

END OF DOCUMENT SYSTEMATIC REVIEW

Indocyanine green in the surgical management of endometriosis: A systematic review

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Abstract

Introduction: Endometriosis is a very common disease that affects up to 10% of the female population. The use of indocyanine green (ICG) dye has been proposed to allow the proper localization of endometriotic lesions during surgery. Our purpose is to offer an overview of near-infrared (NIR)-ICG in the surgical treatment of superficial peritoneal endometriosis and deep infiltrating endometriosis.

Material and methods: Electronic databases were searched, including MEDLINE, Embase, Web of Science, Scopus, ClinicalTrial.gov, OVID and Cochrane Library. The studies were identified with the use of a mesh combination of the following keywords: "indocyanine green", "endometriosis", "deep endometriosis", "robotic surgery", "laparoscopy", "ureter", "rectosigmoid" from 2000 to May 2020. All articles describing the use of ICG applied to endometriosis surgery were considered for review. Only original papers that reported specific experience data on the topic were included. Moreover, video-articles were included in the analysis. Quality and risk of bias were evaluated by two authors, respectively.

Results: Fifty-three studies were reviewed and reviews or comment articles not reporting original data and original articles lacking specific data on the application of ICG in patients affected by endometriosis were excluded. The quality of the 17 studies included was assessed. Eight studies suggested the usefulness of NIR-ICG as a tool in the detection of endometriosis during surgery, and one randomized controlled trial and one prospective study did not confirm the advantage of its use. Eight studies found that NIR-ICG was useful for the evaluation of vascularization in intestinal anastomoses and ureterolysis after surgery for deep infiltrating endometriosis.

Conclusions: NIR-ICG appears useful in the evaluation of vascularization in intestinal anastomoses after segmental resection, confirming its role even after ureterolysis for parametrial deep infiltrating endometriosis. However, its usefulness as a tool in the detection of endometriosis during surgery is inconsistent.

KEYWORDS

bowel endometriosis, deep infiltrating endometriosis, indocyanine green, near-infrared, ureterolysis

Abbreviations: DIE, deep infiltrating endometriosis; ICG, indocyanine green; NIR, near-infrared; PE, superficial peritoneal endometriosis; WL, white light.

No financial support was received for this study.

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1 | INTRODUCTION

Endometriosis is an enigmatic disease that affects about 10% of women in reproductive age.¹ It is strongly associated with significant impairment of quality of life in all its aspects, including sexual function, work and social relationships.^{2,3} Essentially, three types of lesions are reported: ovarian endometriosis, superficial peritoneal endometriosis (PE) and deep infiltrating endometriosis (DIE).⁴

Surgery is usually required for DIE management since the medical treatment alone does not always manage to control symptoms.⁵ Although the medical therapy represents the benchmark for endometriosis, the surgical option has proven to be effective, safe and tolerable where there is serious constipation and intestinal cramping, painful bowel movements, dyschezia, prolonged diarrhea with rectal tenesmus, rectal bleeding and, in severe cases, intestinal stenosis or occlusion.⁶ DIE treatment needs high surgical skill and wide experience to achieve the radicality and to preserve, as much as possible, the vascularization and the neurovegetative function of the pelvic organs.⁷⁻⁹

Considering the high complication rate of DIE surgery¹⁰ and the difficulty of identifying PE with its polymorphic appearance, the use of indocyanine green (ICG) dye, as a support to surgery for endometriosis, has been spreading over the last few years.¹¹⁻¹⁸

The intravenous administration of ICG, when associated with the use of a near-infrared (NIR) camera, can be perceived as the emission of fluorescent light and allows an accurate intraoperative real-time assessment of tissue vascularization and their correlation with clinicopathologic data.^{18,19}

Currently there are no clear and uniform indications concerning the use of NIR-ICG in the surgical treatment of endometriosis, and the scientific literature appears unclear about the dosage of dye to be used, the waiting time from the injection or its real effectiveness.^{8,10,23,25,27}

The aim of this review is to offer an overview of NIR-ICG in the surgical treatment of PE and DIE.

2 | MATERIAL AND METHODS

2.1 | Data sources

Research was conducted using the following electronic databases, MEDLINE, Embase, Web of Science, Scopus, ClinicalTrial.gov, OVID and Cochrane Library. The studies were identified with the use of a mesh combination of the following keywords: "indocyanine green", "endometriosis", "deep endometriosis", "robotic surgery", "laparoscopy", "ureter", "rectosigmoid" from the inception of each database to May 2020.

