Indocyanine green in gynecological surgery

Marie Grobet, Linda Tebache, Geraldine Brichant, Julie Collee, Michelle Nisolle

Department of Obstetrics and Gynecology, University of Liège, CHR Liège

ABSTRACT

Indocyanine green (ICG) is a complex amphiphilic, tricarbocyanine iodide dye initially developed during World War II for infrared photography. It was tested and FDA approved for use in human medicine in the mid-fifties. When injected intravenously and revealed by near infrared light (NIR), ICG can highlight vascularization. ICG-NIR has emerged as an efficient technology, valuably implemented intraoperatively in many gynecological surgeries. Although additional data are needed to optimize protocols, it already stands as an excellent diagnostic and screening tool, which may advantageously replace some established methods, especially for perfusion monitoring and sentinel lymph node mapping. In endometriosis detection, ICG-NIR maps deep infiltrating occult lesions more efficiently than current white light (WL) does. Yet ICG-NIR seems to show lower sensitivity for detecting peritoneal superficial nodules, which suggests that WL and ICG-NIR should be used jointly to achieve optimal intraoperative endometriosis nodule detection.

KEYWORDS

Indocyanine green, endometriosis, vascularization.

Introduction

Endometriosis is one of the most frequently encountered gynecological diseases, occurring in ~10% of women of reproductive age [1]. It takes three major clinical forms: peritoneal superficial endometriosis (PE), ovarian endometriosis, and endometriosis deeply infiltrated in the rectovaginal septum (DIE) [2]. Medical treatments, while unable to cure the disease, can reduce its symptoms; however, they are not devoid of side effects. Surgical resection is required when (mainly in DIE) associated symptoms impair bowel, urinary tract and reproductive function.

Three major surgical techniques for treating DIE lesions have been described, resulting in various rates of complications [3]. Rectovaginal digestive fistula appears to be a prominent complication with technique-specific frequencies ranging from 1.3 to 3.9% [4]. It probably occurs after surgery-induced ischemia or vascular impairment, which underscores the need for use of complementary intraoperative monitoring techniques. Indocyanine green (ICG) use has been suggested as a potential candidate for this purpose [5], as well as for supporting other gynecological tumor-related surgeries [6]. ICG, when injected intravenously and revealed by near infrared light (NIR), can highlight vascularization.

Use of ICG prior to endometriosis surgery can in help identifying inflammation-induced hypervascularization of otherwise occult lesions [7], and in selecting the transection line accordingly [8]. When used at the end of surgery, ICG perfusion can allow monitoring of vascularization near the resection area, thereby allowing better surgical decisions to reduce the risk of fistula [9].

This review aims to analyze current knowledge on and interest in the use of ICG-NIR in gynecological malignancies and endometriosis surgical treatments.

Article history

Received 13 Aug 2020 - Accepted 15 Dec 2020

Contact

Michelle Nisolle; michelle.nisolle@chuliege.be

Department of Obstetrics and Gynecology, Hospital CHR Liège, University of Liège, Boulevard du 12eme de Ligne,1, 4000, Liège, Belgium

Phone number: +32 4 3216529

Properties of indocyanine green

ICG is an complex amphiphilic, tricarbocyanine iodide dye (molecular mass = 774.97), developed by the Kodak company during World War II as a dye for infrared photography [10]. It was tested and FDA approved for use in human medicine in the mid-fifties [11]. ICG can be dissolved to produce a mildly acidic (pH 6.5) aqueous solution for intravenous injection [12]. With its spectral absorption peaking at about 780 nm, it is revealed by NIR (750 to 800 nm), allowing excitation of structures at depths of up to several millimeters with high contrast and sensitivity at a wavelength of ~830 nm [13, 14]. The maximum absorbance wavelength of ICG corresponds to that of hemoglobin and oxyhemoglobin, which therefore show minimal interference with ICG fluorescence measurements [14]. Consequently, ICG is used as a vasculature indicator substance (e.g. for photometric hepatic function diagnostics and fluorescence angiography) in cardiac, circulatory, hepatic and ophthalmic conditions [15].

ICG binds tightly to plasma proteins and remains confined in the intravascular space until hepatic uptake and excretion into bile13. Serum albumin and, less importantly, serum α-and β-lipoproteins bind to the lipophilic part of ICG without being functionally altered. As a consequence, 98% of injected ICG is bound to proteins, with the molecules remaining separated as monomers, while the complementary 2% remains free in

the serum and has a tendency to aggregate. Free ICG is more rapidly eliminated in bile by glutathione S-transferase than the protein-bound fraction [12]. Moreover, it could have a tendency to bind to the phospholipid bilayer of the endothelium after becoming more hydrophobic due to the local microenvironment, with a maximum fluorescence wavelength shifting from 826 to 835 nm; this could explain some of the reported variability during ICG use for angiography [16].

ICG hepatic clearance is quick, reaching ~20% per minute. More precisely, after intravenous injection, ICG is cleared following a bimodal curve. The first exponential stage lasts for 10 to 20 minutes after injection, with a half-life of 3 to 4 minutes. Afterwards, clearance slows down allowing trace amounts to be detected in serum for more than one hour [16, 17]. Contrary to other clinical fluorescent dyes with longer half-lives (e.g. bromsulphthalein), the quick clearance rate of ICG allows for repeated ICG injections during the same procedure, allowing, for example, timely monitoring of vascularization changes [18]. The Vmax of clearance for ICG usually exceeds 3.6 mg/kg/minute in humans with normal hepatic function, the limiting step being hepatocyte uptake via specific carriers [19]. The clearance curve closely correlates with standard enzyme kinetics, bilirubin acting as a competitive inhibitor during hepatic uptake [19]. Some decomposition of ICG occurs in the bloodstream, more quickly for the free forms, leading to the release of singlet oxygen molecules that bind to the breakdown product, resulting in the formation of carbonyl compounds of low toxicity [13].

