases and endometrial cancer in 1 case. In all but 4 cases, the clinical setting was an elective intervention in patients known as having peritoneal carcinomatosis. No series reported a laparoscopic procedure. Technical data of ICG management were consistent across the studies. Overall, 353 lesions were singularly analyzed and evaluated. Sensitivity varied from 72.4–100%, specificity from 54.2–100%. Two series reported that planned intervention changed in 25% and 29% of patients, respectively.

CONCLUSION. Indocyanine Green based fluorescence of peritoneal carcinomatosis is a promising intraoperative tool for detection and characterization of peritoneal nodules in patients with colorectal, hepatocellular, ovarian carcinomas. Further prospective studies are needed, including stanging laparoscopy for pancreato-biliary, gastric cancer and other abdominal malignancies with frequent spread to peritoneum.

Background

Peritoneal carcinomatosis represents a challenging systemic localization of abdominal tumors. In the clinical management of patients suffering from abdominal cancer, detecting the presence of tumor cells on the peritoneum at an early stage could improve oncological results [1]. On the one hand, a better staging would allow to personalize the therapeutic path. On the other hand, the results of cytoreductive surgery, possibly associated with hyper-thermic intraperitoneal chemotherapy (HIPEC), are directly dependent on the completeness of the cytoreduction, and this in turn is directly dependent on the size of the nodules. Thus, detecting a few millimeters peritoneal tumors would make it possible to treat more effectively a significant proportion of patients.

Available preoperative staging systems have low sensitivity in detecting peritoneal carcinomatosis smaller than 5 mm [2, 3]; furthermore, even the visual inspection during staging laparoscopy or

laparotomy may not be entirely sensitive. Often, a negative visual inspection is followed by the appearance of peritoneal localization disease at a short distance of time, demonstrating the substantial inadequacy of simple visualization with the human eye in the early phases of peritoneal implant.

Among the instruments recently proposed to improve the accuracy of peritoneum inspection, the fluorescence generated by indocyanine green (ICG) has been poorly evaluated [4]. Some studies have explored the technical feasibility of highlighting tumor cells on the peritoneum by making them fluorescent, either by simple intravenous injection of the tracer, or trying to bind it to molecules capable of identifying tumor cells in animal models. This systematic review analyzes clinical trials limited to patients studied for peritoneal carcinosis with intravenous indocyanine green injection.

Methods

We conducted a systematic review according to the guidelines set out in the Preferred Reporting in Systematic Review & Meta-Analysis (PRISMA) [5] and Assessing the methodological quality of systematic reviews (AMSTAR)) checklist. The following review methods were stated before starting search: Embase, MEDLINE (PubMed), Cochrane library, Google Scholar Medline and Web of Knowledge databases would be searched for, using free text and MeSH terms for clinical series investigating the role of ICG fluorescence imaging in detecting peritoneal carcinomatosis during surgical treatment of abdominal malignancies. The website www.clinicaltrials.gov was also visited.

Search was performed in April 2020 by 1 Author (LB); papers published in the period 2000–2020 were considered. No language limitations were provided. Key words for search were "*indocyanine green", "carcinomatosis", "peritoneum", "fluorescence"*. Papers providing the utilization of fluorophores other than ICG were excluded. Papers including in vitro and animals experiments were excluded. Case report with < 2 cases were also excluded. Three reviewers (SM, FG and LA) independently revised the literature search, evaluated relevant articles in full text, further searched for other articles included in the references, and achieved consensus on duplicate; they extracted the following data from studies: patients and cancer features, timing, dose and modality of ICG administration, sensitivity, specificity and accuracy of fluorescence diagnosis of peritoneal nodules were extraxted. We analyzed the data and reported the results in tables and text.

Due to the limited number of retrieved papers, and the absence of prospective randomized or retrospective controlled trial, a robust technique for assessing the risk of bias was not implemented. However, the likely impact of selection bias on the results is analyzed and discussed.

This study received no funding.

Results

The process of study selection is reported in Fig. 1. Out of 183 screened papers, we finally retrieved 9 series reporting ICG-guided detection of peritoneal carcinomatosis. All the series were published in the

period 2015–2018. A case report including 1 only patient with peritoneal recurrence of ruptured HCC was analyzed and excluded, according to selection criteria [6]. One series was further not analyzed because the primary outcome was liver metastases detection [7]. Two papers reported the same series [8, 9] (Clinical Trial Number 01982227), thus only 6 series were analyzed [9–14].