Two authors (MMI, LDC) independently screened titles and abstracts of studies obtained in the search. All types of studies were selected and each potentially relevant study was obtained in full text and assessed for inclusion independently by the authors. Disagreements were resolved by consensus with a third reviewer (FC). All references of the retrieved studies were also reviewed to

Key message

Near-infrared indocyanine green appears useful in the evaluation of vascularization in intestinal anastomoses and after ureterolysis for deep infiltrating endometriosis. Its usefulness in the detection of endometriosis during surgery is inconsistent.

avoid missing relevant publications. Only scientific publications in English were included. All reports related to experimental studies conducted on in vitro or animal models were excluded from the analysis. Proceedings of scientific meetings and abstracts were not considered.

2.2 | Study selection

All articles describing the use of ICG applied to endometriosis surgery were considered for review. Only original papers that reported specific experience data on the topic were included. Moreover, we included video-articles to be as comprehensive as possible and because of the lack of original research published so far. Relevant aspects of every article were recorded and commented on, with particular attention to the modality of the ICG applied techniques and described outcomes. To describe the strength and the level of evidence of the results, we applied the recent levels of evidence published by the Center for Evidence-Based Medicine in 2009.

2.3 | Risk of bias assessment

Two authors (LDC, MMI) independently assessed the risk of bias of the included studies via the Methodological Index for Non-Randomized Studies (MINORS), excluding single case reports and video-articles. Seven domains related to the risk of bias were assessed in each study: (1) aim (ie clearly stated aim), (2) rate (ie inclusion of consecutive patients and response rate), (3) data (ie prospective collection of data), (4) bias (ie unbiased assessment of study endpoints), (5) time (ie follow-up time-appropriate), (6) loss (ie loss to follow up), (7) size (ie calculation of the study size).²⁰ Review authors' judgements were categorized as "low risk", "high risk" or "unclear risk of bias". Discrepancies were resolved by discussion with a third author (FC).

3 | RESULTS

3.1 | Study selection and study characteristics

From the bibliographic search, a total of 56 records were retrieved. Thirty-five articles were selected in full text as potentially relevant. Eighteen studies were then excluded for the following reasons:

review or comment articles not reporting original data ($n = 6$), original articles lacking specific data on the application of ICG in patients affected by endometriosis ($n = 12$). Finally, 17 articles were included in the study (Figure 1).

The quality of non-randomized studies included in our systematic review was assessed by the MINORS tool for assessing the risk of bias (Figure 2A,B).²⁸ All studies had a low risk of bias in “aim” and “rate”, and the majority in “data” and “bias”. Given that more than half were single cases described in the form of video-articles/case reports/case series, high risk was reported for “time” and “size”.

These 17 studies included six video-articles (8 patients),^{19-22,26,27} one case report (1 patient),¹⁶ one case series (6 patients),¹⁴ two retrospective observational studies (57 patients),^{12,24} seven prospective longitudinal studies,^{8,11,13,15,18,23,25} one of which randomized¹⁵ within-subject (196 patients). When insufficient information was reported in the available papers, if necessary, we consulted the authors for further completing data; any disagreement was discussed and resolved by consensus.

The results of our analysis showed a deep heterogeneity regarding the type and localization of endometriosis, as well as the type of fluorescence detection modality, although most studies found the application of ICG in the surgical management of their patients useful and feasible (Table 1): this is almost certainly due to a high degree of neovascularization of endometriosis lesions that appear dark green after ICG injection, which enables surgeons to detect

endometriosis that would not have been seen as readily with conventional laparoscopy.

Although a clear distinction is not easy, the results are reported taking into account the different indications and application of ICG about endometriotic involvement of pelvic and/or abdominal peritoneum, bowel, ureter, etc., considering the importance of ureter and bowel visualization and their perfusion.

3.2 | Peritoneal and Deep infiltrating endometriosis

The use ICG fluorescent imaging has been reported in both laparoscopy and robot-assisted surgery. Levey et al were the first to use daVinci Si's fluorescent technology with ICG for the detection and treatment of endometriosis.¹⁶ Jayakumaran et al¹³ reported a statistically significant higher number of pelvic lesions displayed by NIR-ICG imaging technique compared with that of robotic and laparoscopic white light (WL) (13.4 vs 7.4 vs 4.7, $P = .012$).