Provided that patients do not develop iodide allergy, hepatic clearance and trapping of the singlet oxygen species by the degraded products renders ICG virtually non-toxic. The LD50 dose reaches 50 to 80 mg/Kg, greatly exceeding standard working doses, i.e. less than 2 mg/Kg [13]. A thorough study of the physiologic effects of ICG has confirmed its safety in a wealth of clinical applications [16].

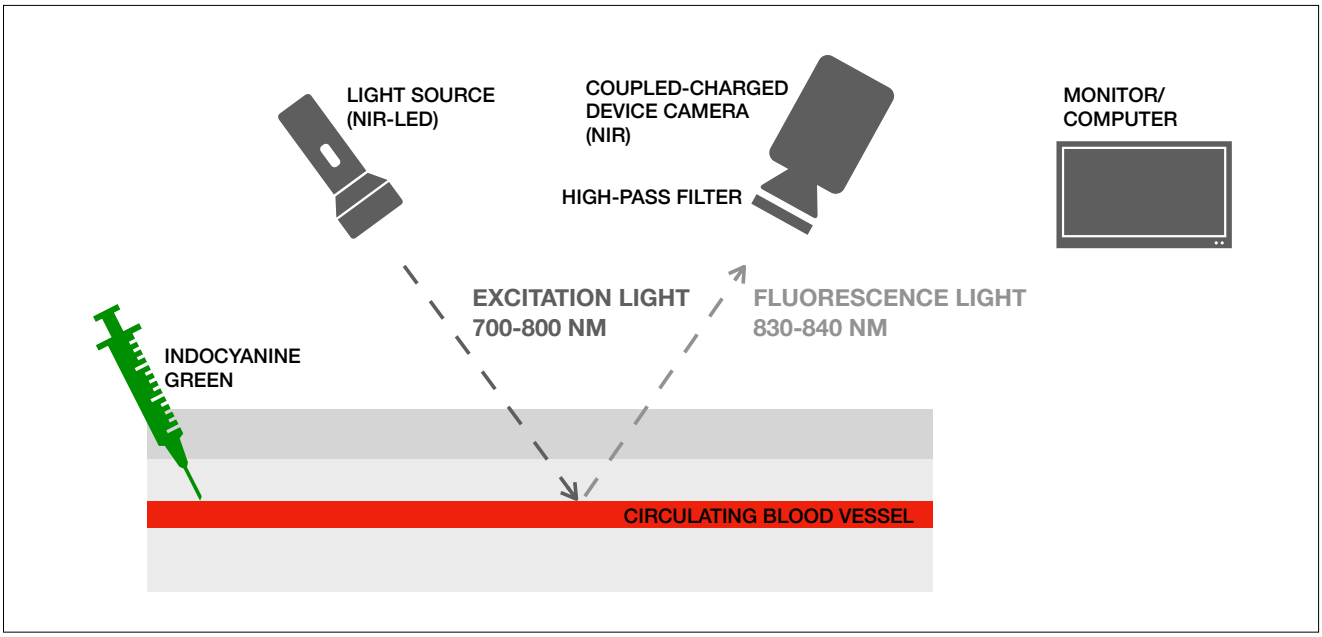
The abovementioned properties of ICG allow its safe clinical use. Intravenous ICG injections and the use of NIR have proven to reveal fluorescence in vasculature lying at depths of several millimeters with high contrast and sensitivity, rendering the tissues more translucent than with other fluorescent dyes [13]. Nevertheless, to ensure efficient use, the tendency of free ICG to aggregate and its intrinsic instability when exposed to light must be taken into consideration. Since saline solutions and high ICG concentrations promote aggregation, a maximum of 80 mg/L in water is the preferred combination for intravenous injection, ensuring a maximum plasma concentration of 15 mg/L. Beyond this limit, aggregation and quenching mitigates fluorescence [16]. The instability of ICG solutions, especially when exposed to light, makes it necessary to inject them no later than 6 to 10 hours after resuspension of the dry powder [14].

Medical uses of indocyanine green

As previously mentioned, ICG was developed as a dye for infrared photography during World War II10, and rapidly thereafter (in the mid-50s) it was tested as a dye for recording time-varying dilatation of blood vessels and cardiac output in valvular and septal defects [20]. ICG was approved by the FDA for general use in human medicine in 1956 [11]. Its use rapidly expanded to monitoring of hepatic clearance [17], and in the seventies it was extensively studied in the field of ophthalmic angiography [21-24], where it remains a reference tool. Peculiar applications relating to interventional surgery were approved later, in the 2000s [13].

Indeed, the advent of digital imaging in the 2000s opened up a wealth of new avenues for ICG-based angiography (ICGA) applications, allowing dynamic recording of tissue perfusion, tumor detection, and intraoperative identification of vascularized structures [18]. Figure 1 schematizes a canonical ICGA-NIR detection system.

