

Indocyanine green in deep infiltrating endometriosis: a preliminary feasibility study to examine vascularization after rectal shaving

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F&S ICG V5 version

- 1 **Title:** Indocyanine Green in Deep Infiltrating Endometriosis (INDIE): a preliminary feasibility
- 2 study to examine vascularization after rectal shaving

3	Running title: Indocyanine Green in Deep Endometriosis	
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Capsule: Indocyanine Green fluorescent imaging is feasible in endometriosis surgery, and
 may be considered a potential candidate to further enhance patient safety in endometriosis
 bowel surgery.

27 Abstract

28 <u>Objective</u>: To evaluate the feasibility of using Indocyanine Green (ICG) to estimate the 29 vascularization of the resected zone during a laparoscopic rectal shaving.

<u>Design</u>: ICG can highlight blood vascularization when injected intravenously. Actually, there is no relevant, objective, intraoperative method to assess the vascularity of the resected zone during a laparoscopic rectal shaving for deep infiltrating endometriosis (DIE) to prevent fistula. We conducted a registered clinical trial examining the feasibility of the use of ICG to evaluate the bowel vascularization after endometriosis rectal shaving (Institutional Review Board no 2016-002773-35).

36 <u>Setting</u>: Tertiary university hospital.

37 <u>Patients:</u> 21 patients underwent laparoscopic surgery for DIE with a rectal shaving.

38 <u>Intervention(s):</u> Patients undergoing laparoscopic surgery for DIE received ICG intravenously

39 at the end of endometriosis resection.

40 <u>Main Outcome Measure(s)</u>: The main evaluation criteria was the fluorescence degree in the 41 operated rectal area, and in the vaginal suture. We used a visual assessment with a Likert-42 type scale from 0 to 4 (0 = no fluorescence; 4 = very good fluorescence).

<u>Results</u>: No adverse reaction was recorded. Most of the patients (81%) showed very good
fluorescence levels at the rectal shaving area. The protocol did not increase the operating
time. In one patient we changed the surgical strategy making two stitches to bring the rectal

46	muscularis closer together, which improved the degree of fluorescence. There was no case
47	of digestive fistula.
48	Conclusion: ICG fluorescent imaging is feasible in endometriosis surgery, and may be
49	considered as a potential candidate to further enhance patient safety in endometriosis
50	bowel surgery
51	clinical trial registration number: NCT03080558
52 53	Keywords: Deep Infiltrating Endometriosis; fistula; indocyanine green (ICG); rectal shaving
54	
55	Introduction
56	There is no consensus regarding the surgical technique for the treatment of
57	rectovaginal septal endometriosis lesions with rectal muscle infiltration. Three surgical
58	techniques are described: rectal shaving, discoid resection and rectal resection (1). The
59	choice between those three techniques consider the symptomatology of the patient, the
60	size of the lesion, the depth of the rectal involvement but also the risk of complications of
61	this kind of surgery and the morbidity that results from it.
62	The major complication of this type of surgery is rectal or recto-vaginal digestive
63	fistula. The fistula rate varies with the technique. According to a recent multicenter study by
64	Roman et al. (1) on 1135 patients, it would be 1.3% after shaving, 3.6% after discoid

65 resection and 3.9% after rectal resection.

66 One of the main mechanism of this type of complication is probably ischemia (2). 67 New techniques for evaluating tissue vascularization are currently under development. 68 Indocyanine green (ICG) is one of the promising techniques in the evaluation of 69 vascularization of tissue. In a recent meta-analysis of 555 patients in the ICG group it has

shown the usefulness of ICG to decrease the rate of anastomotic leakage in rectal colorectal surgery (3), causing surgical modification attributed to the ICG assessment. In gynecological surgery, after deep rectal shaving there is no objective and relevant method to evaluate vascularization of the surgical site. As after resection, ICG could be a method to evaluate the rectal wall perfusion after deep shaving. We published recently our preliminary results (4) describing our method.