Cosentino et al detected and removed 116 suspected endometriosis lesions, reported as PE or DIE from 27 patients through WL imaging (100 lesions) and NIR-ICG (the remaining 16) with positivity of 111 specimens for endometriosis localization. Positive predictive value, negative predictive value, sensitivity and specificity were of 95% vs 97.8%, 86.2% vs 82.3%, 85.6% vs 82%, and 95.2% vs 97.9%, by WL imaging and NIR-ICG, respectively.¹¹

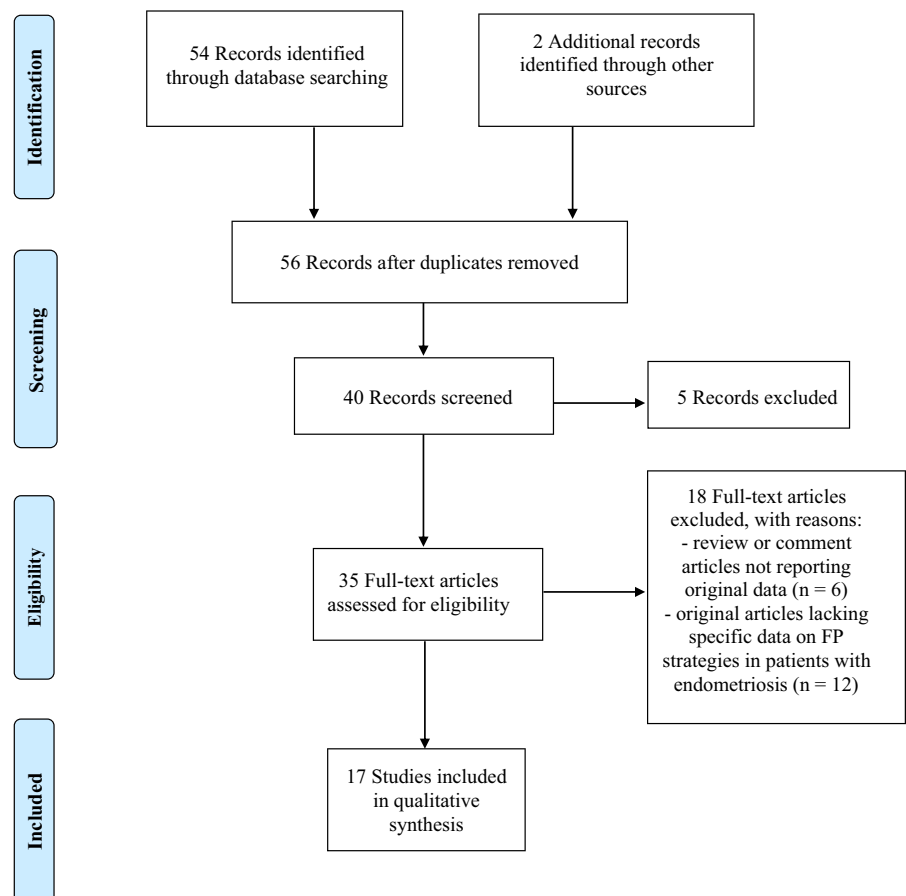


FIGURE 1 Flow diagram of systematic review search

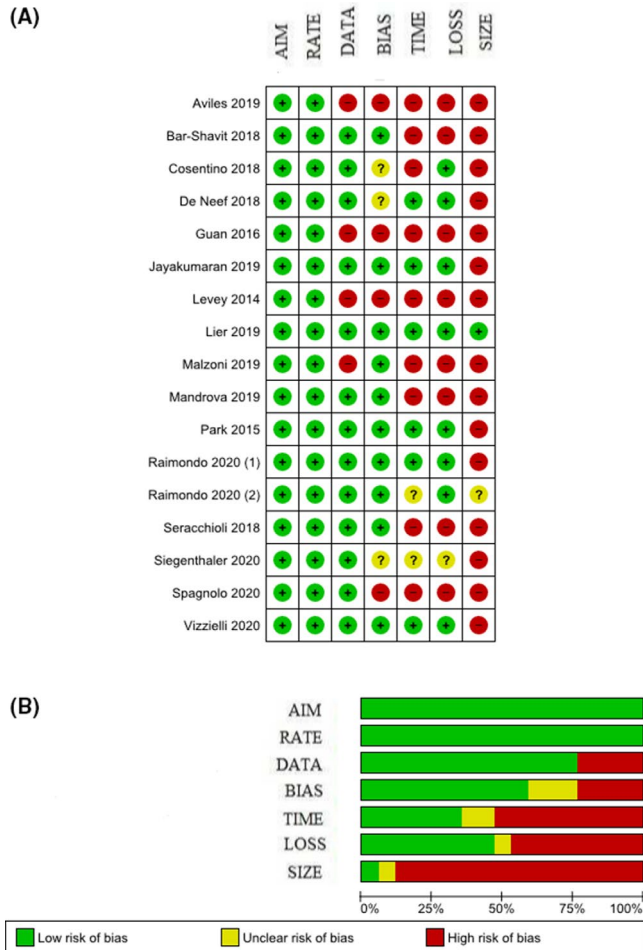


FIGURE 2 Assessment of risk of bias. (A) Summary of risk of bias for each study. Plus sign, low risk of bias; minus sign, high risk of bias; question mark, unclear risk of bias. (B) Risk of bias graph about each risk of bias item presented as percentages across all included studies. (Raimondo 2020 (a): reference 25; Raimondo 2020 (b): reference 18)