Figure 1 Schematic representation of a canonical ICGA-NIR detection system. ICG solution is injected intravenously. Incident NIR light provokes ICG-dependent fluorescence which is captured and processed by an image analysis system.



In ophthalmology, beyond angiography applications, ICG is used as a tool for visualizing the internal membrane of the vitreous humor, to allow its peeling from retinal adhesion areas [25]. Toxicity of ICG degradation products on retinal pigment epithelial cells of the subretinal space has been suggested, promoting either the use of safer dosages or investigations on lower-toxicity analogs such as infracyanine green [26].

ICGA has several advantages over digital subtraction angiography (DSA), which is frequently used in neurological surgery. It does not require use of radioactive isotopes or X-ray irradiation; it does not necessitate in situ bolus injection, which can provoke bleeding or obstruction at the injection site, and it is by far less technically and equipment demanding [27]. Moreover, unlike DSA, ICGA, often integrated within image analysis systems (e.g. FLOW-800, Carl Zeiss Surgical, Germany), can be performed throughout the surgical procedure [27-29].

ICGA has been widely developed for assessing tissue perfusion during reconstructive surgery, especially for skin flap design after mastectomy, and panniculectomy, which may or may not be associated with open ventral hernia repair. Integrated systems such as the SPY Elite® system (Bridgewater, NJ) associates laser-assisted ICGA with real-time image analysis during open surgeries to evaluate regional blood supply and help in designing the best surgical approach to maximize wound perfusion and repair [30-32]. ICGA-assisted reconstructive surgery has significantly reduced hypoperfusion-dependent wound complications, with calculated perfusion indexes accurately predicting post-surgery recovery success [33-34].

ICGA has been applied successfully to guide digestive surgeries where resection/anastomosis of the esophagus [35-36], stomach [37], small bowel [38] or rectal [39] portions were at risk of hypoperfusion. The benefits of adapting surgical approaches so as to integrate ICGA-NIR in robotic-assisted laparoscopic rectal surgery are significant [40].

In addition to its traditional role in hepatic clearance monitoring, ICG, due to its excretion into bile, accumulates along bile ducts and in the gallbladder, thereby helping to visualize the biliary anatomy and thus to guide cholecystectomies41 and pancreaticoduodenectomies [42], as well as to prevent partial hepatectomy-induced bile leaks [43]. Another technique is ICG lymphangiography (ICGLA), which can be used, to monitor lymphatic flow after surgery44 or to identify sentinel lymph nodes (SLNs) downstream of tumors. Using the abovementioned SPY Elite system during breast cancer surgery allows SLN detection rates of up to 94%, similar to the rate with combined use of lymphazuran blue and technetium-9945.

A similar rate is reported for colon cancer surgery, where ICG infusion allows an up to 96% SLN identification rate, equivalent to the performance of the technetium-99/lymphazuran blue method46. ICG thus emerges as a strong competitor to the traditional isotopic method since it requires only 1 to 2 minutes to visualize the region of interest and does not need radioisotopes or gamma probe-mediated comparative radioactivity readings to assess accurate removal of SLNs [47].

The use of ICGA-NIR for intraoperative purposes is frequently coupled with robotic devices (e.g. da Vinci®, Sunnyvale, CA), especially for identifying vascular and tumor tissue in complex areas such as in the pelvic region [6,40,48,49].

ICG may play a role in anti-cancer phototherapy, its photo-induced degradation products (singlet oxygen) killing colonic cancer cells *in vitro* after intracellular lipid peroxide accumulation [50]. Transposing this property *in vivo* is impeded by quick protective trapping of ICG by serum albumin/proteins and rapid hepatic clearance.

Nanoencapsulation systems drastically slow down clearance and extend tissue distribution *in vivo* [51,52], while coating with selected antibodies, whether or not in association with lymphocytes (NK cells), allows precise targeting of specific cancer cells *in vitro* (e.g. cervical cancer cell or head and neck squamous cancer cell lines), where ICG-induced phototherapy can induce up to 90% to 100% apoptosis [53,54].

ICGA and ICGLA have many useful applications in gynecology as well, be it for detecting SLNs, for revealing cryptic tumor or endometriosis-specific vasculature, or for monitoring effective vascularization at the end of a resection process. These applications will be described and discussed in the following sections.

Use of ICG in gynecology

As mentioned above, ICGA and ICGLA assets and efficiencies have been demonstrated in various surgical applications, be it for real-time SLN mapping, to help in decision making on surgical approaches involving vessels, or for evaluating perfusion rates at the end of procedures. The same needs and constraints apply in gynecology, too, where efficient use of ICG for similar purposes is consistently reported.

The first reports mentioning ICGLA-NIR for SLN identification during gynecological surgery date back to 2010 [55,56]. Subsequently, ICGLA and ICGA became increasingly popular as intraoperative tools (i) for mapping SLNs57, (ii) when vasculature alteration can be a concern, e.g. to support transection and anastomosis design decisions [5] and for monitoring postoperative perfusion [9], and (iii) for detecting minute tumors or cryptic endometriosis foci [7].

Quantifying gynecology-related literature reports on ICG

Table 1 estimates the number of PubMed hits when combining indocyanine green and other gynecology-related keywords. Two hundred fifty-eight results were generated in a general search, simply by adding the gynecological keyword, reaching a maximum of 66 hits in 2019.