We describe here a prospective single center clinical study. The main objective was to evaluate the feasibility of injecting ICG after resection of a recto vaginal endometriosis nodule by laparoscopic rectal shaving, with or without vaginal resection, using a fluorescence scale. This could allow the estimation of the vascularization of these resection areas, and could possibly modify our surgical strategy and thus reduce the risk of fistula.

81

82 Material and methods

83 This is a prospective, single center, feasibility clinical trial (one-armed therapeutic 84 trial, evaluating ICG out of its marketing authorization) conducted between august 2017 and 85 october 2018. The main objective of this study was to evaluate the feasibility of using ICG as 86 a fluorescent marker in order to estimate, through the degree of fluorescence revealed by 87 an infrared light source, the vascularization of the resected zone during the treatment of a 88 rectovaginal nodule by laparoscopic shaving technique. Secondary objectives were; to 89 evaluate the immediate or delayed tolerance of ICG, to estimate the time added by the 90 protocol over the total operating time, to estimate the vascularization at the serosa and 91 rectal mucosa level, to estimate the vaginal vascularization when a vaginal resection is 92 associated, and finally to study the relationship between poor vascularization and the 93 occurrence of postoperative complications, including postoperative fistula.

94 Inclusion criteria were patients with a deep endometriosis nodule infiltrating the 95 rectovaginal septum, having a surgical indication of rectal shaving by laparoscopy, with or 96 without vaginal resection. The objectives of this study wasn't to describe the characteristics 97 of our population, that's why we didn't describe precisely the TVS, and MRI results for the 98 patients. But all patients had a deep endometriosis nodule, infiltrating the rectovaginal 99 septum, analyzed by both TVS and MRI, done by a expert radiologist, with a bowel 100 involvement at least of the serosa, which are the criteria usually used in clinical practice in 101 our team for the surgical recruitment. All the included patients agreed to participate in the 102 study.

Exclusion criteria were minors, protected adult patients (under guardianship or trusteeship), and patients who refused the protocol. Patients with a known iodine allergy, pregnant or breastfeeding were not included.

106

107 The protocol: A rectal shaving was performed as described previously by our team (5, 6): 108 shaving was performed using the "reverse technique" starting by the lateral and the vaginal 109 parts of the nodule and ending with the rectal area. The nodule was dissected all around the 110 rectal involvement so as to provide essential exposure of the rectal part of the nodule for 111 the most difficult part of the procedure. At the end of the surgery, 0.2 mg/kg of ICG were 112 injected (one vial with 25 mg diluted in 10ml of solvent composed of water and glucose) 113 intravenously. The degree of fluorescence of the rectal wall was then assessed, with the use 114 of the Likert-type scale (video 1). If present, the vaginal suture was also evaluated. Then a 115 transrectal evaluation was performed (a 10 mm trocar was introduced in the anus to 116 evaluate the fluorescence in the rectal mucosa). We used a fluorescence scale based on a

117 Likert scale, with a score from 0 to 4 to evaluate the degree of fluorescence (0= no 118 fluorescence and 4= very good fluorescence) (7) (video 1). In order to improve the 119 objectivity of the results, we have made a double interpretation of the fluorescence. The 120 surgeon gave a score during the operation, and then another surgeon gave another score 121 from the recovered videos. 122 The gas and blue test methods were also used to verify the rectal zone of dissection but for 123 verify vascularization, there were unsufficient tools. 124 The main evaluation criteria was the degree of fluorescence of the shaving area, in the 125 serosa and rectal mucosa, and in the vaginal suture if a vaginal resection was associated. 126 The secondary evaluation criteria were: side effects related to ICG injection, 127 estimation of vascularization of the shaving area and possibly of the vaginal scar depending 128 on the degree of fluorescence, and occurrence of postoperative complications: infectious, 129 hematoma or fistula. Time limit for bowel activity, indication for re-hospitalization or repeat 130 surgery, and duration of hospitalization were registered as well. Duration of the protocol 131 (time between injection and fluorescence visualization), total dose of ICG used (a repeat 132 injection of 0.2mg/kg was possible when needed) were also collected.