In their multicenter case-control study, Vizzielli et al investigated the effect of 3D robotic surgery on the detection rate of occult endometriosis. The patients were divided in two groups: 20 cases (real 3D) vs 27 controls (2D camera approach). No conversion to laparotomy was needed. No differences in postoperative complications were observed between the two groups, with only two (4.2%) major complications observed during the early postoperative period (<30 days): one intestinal stenosis requiring mechanical dilation after discoid excision in the Cases group, and one vaginal dehiscence that required postoperative resuturing in the Controls group. The patients were dismissed after 4 days in the Cases group (range, 3-5) and 3 days (range, 3-4) in the Controls group ($P = .08$). A total of 116 and 70 suspected lesions, respectively, were identified both with the WL and the NIR-ICG approach in the Controls (2D) and Cases (3D), respectively. The overall NIR-ICG lesion identification showed a positive predictive value and specificity >97.8% and a negative predictive value and sensitivity of about 82.0% for the Control group,

compared with a positive predictive value and specificity of 100%, and a negative predictive value and sensitivity of 97.1% for the Cases group, confirming that NIR-ICG imaging is a good diagnostic and screening test ($P = .643$ and $P = .791$, according to the Cohen kappa tests, respectively for the laparoscopic and robotic groups) and demonstrating that the two procedures are comparable in terms of visually detecting endometriotic lesions, as the differences observed did not seem to be clinically relevant.¹²

In addition, in the single-center, prospective, single-arm pilot study, Siegenthaler et al investigated the diagnostic value of NIR-ICG imaging to identify endometriosis lesions and to differentiate them from other lesions, compared with WL imaging (primary outcome), as well as to determine the optimal time of ICG exposure and to define parameters affecting the detection rate (secondary outcome). The diagnostic value of the NIR-ICG imaging technique in detecting and confirming occult endometriosis was minimal: the positive predictive value was lower than that with WL laparoscopy alone or the combination of WL and NIR-ICG (68.8% vs 89.8% vs 86.7%, respectively). Moreover, only seven additional lesions were identified with ICG, of which only one was pathologically proven to be endometriosis. About the secondary outcome, the ICG detection rate was positively affected by the exposure time over 20 minutes, with no previous abdominal surgery and with a low rASRM.⁸

In their prospective, single-center, randomized within-subject, clinical trial, Lier et al carried out an analysis of 20 patients with moderate and severe endometriosis who had undergone laparoscopic surgery. The conventional 2D WL imaging followed by inspection with narrow-band imaging, NIR-ICG and 3D imaging in a randomized order was used to inspect the pelvic region: the single use of NIR-ICG showed no improvement in the detection of endometriosis.¹⁵

3.2.1 | Ureteral endometriosis

Three studies reported the application of ICG in the case of ureteral involvement and the usefulness of ureteral fluorescence during endometriosis surgery.²³⁻²⁵ Mandrova et al²³ used cystoscopic-guided intraureteral ICG immediately before the laparoscopic pelvic surgery, although only three patients were affected by endometriotic lesions. The fluorescence of ureters was visualized in the NIR mode of the camera system, localizing the ureters precisely and in real-time. No intraoperative or postoperative complications related to ICG administration were reported. The use of ICG allowed the ureters in 10 patients (33%) to be localized where the conventional WL mode failed to visualize them, showing ICG to be a safe and feasible method that provides real-time ureteral demarcation.²³

Park et al included 10 patients affected by severe endometriosis (2 with ovarian cysts) reporting symptoms such as dysmenorrhea, dyspareunia, menorrhagia and pelvic pain. In all cases, an intraureteral ICG injection was performed with NIR light during robot-assisted surgery in order to identify the endometriotic lesions and to prevent iatrogenic ureteral injury. The dosage and the time of visualization were not reported. The operative time ranged from 98 to 140 minutes with an