However, at the time of writing this review (May 2020) [42], publications have already been recorded for 2020, confirming a strong upward trend. When searching with endometriosis, this rising curve is found to be even sharper, with the 2020 hits to date [12] already double the number for 2019 [6]. This rough examination does not take into account that some hits do not precisely fit the search scope. Nevertheless, careful examination of the endometriosis results shows that this was the case for only 2 out of 25 citations. Clearly, the use of ICG in gynecology-related surgery, and particularly in endometriosis treatment procedures, appears to be attracting increasing attention from researchers and clinicians.

Table 1 Number of PubMed hits when combining indocyanine green and other gynecology-related keywords. This table reports the PubMed search results when using indocyanine green and other gynecology-related keywords. Each search scope is mentioned above the keywords. The numbers of results are listed for the publication years 2016 to 2020. The peak years and corresponding publication numbers are indicated, as well as the first year with a reported hit (first occurrence).

	Scope general **keywords** gynecological indocyanine green	**Scope** outcome anastomosis keywords **gynecological anastomosis** indocyanine green	**Scope** endometriosis **keywords** endometriosis indocyanine green
Year			
2020	**42**	**2**	**12**
2019	**66**	**5**	**6**
2018	**48**	**1**	**5**
2017	**58**	**2**	**0**
2016	**44**	**1**	**2**
Peak yr	2019	2019	2020
nr	66	5	12
First occurence	**1993**	**2012**	**2013**
nr	**1**	**1**	**1**
Total	258	11	25
	Scope Sentinel lymph node in breast cancer **keywords** sentinel nodes breast indocyanine green	**Scope** Sentinel lymph node in endometrial cancer **gynecological anastomosis** sentinel nodes endometrial indocyanine green	**Scope** Sentinel lymph node in cervical cancer **keywords** sentinel nodes cervical indocyanine green
Year			
2020	**2**	**8**	**9**
2019	**15**	**17**	**16**
2018	**13**	**15**	**20**
2017	**13**	**19**	**24**
2016	**17**	**17**	**17**
Peak yr	2015	2017	2017
nr	18	19	24
First occurence	**1999**	**2011**	**2005**
nr	**1**	**1**	**1**
Total	60	76	86

ICGLA for SLN mapping

The practice of mapping and analyzing of LNs downstream of malignancies for metastasis prediction dates back to a study on penile carcinoma treatment in 1977 [58], when the SLN concept was first introduced. Hence, biopsy of SLNs identified as draining the tumor region can help in making the decision either to preserve the integrity of the downstream lymphatic system (in the event no metastasis is found in biopsy), or to perform a morbidity-prone complete lymphadenectomy (in the event of a positive biopsy or of SLN mapping failure). SLN analysis was soon incorporated into the routine management of breast cancer [59,60], early gastric cancer [61], and skin melanoma [62]. In gynecological malignancies, the SLN concept was first accepted for vulvar carcinoma [63] and is now extended to early ovarian [64], cervical and uterine6 cancers, where its safety (i.e. accuracy for detecting metastases) has been demonstrated [65], as have its postoperative advantages compared with extensive lymphadenectomy [66]. Yet, SLN predictive value relies primarily on mapping accuracy, which in turn depends on sensitivity in detecting lymphatic vessel-driven migration of a tracer introduced at the tumor site. Three main tracer families have been used for this purpose: blue dyes, such as lymphazuran or isosulfan blue, which may or may not be associated with radioisotopic colloids (technetium-99), and more recently fluorescent dyes like ICG. The abovementioned ergonomic advantages of ICG over blue dyes/technetium-99 have been confirmed for gynecological SLN mapping in open, laparoscopic, and robotic surgeries [57,67,68]. ICGLA allows better bilateral SLN detection sensitivity (consistently more than 80% – the only clinically relevant score since lymphatic drainage in the pelvis is bilateral) and detection of SLN in unexpected body regions [6,67]. The latter finding is important since in up to 10% of uterine and cervical malignancies, ICGLA maps SLNs in the aortic region or in the presacral space, which are unlikely to be explored during traditional lymphadenectomy approaches [6]. ICGLA-mediated SLN mapping efficiency appears to be dependent on the patient's BMI, with heavier patients showing lower bilateral SLN mapping success [6]. However, this high BMI-dependent reduced efficiency appears less pronounced when ICGLA is compared with the use of radiocolloid/blue dye in SLN mapping [68].

ICGA for monitoring perfusion

Gynecological surgeries, either for treating malignancies or for resecting endometriosis nodules or more extensive lesions, can lead to hypoperfusion problems and ultimately necrosis, fistulae or other ischemia-dependent complications requiring

secondary interventions. Intraoperative ICGA-NIR for monitoring anastomotic perfusion has been assessed and found to be a good decision-making tool in gynecological oncology, e.g. after bowel resection and rectal anastomosis [9,69]. Similarly, in conservative surgery for ureteral endometriosis, affecting up to 50% patients with DIE [70], ICGA-NIR, coupled with endoscopic surgery, appears to be an accurate intraoperative means of assessing ureteral perfusion after ureterolysis or nodule removal, allowing selective ureteral stent placement [5].

Hence, ICGA-NIR in gynecological conservative surgery appears straightforward, showing good inter-operator reproducibility, allowing repeated intraoperative perfusion monitoring within minutes of intravenous bolus injection, and suggesting adaptive modification of initial operative plans if required.