Overall, 71 patients were included (Table 1). The primary tumor was colorectal carcinomas in 28 cases, hepatocellular carcinoma in 16 cases, ovarian cancer in 26 cases and endometrial cancer in 1 case. In all but 4 cases, the clinical setting was an elective intervention in patients known as having peritoneal carcinomatosis, and undergoing cytoreductive surgery, eventually associated with HIPEC. Only in 4 cases (3 ovarian cancer, 1 endometrium cancer) the peritoneal carcinomatosis was unknown before the intervention. No series reported a laparoscopic procedure.

Table 1
Analyzed series of peritoneal carcinomatosis assessment by ICG fluorescence

Author	Year	Pts number	Tumor	Setting	Surgical approach
Barabino	*2016*	*10*	*CRC*	*Known PC, undergoing CRS + HIPEC*	*Open*
Liberale	*2016*	*14*	*CRC*	*Known PC, undergoing CRS + HIPEC*	*Open*
Lieto	*2018*	*4*	*CRC*	*Known PC, undergoing CRS + HIPEC*	*Open*
Satou	*2012*	*16*	*HCC*	*Known extrahepatic HCC recurrence*	*Open*
Tummers	*2015*	*7*	*Ovarian (6)* *endometrium (1)*	*4 Staging, 3 Radical surgery, unknown PC*	*Open*
Veys	*2018*	*20*	*Ovarian*	*Known PC, undergoing surgery*	*Open*

CRC, colorectal cancer; HCC, hepatocellular carcinoma; HIPEC, Hyperthermic Intra PEritoneal Chemotherapy

Technical data of ICG management are reported in Table 2. The injection time varied from 24 h before surgery to intra-operative injection. Dosing was consistently 0.25 mg/kg in 5 series; in the remaining 2 series, 0.5 mg/kg and 20 mg were given, respectively. Some 4 different camera systems were utilized in these series, all with hand-easy to use camera allowing exploration of peritoneum without the need for handling the laparoscopic instruments during open intervention.

Table 2
Timing, dosing, route of administration and technological supplies for peritoneal carcinomatosis assessment by ICG fluorescence

Author	Time (h before incision)	Dose	Route for ICG administration	Camera system
Barabino	*24 h*	*0,25 mg/kg*	*Intravenous*	*Fluostick (Fluopics, Grenoble, France)*
Liberale	*0 h (assessment after 5'-40')*	*0,25 mg/kg*	*Intravenous*	*Photodynamic Eye, PDE (Hamamatsu Photonics, Japan)*
Lieto	*0 h (assessment after 20' (10'-30')*	*0,25 mg/kg*	*Intravenous*	*Fluobeam (Fluoptics Imaging Inc, Cambridge, MA, USA),*
Satou	*1–5 d (1 pts 24 d)*	*0, 5 mg/kg*	*Intravenous*	*PDE (Hamamatsu Photonics, Hamamatsu, Japan)*
Tummers	*0 h (assessment after median 37', max 141')*	*20 mg*	*Intravenous*	*Mini-Fluorescence-Assisted Resection and Exploration (Mini-FLARE)*
Veys	*0 h (assessment after 5'-360', mean 60')*	*0, 25 mg/kg*	*Intravenous*	*Photodynamic Eye, PDE (Hamamatsu Photonics, Japan)*

Table 3 reports the clinical results. Overall, 353 lesions were singularly analyzed and evaluated as being ICG + or ICG-, and malignant or benign. Sensitivity varied from 72.4–100%, specificity from 54.2–100%. Two series reported having changed the planned intervention in 25% and 29% of patients, respectively. Two series anlyzed subgroup of patients, with particular reference to mucinous colorectal cancers [10] and to ovarian cancers having been trated with neoadiuvant chemotherapy with good clinical response (the so-called "peritoneal scars") [14]. Both subgroups showed a reduced positive predictive value. In 3 series a quantitative assessment of ICG fluorescence was performed [10, 13, 14], by calculation of the tumor-to-background ratio (TBR). In the remaining serires, only the absolute visual evaluation (ICG + versus ICG -) was provided. The TBR values for peritoneal caricinomatosis nodules were comprised between 1.8 and 2.0.

Table 3
Peritonel carcinomatosis assessment by ICG fluorescence. Results reported by analyzed series.