TABLE 1 Results of studies included in the systematic review

Author and year of publication	Country	Type of study and sample size	Endometriosis type and localization	Indocyanine dosage and injection site	Surgical procedure and detection system of fluorescence	Time to visualization	Failed injection, %	Complications due to ICG	Results
Aviles et al (2019) ²⁰	France	Video article - 1 case	DIE - left ureteral	NR - intravenous	Laparoscopy	NR	NR	NR	NR
Bar-shavit et al (2018) ¹⁹	France - Israel	Video article - 3 cases	DIE - rectal	NR - intravenous	Laparoscopy	NR	NR	NR	ICG fluorescent imaging is feasible in endometriosis surgery
Cosentino et al (2018) ¹¹	Italy	Single center, prospective, single-arm pilot study - 27 cases	PE and DIE	0.25 mg/kg - intravenous	Laparoscopy with Olympus ICG Imaging System Prototype based on the Visera Pro System® and a special lens laparoscope optimized for infrared transmission	5-30 min	NR	No hemorrhage, allergic reactions, and/or any type of intraoperative complications. One case of postoperative bleeding of the colorectal anastomosis	NIR-ICG has: PPV 97.8%, NPV 82.3%, Sensitivity 82.0%, Specificity 97.9%
De Neef et al (2018) ¹⁴	Belgium	Case series - 6 cases	RVDIEN (rectovaginal DIE nodules)	0.25 mg/kg - intravenous	da Vinci devices and different conventional laparoscopic devices (NIR imager device Image 1 Spies and Visera Elite II)	NR	NR	NR	ICG fluorescence guided laparoscopy is helpful in separating the RVDIEN from the healthy rectal tissue and also to decide if the resection need to be enlarged to the posterior vaginal fornix
Guan et al (2016) ²¹	USA	Video article - 1 cases	DIE - ureteral and rectal	NR - intravenous	Firefly® technology of da Vinci SI Surgical Systems	NR	NA	NR	ICG fluorescent imaging is useful in endometriosis surgery to localize all nodules of advanced endometriosis
Jayakumar et al (2019) ¹³	USA	Prospective, comparative, observational study - 7 cases	Pelvic endometriosis	0.25 mg/kg - intravenous	2DWL, 3DWL, and 3D robotic Firefly® imaging system of daVinci® Xi Surgical System	NR	NR	No hemorrhage, blood transfusions, allergic reactions, or any other form of intraoperative complications. No conversions to laparotomy	ICG fluorescence system may potentially be useful for more complete intraoperative endometriosis lesion detection and excision
Levey et al (2014) ¹⁶	USA	Case report - 1 case	DIE - bilateral uterosacral ligaments, pelvic sidewalls and rectovaginal peritoneal reflections	NR - intravenous	da Vinci Si surgical assistant platform with built in fluorescence detection technology	60 s	NA	NR	The first reported use of the daVinci Si fluorescent technology and ICG for the detection and treatment of endometriosis

(Continues)

TABLE 1 (Continued)

Author and year of publication	Country	Type of study and sample size	Endometriosis type and localization	Indocyanine dosage and injection site	Surgical procedure and detection system of fluorescence	Time to visualization	Failed injection, %	Complications due to ICG	Results
Lier et al (2019) ¹⁵	Netherlands	Prospective, single-center, randomized clinical trial – 20 cases	Stage III-IV (ASMR)	Bolo of 1 mL – intravenous	NBI, NIR-ICG, and 3D WL imaging compared to conventional 2D high-definition WL imaging using the laparoscopic system CLV-180 EVIS EXERA II platform with an ENDOEYE FLEX 3D deflectable videoscope in the 2D viewing mode	5 min	NR	No complications or adverse events	The single-use of NIR-ICG showed no improvement in the detection of endometriosis
Malzoni et al (2019) ²²	Italy	Video article – 1 case	DIE – colorectal involvement	NR	3D laparoscopy	NR	NR	No intraoperative complications	The use of ICG fluorescent imaging requires an important laparoscopic training
Mandvra et al (2019) ²³	India	Prospective – 30 cases	Endometriotic cysts	5-mg ICG diluted in 2 mL of distilled water – cystoscopy and ureteric cannulation	Laparoscopy with NIR mode of the camera system	7 min	NR	No intraoperative and postoperative complications.	NIR-ICG is an easily replicable, sensitive, and specific method of ureteral visualization and can make complex laparoscopic pelvic surgeries safer
Park et al (2015) ²⁴	USA	Retrospective study – 10 cases	DIE – ureteral involvement	NR – intraurethral	Robotic system with NIR-ICG light	NR	NR	No intraoperative and postoperative complications.	Intraurethral injection of ICG allows to detect endometriotic lesions and also to prevent iatrogenic ureteral injury thanks to visualization of entire course of them
Raimondo et al (2020) ²⁵	Italy	Prospective case series study – 36 cases	DIE – ureteral involvement	0.25 mg/kg – intravenous	Laparoscopy with NIR camera-head (by KARL STORZ)	5.4 ± 2.3 min	NR	No intraoperative complications and no adverse effects related to ICG. No leakage after ureteral procedures	NIR-ICG imaging is a feasible, safe and useful technique that supports surgeons to assess decision-making process

(Continues)

TABLE 1 (Continued)