ICGA for localizing endometriosis nodules

Identifying endometriosis lesions may be challenging due either to polymorphic appearances (mainly when superficial and peritoneal - PE) or to the small size or hidden localization of lesions (mainly in DIE). Failure to identify and resect all endometriosis nodules often leads to persistence and/or recurrence of symptoms and associated complications [71]. Although traditional white light (WL) imaging is still the gold standard for detection, with this method recurrence or persistence of symptoms after laparoscopic resection occurs in up to 50% of patients at 5 years [72]. This emphasizes the need for enhanced endometriosis lesion detection solutions. ICGA-NIR imaging appears to be a good candidate for this purpose since PE and DIE are usually associated with hypervascularization [7,73]. Using ICGA-NIR does not lengthen the operative process since ICG injection can be performed during the preparation of the operating field in order to reach maximum fluorescence upon laparoscopic exploration. Yet, the optimal doses and the time needed to attain maximum sensitivity are still under debate [74,75]. Ovarian and fallopian tube endometriosis lesions may not be detected with ICGA-NIR due to lack of fluorescence and hypervascularization, respectively [7]. Nevertheless, pilot studies show high sensitivity and specificity of ICGA-NIR mainly for DIE screening. For PE, although specificity of ICGA-NIR appears to be superior to that of WL detection, its sensitivity was inferior [7,74,75]. Even though additional data are needed to optimize the detection protocols, ICGA-NIR already stands as an excellent diagnostic and screening tool, especially for detecting DIE occult lesions [7,49]. Since the optimal detection range of each method, although largely overlapping, retains some specificities, WL and ICGA-NIR detection should be used jointly to achieve optimal intraoperative endometriosis nodules detection [7,76].

Discussion and perspectives

From as early as the mid- and late 1950s, ICG has been tested for medical applications, i.e. as a fluorescent dye for monitoring cardiac ejection flows and volumes [20] and to evaluate hepatic clearance [17]. It was FDA approved for general use in human medicine in 1956 [11]. In the seventies, its use was extensively studied in the field of ophthalmic angiography [21–24], where it continues to be a reference tool. Applications relating to interventional surgery were approved later, in the 2000s [13], boosted by the advent of digital imaging. Three major ICG-NIR application fields can be distinguished, related to blood, bile and lymph flow visualization. ICGA-NIR allows intraoperative and dynamic recording of tissue perfusion, tumor detection, and identification of otherwise occult vascularized structures [18]. ICG hepatic clearance helps in visualizing bile ducts and the gallbladder, thereby guiding cholecystectomies [41] and pancreaticoduodenectomies [42], as well as preventing partial hepatectomy-induced bile leaks [43]. ICGLA allows monitoring of post-surgical lymphatic flow [44] and identification of SLNs downstream of tumors [45]. More speculatively, ICG may play a role in anti-cancer phototherapy [50].

Beyond rare sodium iodide allergic reactions, ICG appears virtually non-toxic with reassuring useful dosage safety [16]. Its short half-life, quick distribution and easy detection throughout tissues several millimeters thick explain the appeal of ICG-NIR as a real-time intraoperative detection method. Furthermore, NIR excitation detection systems can be integrated into endoscopic or robotic devices, further increasing the interest in minimally invasive surgical approaches [6,40,48,49].

The assets of ICGA and ICGLA have been demonstrated in various gynecology-related surgical procedures, and these techniques have become increasingly popular amongst researchers and clinicians as shown by a PubMed search for reports.

The intraoperative efficiency of ICGA-NIR has been confirmed for monitoring perfusion before and after gynecology-related resections/anastomoses, allowing direct modification of operative plans if required [9,69,70].

ICGLA-NIR appears to be more ergonomic and sensitive than classical blue dyes/technetium-99 tracing for bilateral SLN mapping in uterine and cervical malignancies [67]. It allows SLN detection in body regions unlikely to be explored during usual lymphadenectomy approaches [6,67]. Hence, in up to 10% of uterine and cervical malignancies, ICGLA maps SLNs in the aortic region or in the presacral space [6]. ICGLA-mediated SLN mapping efficiency dependency on patient BMI appears to be less pronounced when ICGLA is compared with the use of radiocolloid/blue dye [68].

The identification of endometriosis lesions remains challenging since current WL imaging fails to detect all endometriosis nodules, leading to recurrence or persistence of symptoms after laparoscopic resection in up to 50% of patients at 5 years [72]. ICGA-NIR imaging appears to be a good candidate for improving this rate since PE and DIE are usually associated with hypervascularization [7,73]. Using ICGA-NIR does not lengthen the operative process [7]. High sensitivity and specificity of ICGA-NIR have been demonstrated, especially for DIE screening. For PE, although the specificity of ICGA-NIR appears superior to that of WL detection, its sensitivity is lower [7,74,75]. Ovarian and fallopian endometriosis lesions may not be detected with ICGA-NIR only due to lack of fluorescence and hypervascularization, respectively [7].

In short, ICG-NIR appears to be an efficient technology that may be valuably implemented intraoperatively in many gynecological surgeries. Although additional data are needed to optimize protocols, it already stands as an excellent diag-

nostic and screening tool, which may advantageously replace some established methods especially for perfusion monitoring and SLN mapping. For detecting endometriosis lesions, ICG-NIR maps DIE occult lesions more efficiently than WL imaging does [7,49]. Yet the sensitivity of ICG-NIR for detecting PE nodules appears inferior, suggesting that WL and ICGA-NIR detection should be used jointly to achieve optimal intraoperative endometriosis nodule detection [7,76].