Author	Lesions analyzed	Sensitivity	Speificity	TBR	Notes
Barabino	*88*	*72.4%*	*60.0%*	*NP*	
Liberale	*63*	*87.5% non mucinou*	*100% non mucinous*	*1.92 (SD 0.67) for nonmucinous* *0.98 (SD 0.21) for mucinous*	*29% changes in planned operation*
Lieto	*69*	*96.9%*	*75%*	*NP*	*Accuracy 95.6%* *25% changes in planned operation*
Satou	*10*	*100%*	*100%*	*NP*	
Tummers	*21 in 2 pts*	*100%*	*NC*	*2.0*	*FP 62%*
Veys	*102*	*72.6%*	*54.2%*	*1.8 (SD 1.3), in scars 2.06 (SD 1.16)*	*PPV 76.8%, in scars 57.1%*
NP, not provided					

Discussion

Many solid abdominal malignancies may cause peritoneal carcinomatosis. Tumor diffusion to the peritoneum represents a systemic cancer extension which, similar to the presence of hematogenous metastases, marks the substantial impossibility of definitively healing the patient. However, it is still possible to cure a selected subgroup of these patients, with results dependent either on biological aspects (for example, peritoneal seeding from ovarian is less aggressive than seeding from pancreatic and stomach tumors), either on stage in which the diagnosis is made [15]. It is therefore very important to detect peritoneal carcinosis at an early stage, allowing to establish the prognosis with greater precision, giving to the patient the correct pathway of care. From the therapeutic point of view, the only possibilities of peritoneal carcinomatosis treatment are linked to a complete surgical reduction, eventually associated with intraperitoneal chemotherapy. Complete cytoreduction is possible only in the presence of small nodules [16]. Unfortunately, the radiological instruments commonly used in the staging of abdominal tumors (CT, MRI, Pet, US) have a poor sensitivity for small peritoneal nodules [2, 3]. The best diagnostic tool is surgical exploration, most frequently by laparoscopic approach, associated with cytological examination on spontaneously present fluid or on peritoneal washing. However, even this technique has a limited sensitivity for peritoneal implants few millimeters-sized.

ICG, approved for clinical use by the Food and Drug Administration (FDA) since 1959, is the most commonly utilized fluorescent probe. It is a low-cost molecule, easy to use, widely available and with

negligible toxicity [17]. The use of ICG fluorescence in abdominal surgery has been introduced in recent years and represents a common tool for perfusion evaluation, extrahepatic bile duct anatomy, lymph node navigation and liver surgery [18–20]. ICG binds primarily to serum albumin and other serum globulins such as alpha1-lipoprotein, and then it circulates behaving like a macromolecule [21]. In tumor tissues, such as peritoneal cancer implants, an “enhanced permeability and retention” (EPR) effect has been demonstrated, owing to tumor-induced angiogenesis, different metabolic activity and lack of efficient lymphatic drainage [22, 23]. ICG has theorical advantages as a possible contrast agent for macro- and microcirculatory tissue characterization, and consequently for EPR effect: it is uninfluenced by tissue optical properties and has half-life in plasma of few minutes [24, 25]. Some observations seem to indirectly confirm this point. In a series of patients with colorectal cancer, Filippello and Coll. reported that the fluorescence of carcinomatosis nodules was higher, and conversely that the rate of false-negative results was lower, in patients who did not receive bevacizumab compared with those who received the drug (76.3% and 65.0%, 42.9% and 53.8%, respectively). The anti-angiogenetic properties of bevacizumab may attenuate the enhanced permeability and retention of ICG [8]. To date, it is not known whether these theoretical considerations have clinical confirmation. Furthermore the dosage, and above all the ideal timing of the injection are not clear. Looking at the results, the possible use of this technique compared to simple visual observation in terms of sensitivity, specificity and accuracy has not been clarified.

For this reasons, in the present systematic review we analyze methods and results of intravenous ICG injection in the diagnosis of peritoneal carcinosis. We found only 6 papers, all published in a short period of time (2015–2018) and by a few centers (Saint Etienne, Bruxelles, Naples, Tokyo, and Leiden). Modalities and timing of ICG injection were very similar. After some initial cases, almost all the Authors injected ICG at the time of anesthesia induction and detected fluorescence starting from 5’ after the injection, for a rather long period (someone up to 360'). Some experimental observations suggested that the best timing for ICG visualization due to the EPR is 6 hours after injection because owing to the rapid clearance of ICG, resulting in a better tumor-to-background ratio starting after 6 hours and lasting until 24 hours (20). In case of HCC (nodules in the peritoneum are usually not due to truly carcinosis, but rather implants due to the rupture of primitive cancer) the timing is different, as ICG is metabolized by normal hepatocytes and unexcreted because of bile ducts alteration. Indeed, papers reporting the usefulness of ICG in liver surgery always report intravenous injection from 1 to several days before surgery [20]. In the case report of peritoneal implant of previously ruptured HCC excluded from the present systematic review, injection of 0,5 mg/kg ICG was performed 72 h before surgery [6]. From a dosing point of view, virtually all series carry the same dosage (0.25 mg/kg), except one that carries twice and one that uses a fixed dose independently from weight (20 mg). All reported injected schedules are similar to that used in other areas for perfusion studies [19].