Author and year of publication	Country	Type of study and sample size	Endometriosis type and localization	Indocyanine dosage and injection site	Surgical procedure and detection system of fluorescence	Time to visualization	Failed injection, %	Complications due to ICG	Results
Raimondo et al (2020) ¹⁸	Italy	Prospective pilot study – 30 cases	Rectosigmoid endometriosis (RSE)	0.25 mg/kg – intravenous	Laparoscopy with NIR camera head (KARL STORZ) and 3D robotic Firefly® imaging system of daVinci® Xi Surgical System	5-50 sec	NR	No intraoperative and postoperative complications	Diffuse or abundant fluorescence (hypervascular pattern) of RSE in 12/30 (40%) women, poor or absent (hypovascular pattern) 18/30 (60%). No statistical differences between these two groups regarding pre-/intraoperative, and histological variables analyzed, except for MVD and a maximum diameter of bowel lesion. Very good agreement of RSE perfusion pattern assessment using NIR-ICG across 2 surgeons ($\kappa = 1.0$)
Seracchioli et al (2018) ²⁶	Italy	Video article – 1 case	DIE – rectosigmoid involvement	1.5 mL solution containing 3.75 mg dose of ICG – intravenous	3D robotic Firefly® imaging system of daVinci® Xi Surgical System	Few seconds	NR	No intraoperative complications	ICG allows to assess the perfusion of the bowel, to select the transaction line and also to evaluate whether blood supply to anastomosis is adequate
Siegenthaler et al (2020) ⁸	Switzerland	Single-center, prospective, single-arm pilot study – 63 cases	PE and DIE	0.3 mg/kg – intravenous in patients with bladder endometriosis: 25 mg – intraurethral	Laparoscopy with the Karl Storz NIR-ICG System using OPAL1® technology with the modular IMAGE1 S™ system	In 44.4%: 2-5 min In 20.6%: 5-10 min In 34.9%: least 20 min	NR	No intraoperative or postoperative complications.	NIR-ICG is helpful in the resection of deep infiltrating nodules, by providing better demarcation, but its diagnostic value is minimal (sensitivity 14.7%)
Spagnolo et al (2020) ²⁷	Spain	Video vignette – 1 case	DIE – ureteral and bowel involvement	ICG solution: 1.25 mg/mL 7 mL – intraureteral (cystoscopy) After rectal segmental 4 mL – intravenous	Laparoscopy with Olympus Medical System and Stryker Iberia SL NIR-ICG camera	NR	NR	NR	ICG enhanced fluorescence is very helpful in DIE surgery that provides a real time evaluation of ureter and bowel

(Continues)

TABLE 1 (Continued)

Author and year of publication	Country	Type of study and sample size	Endometriosis type and localization	Indocyanine dosage and injection site	Surgical procedure and detection system of fluorescence	Time to visualization	Failed injection, %	Complications due to ICG	Results
Vizzielli et al (2020) ¹²	Italy	Retrospective, multicenter case-control study – 20 cases vs 27 controls	PE and DIE	0.25 mg/kg – NR – intravenous	3D robotic Firefly@imaging system of daVinci@ Xi Surgical System vs 2D-Laparoscopy with Olympus ICG Imaging System Prototype based on the Visera Pro System® and a special lens laparoscope optimized for infrared transmission	15-30 min	0%	NR	NIR-ICG is a valid surgery tool to recognize the endometriotic lesions. No statistically significant difference was observed between 3D and 2D imagine

DIE, deep infiltrating endometriosis; MVD, microvessel density; NA, not available; NBI, narrow-band imaging; NIR-ICG, near infrared radiation-indocyanine green; NIR-ICG, near-infrared imaging with indocyanine green; NPV, negative predictive value; NR, not reported; PE, peritoneal superficial endometriosis; PPV, positive predictive value; WL, white light.

estimated blood loss of 23 mL. The length of hospital stay was 1 day with no perioperative or postoperative complications attributable to ICG administration during the follow up of 5.6 months.²⁴

Unlike the aforementioned authors,^{23,24} Raimondo et al investigated the ureteral perfusion with intravenous administration of ICG in 36 symptomatic patients who had undergone laparoscopic conservative surgery for ureteral endometriotic involvement. The ICG assessment required 5.4 ± 2.3 minutes. Local ischemia supporting ureteral stent placement was suspected in five ureters (16.1%) at WL. Of these, two (40.0%) presented regular fluorescence and ureteral stent placement was avoided. In the remaining three (60.0%), ureteral stent placement was necessary. Inter-operator agreement regarding NIR-ICG evaluation was high, both using WL (Cohen's kappa coefficient [κ] = 0.87, 95% confidence interval [CI] 0.70-1.0] and NIR-ICG (κ = 1.0, 95% CI 1.0-1.0), respectively. At the 3-month follow up, all procedures were clinically and radiologically successful.²⁵