References

1. Giudice LC, Kao LC. Endometriosis. Lancet. 2004;364:1789-99.
2. Nisolle M, Donnez J. Peritoneal endometriosis, ovarian endometriosis, and adenomyotic nodules of the rectovaginal septum are three different entities. Fertil Steril. 1997;68:585-96.
3. Nisolle M, Brichant G, Tebache L. Choosing the right technique for deep endometriosis. Best Pract Res Clin Obstet Gynaecol. 2019;59:56-65.
4. Roman H; FRIENDS group (French coloRectal Infiltrating ENDometriosis Study group). A national snapshot of the surgical management of deep infiltrating endometriosis of the rectum and colon in France in 2015: a multicenter series of 1135 cases. J Gynecol Obstet Hum Reprod. 2017;46:159-65.
5. Raimondo D, Borghese G, Mabrouk M, et al. Use of indocyanine green for intraoperative perfusion assessment in women with ureteral endometriosis: a preliminary study. J Minim Invasive Gynecol. 2021;28:42-9.
6. Jewell EL, Huang JJ, Abu-Rustum NR, et al. Detection of sentinel lymph nodes in minimally invasive surgery using indocyanine green and near-infrared fluorescence imaging for uterine and cervical malignancies. Gynecol Oncol. 2014;133:274-7.
7. Cosentino F, Vizzielli G, Turco LC, et al. Near-infrared imaging with indocyanine green for detection of endometriosis lesions (Gre-Endo Trial): a pilot study. J Minim Invasive Gynecol. 2018;25:1249-54.
8. Seracchioli R, Raimondo D, Arena A, Zanello M, Mabrouk M. Clinical use of endovenous indocyanine green during rectosigmoid segmental resection for endometriosis. Fertil Steril. 2018;109:1135.
9. Bar-Shavit Y, Jaillet L, Chauvet P, Canis M, Bourdel N. Use of indocyanine green in endometriosis surgery. Fertil Steril. 2018;109:1136-7.
10. Brooker LGS, Dent SG, Heseltine DW, Van Lare E. The significance of basicity and acidity of nuclei in cyanine type condensations. J Am Chem Soc. 1953;75:4335-6.
11. Fox IJ, Wood EH. Indocyanine green: physical and physiologic properties. Proc Staff Meet Mayo Clin. 1960;35:732-44.
12. Engel E, Schraml R, Maisch T, et al. Light-induced decomposition of indocyanine green. Invest Ophthalmol Vis Sci. 2008;49:1777-83.
13. Alander JT, Kaartinen I, Laakso A, et al. A review of indocyanine green fluorescent imaging in surgery. Int J Biomed Imaging. 2012;2012:940585.
14. Landsman ML, Kwant G, Mook GA, Zijlstra WG. Light absorbing properties, stability, and spectral stabilization of indocyanine green. J Appl Physiol. 1976;40:575-83.
15. Yannuzzi LA. Indocyanine green angiography: a perspective on use in the clinical setting. Am J Ophthalmol. 2011;151:745-51.e1.
16. Desmettre T, Devoisselle JM, Mordon S. Fluorescence properties and metabolic features of indocyanine green (ICG) as related to angiography Surv Ophthalmol. 2000;45:15-27.
17. Cherrick GR, Stein SW, Leevy CM, Davidson CS. Indocyanine green: observations on its physical properties, plasma decay, and hepatic extraction. J Clin Invest. 1960;39:592-600.
18. Reinhart MB, Huntington CR, Blair LJ, Heniford BT, Augenstein VA. Indocyanine green: historical context, current applications, and future considerations. Surg Innov. 2016;23:166-75.
19. Paumgartner G, Probst P, Kraines R, Leevy CM. Kinetics of indocyanine green removal from the blood. Ann N Y Acad Sci. 170:134-47.
20. Burchell HB. Assessment of clinical value: symposium on diagnostic applications of indicator-dilution technics. Proc Staff Meet Mayo Clin. 1957;32:551-3.
21. Kogure K, Choromokos E. Infrared absorption angiography. J Appl Physiol. 1969;26:154-7.
22. Hochheimer BF. Angiography of the retina with indocyanine green. Arch Ophthalmol. 1971;86:564-5.