Overall, in the present systematic review we identified 71 patients. The vast majority (67 cases) were patients with known peritoneal carcinomatosis, undergoing elective surgery for cytoreduction and eventually HIPEC. This clinical setting was ideal for assessing the diagnostic performance of ICG on peritoneal carcinosis, being able to classify each lesion as ICG+/ICG -, malignant/benign by histological

examination. By this way, 322 nodules were assessed. Statistical analysis confirmed that ICG is accurate, with sensitivity ranging from 72–100% and specificity from 54% and 100%. The average of these values was sensitivity 88.2% and specificity 77.8%. In some papers, subgroups of patients were also investigated. Colorectal carcinomas have been studied in relation to the mucinous component, concluding that this type of cancer has a poor affinity for ICG [10]; furthermore, in series investigating ovarian tumours, the accuracy of ICG on peritoneal scars after neoadjuvant chemotherapy was studied, reporting that this tissue also has little affinity for ICG [14]. Some papers provided quantitative data, calculating the tumor-to-background ratio (TBR) [10, 13, 14]. TBR values around 2.0 have been consistently observed in ICG positive carcinosis nodules. However, in the remaining series, in which TBR has not been calculated, carcinosis nodules have still been detected as fluorescent. Aiming at an immediate and wider clinical spreading of this staging technique in clinical practice, we consider the quantitative aspect not essential.

Only in 4 cases peritoneal carcinosis was not known before surgery (all were open staging of ovarian (3 cases) and uterus cancer (1 case)) [13]. Surprisingly, no paper focuses on ICG use during laparoscopic staging of abdominal cancers, with the exception of a single case report [7] and a series mainly focused on small hepatic surface metastases from periampullary cancers [8]. Laparoscopic staging and therapeutic approach is now standard in colorectal cancers; for many other abdominal malignancies, such as gastric and HPB cancers, laparoscopic staging is widely performed [26, 27]. In laparoscopic staging, it would seem very easy to detect the fluorescence generated by ICG on the peritoneum, as many laparoscopic vision systems are currently equipped with fluorescence-driven surgery technology. Moreover, this setting appears even easier than the open one, in which a camera held by the hand, often quite cumbersome, may slowing down the intervention. For this reason, based on the promising data contained in this systematic review, we believe that the time has come to propose a multicenter prospective study to establish feasibility, technique and results of laparoscopic exploration of peritoneal carcinosis by fluorescence generated by ICG. A monocentric study on pancreatic malignancies has been proposed in 2019 [28]. We personally believe the setting of gastric cancer may be also suitable for this kind of prospective study.

In the present systematic review we decided to consider only papers describing the use of ICG to detect nodules of peritoneal carcinosis, with the aim of evaluating the practical effectiveness of this technique in terms of an immediate translation in the daily practice. Some other fluorophores have been studied in humans, but none of them can currently be used outside experimental setting [29–32]. For the same reasons we decided not to consider studies on animal models and in vitro studies [20, 31–33]. Furthermore, we have not considered studies in which ICG is linked to molecules that bind directly to cancer cells [31, 34, 34]. This field of research, although very exciting from a theoretical point of view, as it could make fluorescence a truly oncological navigation, is however still far from a practical application [36].

Abbreviations

ICG, IndoCyanine Green

HIPEC, Hyperthermic IntraPEritoneal Chemotherapy

TBR, Tumor-to-Background Ratio

CT, Computed Tomography

MRI, Magnetic Resonance Imaging

US, UltraSonography

FDA, Food and Drug Administration

Declarations

Competing Interests

Prof. Baiocchi received travel grant from Carlo Bianchi SPA and from Styker Corp.; Prof. Baiocchi has a paid consultation contract with Stryker Corp.

Sources of funding

This study received no funding.

Ethical Approval

Ethical approval by Institutional (University of Brescia) Review Board Committee on 1/4/2020, reference number 032020.

Research Registration Unique Identifying Number (UIN)

Name of the registry: PROSPERO; Unique Identifying number or registration ID: 180238; Hyperlink to your specific registration (must be publicly accessible and will be checked): https://www.crd.york.ac.uk/PROSPERO/#myprospero

Author contribution

CRediT author statement

BGL: Conceptualization, Methodology, Writing- Original draft preparation **GF, MS, AL:** Software, Data curation. Visualization, Investigation. **VM, GS**: Supervision, Writing- Reviewing and Editing. All Authors have read and approved the manuscript.

Availability of data and materials

Data were extracted directly from full-text papers (see references, in particular the 6 case series included in the systematic review are listed as reference 9-14), and are accessible on pub-med.