<u>Study approval:</u> The study was approved by the French Ethic committee "Comite de
 Protection des Personnes Sud-Est VI, France", 2016-002773-35. The protocol was registered
 in Clinicaltrials.gov (NCT03080558).

136 Statistical method

137 Considering this study as pilot aiming to evaluate the feasibility, the sample size justification 138 was determined sequentially, after analyses every each 5 included patients. More precisely, 139 the sample size estimation was fixed according to Fleming's multi-stage design, which 140 includes only one group and between 1 and 5 multi-stages in order to provide filtering steps 141 leading to a go/no go decision. According to the recruitment capacity and feasibility, it was 142 decided to consider 3 steps, with the following assumptions: lower boundary of 50% 143 (maximum inefficacy) and an upper boundary of 80% (minimum efficacy defined as 144 fluorescence levels very good). The type I error and statistical power were fixed, respectively 145 to 5% and 90%. The following decision rules were determined according to Fleming's sample 146 size calculation: with 10 patients included at the end of the first stage, treatment was 147 considered not efficient if 4 or less patients reported a fluorescence levels very good, and 148 efficient if 10 or more fluorescence levels very good were observed. In the event of 5 to 9 149 responses being observed, 10 additional patients would be needed. At the second step, 150 treatment was considered not efficient if 12 (/20) or less patients reported a fluorescence 151 levels very good, and efficient if 16 (/20) or more fluorescence levels very good were 152 observed. In the event of 13 to 15 responses being observed, 10 additional patients would 153 be needed, for a definitive conclusions at 21 patients (/30). With 17 fluorescence levels very 154 good for 21 patients (two patients were included at the same time), the study could be 155 stopped according to Fleming's calculation.

The statistical analysis was performed using Stata software (version 13, StataCorp, College Station). As this study can be seen exploratory, the statistical analyses were principally descriptive. The continuous data were expressed as mean ± standard deviation (SD) or as median [interquartile range] according to the statistical distribution. Assumption of

normality was assessed with the Shapiro-Wilk test. No other inferential statistical test wasperformed

162 **Results**

163 A total of 23 were recruited for an endometriosis surgery with a rectal shaving, 21 patients 164 underwent endometriosis rectovaginal node resection with the shaving technique, and 2 165 patients were finally excluded because underwent a rectal resection at the end (Figure 1, 166 Flow-chart). Patient characteristics are presented in Table 1. All had preoperative imaging 167 with ultra-sound evaluation, and were additionally evaluated by MRI. For 81% of patients, 168 the muscularis was involved. At the end of the surgery, the time lag between ICG injection to 169 visual detection was 60 seconds (45 to 60). The fluorescence degree of the rectal serosa was: 170 II, III, IV in 1 (4.8%), 3 (14.3%), and 17 (81.0%) patients respectively. The values upon second 171 reading were equal. Fluorescence degree of rectal mucosa was III in 1 (4.8%) patient, IV in 12 172 (57.1%), and not evaluated in 8 (38.1%). On second reading all 13 patients were evaluated as 173 IV (100%). A total of 15 patients (71,4%) had vaginal resection. In the presence of a palpable 174 nodule during vaginal examination, preferably a full-thickness excision of the vaginal wall 175 was performed. The vaginal defect was sutured most of the time by laparoscopy, or by 176 vaginal approach, depending on the defect localization. The vaginal fluorescence degree on 177 the first reading was 0, I, II, III, IV in 3 (14.3%), 2 (9.5%), 3 (14.3%), 2 (9,5%) and 4 (19.0%) 178 patients respectively (in one patient the assessment was not done); on the second reading 0, 179 4 (19.0%), 3 (14.3%), 5 (23.8%) and 1 (4,8%) patients respectively (**supplemental figure 1**). 180 The total dose of ICG injected was 12 mg [10 to 15] with no related adverse reactions. 181 Operation time was 240 min [180 to 254] and the time added by the protocol over the total 182 operating time was evaluated at 5 min.