23. Flower RW, Hochheimer BF. Indocyanine green dye fluorescence and infrared absorption choroidal angiography performed simultaneously with fluorescein angiography. Johns Hopkins Med J. 1976;138:33-42.
24. Flower RW. Infrared absorption angiography of the choroid and some observations on the effects of high intraocular pressures. Am J Ophthalmol. 1972;74:600-14.
25. Gandorfer A, Haritoglou C, Gass CA, Ulbig MW, Kampik A. Indocyanine green-assisted peeling of the internal limiting membrane may cause retinal damage. Am J Ophthalmol. 2001;132:431-3.
26. Engelbrecht NE, Freeman J, Sternberg P Jr, et al. Retinal pigment epithelial changes after macular hole surgery with indocyanine green-assisted internal limiting membrane peeling. Am J Ophthalmol. 2002;133:89-94.
27. Raabe A, Nakaji P, Beck J, et al. Prospective evaluation of surgical microscope-integrated intraoperative near-infrared indocyanine green videoangiography during aneurysm surgery. J Neurosurg. 2005;103:982-9.
28. Faber F, Thon N, Fesl G, et al. Enhanced analysis of intracerebral arterioveneous malformations by the intraoperative use of analytical indocyanine green videoangiography: technical note. Acta Neurochir (Wien). 2011;153:2181-7.
29. Uchino H, Nakamura T, Houkin K, Murata J, Saito H, Kuroda S. Semiquantitative analysis of indocyanine green videoangiography for cortical perfusion assessment in superficial temporal artery to middle cerebral artery anastomosis. Acta Neurochir (Wien). 2013;155:599-605.
30. Holm C, Mayr M, Höfter E, Becker A, Pfeiffer UJ, Mühlbauer W. Intraoperative evaluation of skin-flap viability using laser-induced fluorescence of indocyanine green. Br J Plast Surg. 2002;55:635-44.
31. Moyer HR, Losken A. Predicting mastectomy skin flap necrosis with indocyanine green angiography: the gray area defined. Plast Reconstr Surg. 2012;129:1043-8.
32. Kanuri A, Liu AS, Guo L. Whom should we SPY? A cost analysis of laser-assisted indocyanine green angiography in prevention of mastectomy skin flap necrosis during prosthesis-based breast reconstruction. Plast Reconstr Surg. 2014;133:448e-454e.
33. Patel KM, Bhanot P, Franklin B, Albino F, Nahabedian MY. Use of intraoperative indocyanin-green angiography to minimize wound healing complications in abdominal wall reconstruction. J Plast Surg Hand Surg. 2013;47:476-80.
34. Colavita PD, Wormer BA, Belyansky I, et al. Intraoperative indocyanine green fluorescence angiography to predict wound complications in complex ventral hernia repair. Hernia. 2016;20:139-49.
35. Kumagai Y, Hatano S, Sobajima J, et al. Indocyanine green fluorescence angiography of the reconstructed gastric tube during esophagectomy: efficacy of the 90-second rule. Dis Esophagus. 2018;31.
36. Shimada Y, Okumura T, Nagata T, et al. Usefulness of blood supply visualization by indocyanine green fluorescence for reconstruction during esophagectomy. Esophagus. 2011;8:259-66.
37. Carus T, Dammer R. Laparoscop fluorescence angiography with indocyanine green to control the perfusion of gastrointestinal anastomoses intraoperatively. Surg Technol Int. 2012;22:27-32.
38. Iinuma Y, Hirayama Y, Yokoyama N, et al. Intraoperative near-infrared indocyanine green fluorescence angiography (NIR-ICG AG) can predict delayed small bowel stricture after ischemic intestinal injury: report of a case. J Pediatr Surg. 2013;48:1123-8.
39. Sabbagh C, Guerin O, Chaibi S, et al. Does the use of intraoperative fluorescence imaging with indocyanin green (ICG) reduce the rate of anastomotic leakage after colorectal surgery. A propensity score-matched study. ESCP, 2018. Abstract WP 31.
40. Jafari MD, Lee KH, Halabi WJ, et al. The use of indocyanine green fluorescence to assess anastomotic perfusion during robotic assisted