Guarantor

The Guarantor is the one or more people who accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Prof. Gian Luca Baiocchi

III Chirurgia – ASST Spedali Civili

P.le Spedali Civili, 1

25123 Brescia

Italy

Tel: ++39 030 3995600; ++39 338 5949921

Fax: ++39 030 3397476

Mail: gianluca.baiocchi@unibs.it

Consent to publish

All the Authors approved the manuscript and agree to publish in its present form

Acknowledgement

Not Applicable

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Figures

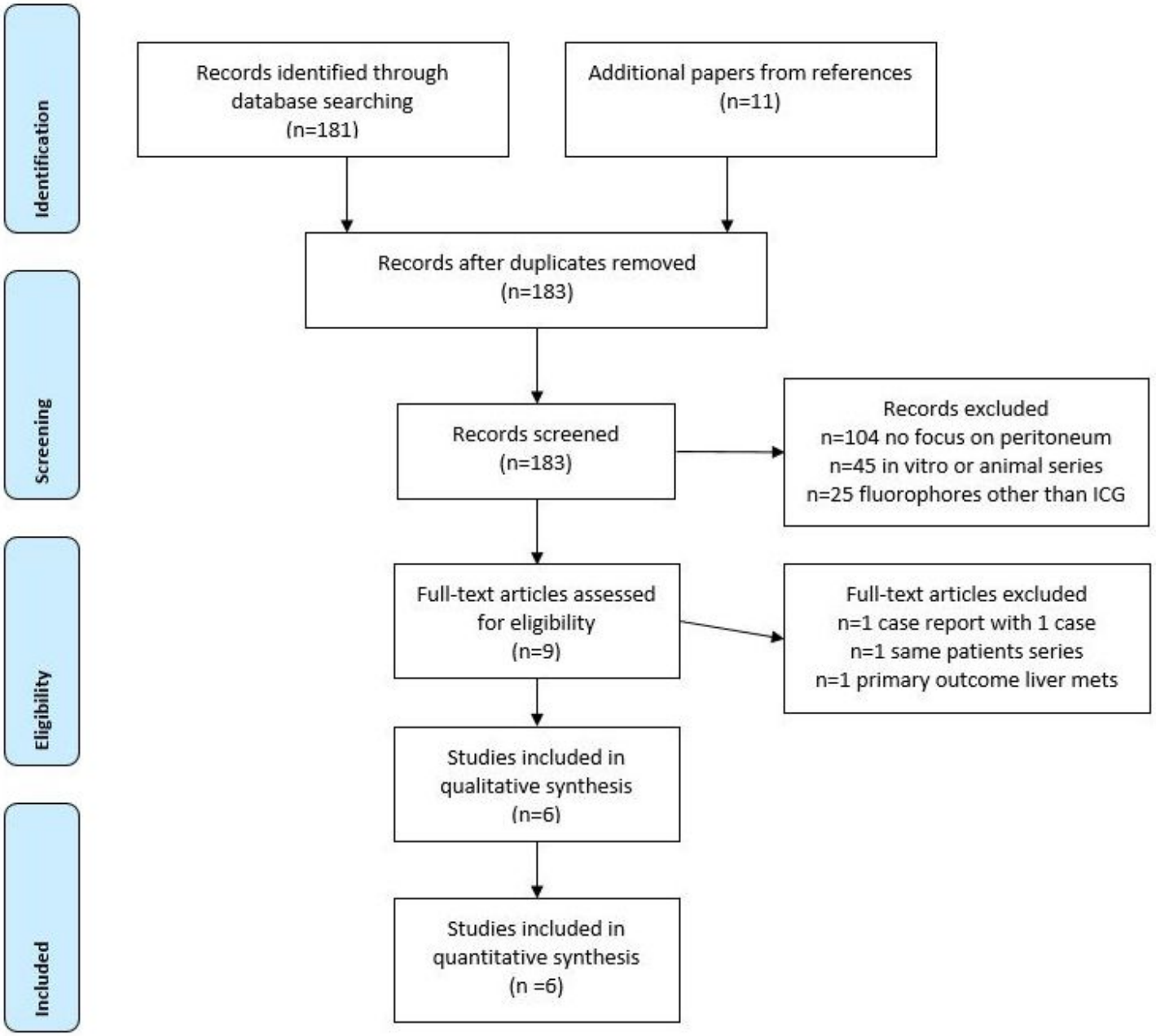

Figure 1

Flow diagram of studies selection. Articles retrieval strategy, according to the Preferred Items for Reporting of Systematic Reviews and Meta-Analyses guidelines.