183 Bowel activity recovery occurred on post-operative day one in 16 (84.2%) patients.

184 Minor complications were post-operative fever (3), lab test with inflammation (3), vaginal 185 disunion (7), hematoma (3), vaginal suture abscess (2). 7 patients were readmitted within 30 186 days: 6 with fever and 1 with active bleeding. One patient had a surgical reoperation a few 187 weeks after the initial surgery, for abnormal vaginal bleeding, with hemorrhagic shock. The 188 patient was reoperated for vaginal bleeding, near to the vaginal suture. A pelvic CT scan was 189 realized, and showed also the presence of an aneurysm of the uterine artery, near the 190 vaginal suture. The aneurysm was radiology embolized, and the post treatment course was 191 after uneventfull.

The follow-up duration was at least 3 months for all patients. No patient had a postoperative fistula. One patient, with rectal serosa fluorescence intra-operatively evaluated as I, had a surgical strategy modification: the surgeon added two stitches, to approximate the serosa and muscularis layer of the rectal wall, resulting in improved fluorescence (degree IV after the suture) **(figure 2).** Before this suture, the surgeon did the Blue test, and the gas test. Both were negative, and only the ICG fluorescence allowed us to identify the serosa defect.

199

200 Discussion

201 ICG is a molecule that fluoresces in contact with infrared light. During an intravenous 202 injection, in a few seconds, it can easily highlight blood vascularization. Historically used for 203 the study of cardiac output, the detection of choroidal vascularization and the measurement 204 of liver function, its use has been recently developed in digestive surgery to estimate the 205 vascularization of colorectal anastomoses (4).

207 Rectovaginal node excision for deep infiltrating endometriosis is a complex surgical 208 procedure. The recommended surgical technique is still controversial in the literature. A 209 recent review comparing rectal shaving, disc excision and bowel resection found a higher 210 rate of complications in bowel resection; mainly rectovaginal fistulas, anastomotic leakage, 211 delayed hemorrhage, and long term bladder catheterization (8). Specifically the rates for 212 rectovaginal fistula for rectovaginal node shaving, disc excision and bowel resection were up 213 to 2.3%, 11.6% and 18.1%, respectively. These higher rates as compared to a previously 214 mentioned study (1) with fistula rates of 1.3%, 3.6% and 3.9% respectively, are attributed 215 mainly to the lower level of rectal endometriosis involvement correlated with higher 216 complication rates. Additionally, with the demonstrated feasibility of rectovaginal shaving 217 technique in the vast majority of cases, better functional outcomes and equal rates of 218 recurrence, the authors concluded that rectovaginal shaving should be the first-line choice of 219 surgical treatment, keeping the alternative techniques for the situations in which the results 220 are unsatisfactory. Anyway, a randomized controlled trial is the only way to get good 221 answers on complication rates. However, to this date there is no intraoperative tool to 222 objectively assess the surgical result of endometriosis bowel surgery. In our center, we try as 223 much as possible to perform a deep rectal shaving, because of low rates of post-operative 224 complications. The patients are always informed before surgery about the risks of digestive 225 resection, or even transient colostomy. Intraoperative estimation of the rectal residual 226 vascularization after shaving is difficult, while this seems to be a good indicator of the risk of 227 postoperative fistula (2). We have reported (4) ICG (pilot study) to intraoperatively evaluate the vascular perfusion of the bowel after rectal shaving. Our series supports the evidence in 228 229 the literature for a high safety profile of ICG use, with no related adverse reactions

registered. The high level evidence that in colorectal surgery ICG use reduces rates of anastomotic leaks (2, 3, 9), with intraoperative assessment causing change of surgical plan in 8-13% of patients, supports its use to evaluate bowel perfusion intraoperatively.