laparoscopic rectal surgery. Surg Endosc. 2013;27:3003-8.
41. Osayi SN, Wendling MR, Drosdeck JM, et al. Near-infrared fluorescent cholangiography facilitates identification of biliary anatomy during laparoscopic cholecystectomy. Surg Endosc. 2015;29:368-75.
42. Hutteman M, van der Vorst JR, Mieog JS, et al. Near-infrared fluorescence imaging in patients undergoing pancreaticoduodenectomy. Eur Surg Res. 2011;47:90-7.
43. Sakaguchi T, Suzuki A, Unno N, et al. Bile leak test by indocyanine green fluorescence images after hepatectomy. Am J Surg. 2010;200:e19-23.
44. Chan JYW, Wong STS, Wei WI. Real time indocyanin green near infrared lymphangiography for the reduction of drainage volume after neck dissection. Oral Oncol. 2018;78:52-55.
45. Kitai T, Inomoto T, Miwa M, Shikayama T. Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. Breast Cancer. 2005;12:211-5.
46. Murawa D, Hirche C, Dresel S, Hünerbein M. Sentinel lymph node biopsy in breast cancer guided by indocyanine green fluorescence. Br J Surg. 2009;96:1289-94.
47. Sugie T, Kassim KA, Takeuchi M, et al. A novel method for sentinel lymph node biopsy by indocyanine green fluorescence technique in breast cancer. Cancers (Basel). 2010;2:713-20.
48. Bates AS, Patel VR. Applications of indocyanine green in robotic urology. J Robot Surg. 2016;10:357-9.
49. Jayakumaran J, Pavlovic Z, Fuhrich D, Wiercinski K, Buffington C, Caceres A. Robotic single-site endometriosis resection using near-infrared fluorescence imaging with indocyanine green: a prospective case series and review of literature. J Robot Surg. 2020;14:145-54.
50. Bäumler W, Abels C, Karrer S, et al. Photo-oxidative killing of human colonic cancer cells using indocyanine green and infrared light. Br J Cancer. 1999;80:360-3.
51. Yaseen MA, Yu J, Jung B, Wong MS, Anvari B. Biodistribution of encapsulated indocyanine green in healthy mice. Mol Pharm. 2009;6:1321-32.
52. Sheng D, Liu T, Deng L, et al. Perfluorooctyl bromide & indocyanine green co-loaded nanoliposomes for enhanced multimodal imaging-guided phototherapy. Biomaterials. 2018;165:1-13.
53. Yu J, Javier D, Yaseen MA, et al. Self-assembly synthesis, tumor cell targeting, and photothermal capabilities of antibody-coated indocyanine green nanocapsules. J Am Chem Soc. 2010;132:1929-38.
54. Huang S, Fong CI, Xu M, Han B, Yuan Z, Zhao Q. Nano-loaded natural killer cells as carriers of indocyanine green for synergetic cancer immunotherapy and phototherapy. J Innov Opt Health Sci. 2019;12:1941002.
55. Furukawa N, Oi H, Yoshida S, Shigetomi H, Kanayama S, Kobayashi H. The usefulness of photodynamic eye for sentinel lymph node identification in patients with cervical cancer. Tumori. 2010;96:936-40.
56. Crane LM, Themelis G, Buddingh KT, et al. Multispectral real-time fluorescence imaging for intraoperative detection of the sentinel lymph node in gynecologic oncology. J Vis Exp. 2010:2225.
57. Buda A, Dell'Anna T, Vecchione F, Verri D, Di Martino G, Milani R. Near-infrared sentinel lymph node mapping with indocyanine green using the VITOM II ICG exoscope for open surgery for gynecologic malignancies. J Minim Invasive Gynecol. 2016;23:628-32.
58. Cabanas RM. An approach for the treatment of penile carcinoma. Cancer. 1977;39:456-66.
59. Zavagno G, De Salvo GL, Scalco G, et al; GIVOM Trialists. A randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the sentinella/GIVOM trial. Ann Surg. 2008;247:207-13.
60. Somashekhar SP, Kumar CR, Ashwin KR, et al. Can low cost indo cyanine green florescence technique for sentinel lymph node biopsy replace dual dye (radio-colloid & blue dye) technique in early breast cancer: a prospective two arm comparative study. Clin Breast Cancer. 2020;20:e576-e583.
61. Kelder W, Nimura H, Takahashi N, Mitsumori N, van Dam GM, Yanaga K. Sentinel node mapping with indocyanine green (ICG) and infrared ray detection in early gastric cancer: an accurate method that enables a limited lymphadenectomy. Eur J Surg Oncol. 2010;36:552-8.
62. Chao C, Wong SL, Edwards MJ, et al; Sunbelt Melanoma Trial Group. Sentinel lymph node biopsy for head and neck melanomas. Ann Surg Oncol. 2003;10:21-6.
63. Levenback C, Burke TW, Gershenson DM, Morris M, Malpica A, Ross MI. Intraoperative lymphatic mapping for vulvar cancer. Obstet Gynecol. 1994;84:163-7.
64. Lago V, Domingo S. New horizons of sentinel lymph node technique in early ovarian cancer. Am J Obstet Gynecol. 2020;222:94.
65. Kogan L, Matanes E, Wissing M, et al. The added value of sentinel node mapping in endometrial cancer. Gynecol Oncol. 2020;158:84-91.
66. Togami S, Kubo R, Kawamura T, Yanazume S, Kamio M, Kobayashi H. Comparison of lymphatic complications between sentinel node navigation surgery and pelvic lymphadenectomy in patients with cervical cancer. Jpn J Clin Oncol. 2020;50:543-7.
67. Darin MC, Gómez-Hidalgo NR, Westin SN, et al. Role of indocyanine green in sentinel node mapping in gynecologic cancer: is fluorescence imaging the new standard? J Minim Invasive Gynecol. 2016;23:186-93.
68. Papadia A, Gasparri ML, Buda A, Mueller MD. Sentinel lymph node mapping in endometrial cancer: comparison of fluorescence dye with traditional radiocolloid and blue. J Cancer Res Clin Oncol. 2017;143:2039-48.
69. Nguyen JMV, Bouchard-Fortier G, Hogen LF, et al. The use of indocyanine green fluorescence angiography for colorectal anastomoses in cytoreductive surgery for ovarian carcinoma. Gynecol. Oncol. 2019;154:Suppl 1:134-5.
70. Knabben L, Imboden S, Fellmann B, Nirgianakis K, Kuhn A, Mueller MD. Urinary tract endometriosis in patients with deep infiltrating endometriosis: prevalence, symptoms, management, and proposal for a new clinical classification. Fertil Steril. 2015;103:147-52.
71. Taylor E, Williams C. Surgical treatment of endometriosis: location and patterns of disease at reoperation. Fertil Steril. 2010;93:57-61.
72. Guo SW. Recurrence of endometriosis and its control. Hum Reprod Update. 2009;15:441-61.
73. Asante A, Taylor RN. Endometriosis: the role of neuroangiogenesis. Annu Rev Physiol. 2011;73:163-82.
74. Siegenthaler F, Knabben L, Mohr S, Nirgianakis K, Imboden S, Mueller MD. What is the future of indocyanine green and near-infrared imaging in the surgical management of endometriosis? Acta Obstet Gynecol Scand. 2020;99:1419-20.
75. Siegenthaler F, Knabben L, Mohr S, Nirgianakis K, Imboden S, Mueller MD. Visualization of endometriosis with laparoscopy and near-infrared optics with indocyanine green. Acta Obstet Gynecol Scand. 2020;99:591-7.
76. Maheux-Lacroix S, Belanger M, Pinard L, Lemyre M, Laberge P, Boutin A. Diagnostic accuracy of intraoperative tools for detecting endometriosis: a systematic review and meta-analysis. J Minim Invasive Gynecol. 2020;27:433-40.e1.

Conflict of interest: *The author(s) declare(s) that there is no conflict of interest*