3.3 | Bowel endometriosis

The simultaneous involvement of multiple abdominal and pelvic organs, such as ureter and bowel, is rather common in patients with advanced endometriosis. In two video articles^{21,27} the use of ICG, in laparoscopy and robot-assisted surgery, turned out to be very helpful in DIE surgery, enabling real-time evaluation of ureters and bowel and a successful resection of nodules overlying the ureter and rectum. Recently, Raimondo et al have published a prospective pilot study to describe the different rectosigmoid endometriosis vascular patterns and to find a correlation with clinicopathologic data. A diffuse or abundant fluorescence, through intraoperative (ICG) angiography, was reported in 12/30 women (40%). In the remaining 18/30 women (60%), the nodules appeared hypovascularized; these did not show any significant difference from the first group of nodules regarding preoperative, intraoperative or histological variables analyzed, except for a greater maximum diameter of bowel lesions (MVD) (39.5 ± 15.6 vs 30.3 ± 11.4 mm, $P < .05$) and a lower microvessel density ($154.6+ / 43.6$ vs $281.1+ / 77.4$, $P < .05$). ICG angiography turned out to be an intraoperatively feasible and safe technique for the evaluation of rectosigmoid endometriosis vascularization, showing how the nodules with hypovascular pattern seemed to be associated with a larger nodule size and lower MVD.¹⁸

Encouraging data comes from a study where patients with symptomatic rectovaginal DIE nodules, scheduled for a laparoscopic rectal shaving, were enrolled.¹⁴ Six patients underwent a fluorescence-guided laparoscopic shaving procedure for the treatment of non-obstructive rectovaginal DIE nodules. In one patient, the main lesion as well as the posterior vaginal fornix were removed without intraoperative rectal perforation. After 2 days, the patients were dismissed. During the follow-up period of 16 months (range = 2-23 months), no postoperative rectovaginal fistula was reported.¹⁴

Bar-shavit et al used ICG fluorescent imaging to perform rectal shaving in 3 patients with DIE: they found it useful because a very good fluorescence level (score = 4) at the rectal shaving area, assessed by the Likert-type, was obtained.¹⁹ Finally, Seracchioli et al described the ICG fluorescence-guided laparoscopy as helpful in separating the endometriotic nodules overlying the ureter and rectum from the healthy tissue in the case of resection and in allowing assessment of the perfusion of the bowel, selection of the transection line as well as evaluation of the adequacy of the blood supply to anastomosis.²⁶

4 | DISCUSSION

One of the main objectives of surgical techniques for the treatment of endometriosis, in addition to managing pain and achieving pregnancy when desired,^{29,30} is to reduce the complications related to such a demanding surgery.⁹

The rationale for the use of NIR-ICG is well known and in the last few years its ability to bind to plasma proteins has been exploited to visualize in real-time the perfusion of organs or tissues and to evaluate the possible risk of leakage of intestinal anastomosis or skin flap necrosis.³¹

Perfusion is vital for healing and inadequate blood flow can result in failure of anastomotic healing and leakage.³² The NIR-ICG usefulness and effectiveness have been extensively described in colorectal surgery to assess the perfusion of the bowel and select the transecting line.³³⁻³⁶ Nevertheless, the data related to endometriosis surgery are still being debated. Seracchioli and Malzoni recently confirmed in their video abstract, encouraging results on the feasibility, safety and usefulness of NIR-ICG during segmental resection for bowel endometriosis.^{22,26} In 2020, Raimondo et al tried to find a correlation between different rectosigmoid endometriosis vascular patterns and clinicopathologic data demonstrating a higher frequency of hypovascular patterns (60%) among larger endometriosis bowel nodules.¹⁸

Starting from the same concept, its use has also been reported for the evaluation of ureteral vascularization after ureterolysis for parametrial endometriosis, proving to be more sensitive than WL observation.²⁵ A better evaluation of the ureteral arterial microcirculation could allow more rational use of the positioning of a "protection" ureteral stent after ureterolysis for DIE.²⁵ Furthermore, exploiting the fluorescence of the ICG by cystoscopy-guided intraureteral injection can potentially allow easier visualization of the entire course of the ureter,²⁴⁻²⁷ thus limiting possible iatrogenic lesions.

The major limitation of NIR-ICG is the subjectivity of the fluorescence assessment; currently, in fact, evaluation of the microcirculation is based on an "impression" of the surgeon and not on a quantitative analysis.^{19,25} In this sense, a more objective analysis of fluorescence has been proposed in colorectal surgery, based on its variation in intensity from the first visualization to the maximum luminescence. The time needed to obtain adequate perfusion is

directly proportional to the risk of leakage of the colorectal anastomosis.³⁷ Moreover, as reported in Table 1, there is moderate heterogeneity in the type of fluorescence detection modality by 2D/3D-laparoscopy and 3D robotic imaging system; currently, we cannot assess whether it has any influence on endometriosis detection during surgery.