233 Fistula is a rare complication of rectovaginal node shaving as mentioned above, and 234 presumably, fistula formation pathogenesis is of vascular impairment origin. ICG use for 235 perfusion assessment has the potential to increase the diagnosis of impaired vascularization, 236 and so to reduce fistula rates. This study has shown ICG as a feasible tool for intraoperative 237 objective evaluation of bowel perfusion after rectovaginal node shaving. For all the patients 238 included, , we also tried gas method or blue test method to verify the rectal zone of 239 dissection, as we always do in this shaving technique at the end of the dissection. In our 240 point of view, the gas and blue test methods are effective tools to identify microperforation 241 and real perforation, but not really for unsufficient vascularization, so those two methods 242 have different objectives, and are more complementary than comparable. With the IV 243 injection of ICG, the detection of fluorescence from injection was rapid and convenient 244 (average 60 seconds), and the protocol did not interfere severely with the operation time 245 (adding 5 minutes on average). Other strengths of our study is that it is prospective, reducing 246 selection bias. We have also demonstrated the feasibility of rectal mucosa perfusion 247 assessment technique, which is done with proctoscopy in the colorectal surgery studies 248 assessing anastomosis sites. The subjective evaluation of the fluorescence is a limitation in 249 our study. We tried to manage that by having 2 independent evaluations that showed good 250 correlation (correlation coefficient at 0,82 (p<0.001) which is good and relevant).

In the digestive surgery literature, subjective fluorescence analysis has been used as well, and proved to be of clinical benefit. However, even if the evaluation remains really

253 subjective, there is good correlations between evaluation and clinical events. Future studies 254 might incorporate objective evaluation systems. One promising tool is discrimination 255 between arterial and venous bowel ischemia by computer-assisted analysis of the 256 fluorescent signal (intensity and time to maximum fluorescence) (7). Our small sample size is 257 a limitation, with no power to show rare fistula events. However, ICG has led to modify the 258 surgical plan in our series in one case (placing a protective suture on the serosa) showing a 259 potential surgical impact. The benefits of the technique are not already proven, but this 260 study made us think about our surgical habits.

261

262 Recently, there is a rise in reports of IV injection of ICG use in endometriosis surgery, 263 exercising different strategies. In this study we used ICG to evaluate the perfusion of the 264 rectal area after the rectovaginal node shaving procedure, aiming to reduce fistula rate. 265 Another report of ICG use was in a case with recto-sigmoid resection of endometriosis: ICG 266 was injected IV prior to the resection, perfusion assessment helped selecting the transecting 267 line, and after resection ICG was used to assess the anastomosis site (11). A pilot study using 268 ICG to detect occult endometriosis lesions was published. The authors showed the 269 possibility to mark the hyper vascularization of the chronic inflamed lesions (12). In their 270 study of 27 patients, a total of 100 lesions were identified and resected in white light, 271 followed by 16 new lesions (histologically confirmed for endometriosis) in near infrared light. 272 In another series of 5 patients undergoing shaving procedure (13), ICG marked the 273 rectovaginal node. In one patient after the node removal, the posterior vaginal fornix still 274 appeared fluorescent even though no lesion was palpated and was removed, potentially 275 helping achieve a more complete excision of endometriosis (histologic confirmation was not

276 mentioned). All of those reports lead to the interest of using ICG in endometriosis surgery,277 and larger studies are called for better evidence.

278 One of the weaknesses of our study is the important rate of post-operative vaginal disunion. 279 The possible explanation of the high frequency of the vaginal disunion is that most of the 280 time the objectives of the vaginal suture is hemostatic, so induce necessarily low 281 vascularization. Most of the time, during the post-operative period those vaginal disunion 282 are not really symptomatic, and not major complications. Furthermore, for an experimental 283 studie during lots of cases we also analyzed the vascularization directly through the vagina 284 after the suture, and conversely to the pelvic analyses the fluorescence was mostly really 285 satisfying, so we don't really know which size of the suture can be predictive of the healing 286 quality, and these reports lead to the interest of further studies on this subject.

287

288

289 **Conclusion**

290 Endometriosis bowel surgery complications are at the frontier of endometriosis treatment 291 dilemmas. We cannot conclude from this study that rectovaginal fistula rates are reduced 292 with ICG use after RectoVaginal Nodule shaving, but we propose that with a rare-event 293 complication as rectovaginal fistula, a specific technique is needed to decrease this rate. 294 Given the evidence known in colorectal surgery studies as mentioned, and the report of this 295 study on the specific use of ICG for bowel evaluation in endometriosis surgery, ICG should be 296 considered a potential candidate to further enhance patient safety in endometriosis bowel 297 surgery.

298

299 Funding

302 Conflicts of interest

303 The authors report no conflict of interest

304

305 Contribution to Authorship

306 NB, LJ, BP, MC, PC: conception and design of the study, performed the surgical procedures

307 NB, LJ, AC, BSY, BP, MC, PC: acquisition of data, analysis and interpretation of data, drafting

- 308 the article
- 309 NB, LJ, BSY, MC, PC: final approval of the version to be submitted
- 310
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Figures captions:

- 362 Video 1: ICG fluorescence: Time lag between injection to visual detection and the degree of
- 363 fluorescence with the use of the Likert-type scale
- 364 Figure 1: Flow-chart
- 365 Table 1: Patients characteristics
- 366 Supplemental figure 1: Illustration of fluorescence at the rectal mucosa (left) and of the
- 367 vaginal scar (right), A: rectal mucosa (white light); B: rectal mucosa (ICG); C: vaginal scar
- 368 (white light); D: vaginal scar (ICG)
- 369 Figure 2: Patient with modification of the surgical procedure
- A: Before suture (white light). Rectal serosa fragility; B: Before suture (ICG). Rectal serosa
- 371 fluorescence intra-operatively evaluated as I; C: After suture (white light). Rectal shaving
- 372 zone after the add of the two stiches; D: After suture (ICG). Improved fluorescence (degree
- 373 IV)
- 374
- 375

table 1: patients characteristics	n=21
Age (years) (Mean ± SD)	35±6.7
BMI (median. range)	25 [22.7-30.8]
Smoking n (%)	7 (33.3)
Previous surgery n (%)	
Cesarean section	3 (14.2)
Appendicectomy	6 (28.6)
Ectopic pregnancy	1 (4.8)
Laparoscopy	6 (28.6)
Caucasian n (%)	20 (95.2)
Associated endometriosis distribution n (%)	
Ovarian endometrioma	14 (66.7)
Bladder	2 (9.5)
Adenomyosis	8 (38.1)
Preoperative imaging n (%)	
Pelvic ultrasound	21 (100)
X-ray Scan	1 (4.8)
MRI	21 (100)
rectal infiltration (%)	
serosa	100
muscularis	100
submucosa	81.0
mucosa	0.0
lesions involved (%)	
uterosacral ligaments	71.4
rectum	81.0
torus	57.1
rectosigmoid junction	23.8
vagina pouch	57.1
pouch of Douglas	33.3
dimensions of rectovaginal nodule (cm)	
height	2.02±0.7
thickness	1.8±0.9
Time between ICG injection and visual detection sec (median, range)	60 [45-60]
Fluorescence degree of the rectal serosa n (%)	
li li	1 (4.8)
111	3 (14.3)
IV	17 (81.0)
Fluorescence degree of the rectal mucosa n (%)	()
	1 (4.8)
IV	12 (57.1)
not evaluated	8 (38.1)
Fluorescence degree of the vaginal suture (15 patients) n (%)	- (30)
0	3 (20.0)
- 1	2 (13 3)
- 2	3 (20.0)
3	2 (13.3)
- 4	2 (15.5) 2 (26.7)
not evaluated	1 (6 7)
	I (0.7)

Mean dose of ICG injected (mg) (median. range)	12 [10;15]
Operative time (min) (median. range)	240 [180;254]
Duration of protocole (min) (median. range)	5 [5;5]
Transit recovery J1 n (%)	16 (84.2%)
Minor complications n (%)	
post-operative fever	3 (14.3)
biologival inflammatory syndrome	3 (14.3)
vaginal disunion	6 (42.9)
hematoma	3 (14.3)
vaginal suture abscess	2 (9.5)
rehospitalization	7
- fever	6 (28.6)
- bleeding	1 (4.8)
surgical reoperation	1 (4.8)
fistula	0



serosa