Recently, Gonzàles-Abòs et al reported on the use of a new device for fluorescent-guided surgery with quantitative measurement of the luminescence intensity, which may play a role in discriminating between benign and malignant tissue, during debulking surgery for peritoneal carcinomatosis.³⁸

Moving in this direction, the use of mathematical algorithms and software applied to the biomedical field will make it possible to use NIR-ICG in a more objective and systematic way, limiting the interpretation error of the individual surgeon.

ICG as a diagnostic tool for the detection of endometriosis was investigated in three larger trials and three case reports.^{8,11,12,14,15,24} Cosentino et al described how NIR-ICG may be a tool for intraoperative diagnosis, for confirmation of visible endometriosis lesions, such as PE, and as a marker for identifying occult endometriosis when the WL evaluation had misinterpreted several lesions.¹¹ However, these data should be analyzed by evaluating the real advantage of surgical radicality in the treatment of DIE, which is not acknowledged by all authors.⁵

In a case series, the use of NIR-ICG was investigated as optical guidance for the resection of DIE, allowing surgeons to separate the rectovaginal DIE nodules from the healthy rectal tissue and also to decide whether the resection needs to be enlarged to the posterior vaginal fornix.¹⁴

The dosage of ICG, waiting time to visualization and way of application vary substantially between these papers, and in some cases is not reported at all (Table 1). Worthy of mention is the use of ICG for visualization of the ureters after intraureteral injection reported by Park et al:²⁴ used in this way, ICG allowed the detection of endometriotic lesions and also the prevention of iatrogenic ureteral injury.²⁴

Although the neoangiogenesis and increased blood vessel density typical of DIE^{39,40} present a rationale for the use of NIR-ICG technology, there are elements to consider that can influence the success of this method and that may explain the difference in sensitivity reported by various authors.^{8,11,12,15} Previous retroperitoneal surgery, fibrosis and the reduction of neoangiogenesis related to the use of estrogen-progestin or gonadotropin-releasing hormone agonist, may be responsible for an altered microcirculation at the level of peritoneal lesions or DIE nodules.⁸ The variability among the various authors, regarding the times reported between the administration of ICG and the visualization of the fluorescence, should also be considered, with times for viewing varying from a few seconds to 30 minutes.^{8,11,12,15,16,23,25-27}

Conversely, Siegenthaler et al⁸ and Lier et al¹⁵ showed no advantage for NIR fluorescence imaging with ICG. Indeed, in their pilot study of 63 patients, Siegenthaler et al⁸ reported a sensitivity of NIR-ICG of 14.7%, very different from that found by Cosentino¹¹ and Vizzielli,¹² whose sensitivity was 82%. This inhomogeneity

is difficult to interpret: in the two papers, the substantial differences concern the percentage of patients with previous surgery for endometriosis, 54% for Siegenthaler⁸ and 44% in Cosentino's work¹¹ and the fluorescence display time, which varies for the Siegenthaler between 2 and 20 minutes and for Cosenti between 5 and 30 minutes.

Regarding the detection system of fluorescence, Vizzielli et al¹² investigated the effect of the 3D robotic Firefly® imaging system of daVinci® Xi Surgical System compared with 2D-laparoscopy on the detection rate of occult endometriosis, finding no statistically significant difference. The usefulness of robotic NIR fluorescence-ICG imaging technique compared with robotic and laparoscopic WL was also demonstrated in a further study where a statistically significant higher number of lesions (13.4 vs 7.4 vs 4.7, $P = .012$) were detected.¹³

De Neef et al¹⁴ investigated the use of ICG as optical guidance for the resection of DIE. Park et al²⁴ along with Mandrova et al²³ used ICG for visualization of the ureters after intraurethral injection.

This paper represents the first review on this topic. Nevertheless, two limitations have to be reported: First, the lack of randomized controlled studies in the literature and as a consequence in our review, with one exception.¹⁵ and second, the heterogeneity of included studies in the analysis due to the presence of case report/series, video-articles, retrospective and prospective studies.

5 | CONCLUSION

NIR-ICG appears useful in the evaluation of vascularization of intestinal anastomoses after segmental resection, confirming its role even after ureterolysis for parametrial DIE. However, its usefulness as a tool in the detection of endometriosis during surgery is consistent. Despite the growing interest in the use of NIR-ICG in the surgical treatment of endometriosis and its promising role, data of the scientific literature are still not of adequate quality to recommend its systematic use. But with increasing application of the tool, the quality and volume of the evidence for fluorescence dye use in surgery for DIE will continue to grow.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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How to cite this article: Ianieri MM, Corte LD, Campolo F, et al. Indocyanine green in the surgical treatment of endometriosis: A systematic review. *Acta Obstet Gynecol Scand.* 2020;00:1-11. <https://doi.org/10.1111/aogs.13971>