Real three-dimensional approach vs two-dimensional camera with and without real-time near-infrared imaging with indocyanine green for detection of endometriosis: A case-control study

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Real 3D approach vs 2D camera with and without real-time near-infrared imaging with indocyanine green for detection of endometriosis: a case-control study

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Conflicts of Interest

None

ABSTRACT

Introduction: The complete surgical removal of endometriosis lesions is not always feasible because some implants may be very small or hidden. The use of intra-operative near-infrared radiation (NIR) imaging after intravenous injection of indocyanine green (ICG) coupled with robotic technical advances, including tridimensional and high-resolution vision, might improve detection rates. **Material and methods:** This is a retrospective, multicenter case-control study (Canadian Task Force classification II-2) on medical records of women with endometriosis that submitted to surgery at the Catholic University of Rome (controls) and the University of Bologna (Cases) between January, 2016, and March, 2018. Surgical and post-surgical data from the procedures were collected. We compared the visual detection rate of endometriotic lesions using near-infrared radiation imaging after intravenous injection of indocyanine green (NIR-ICG) in Real 3D (Cases) with the 2D Camera approach (Controls) in symptomatic women with pelvic endometriosis. **Results:** Twenty cases were matched as closely as possible with 27 controls. The suspected lesions identified both with the WL and the NIR-ICG approach were 116 and 70 in the

Controls (2D) and Cases (3D), respectively. Among them, 16 of 116 controls (13.8%) and 12 of 70 cases (17.1%) were identified using only NIR-ICG imaging and collected as occult lesions (p=0.536). The overall NIR-ICG lesion identification showed a positive predictive value of 97.8%, negative predictive value of 82.3%, sensitivity of 82.0%, and specificity of 97.9% for the Control group, and a positive predictive value of 100%, negative predictive value of 97.1%, sensitivity of 97.1%, and specificity of 100% for the Cases group, confirming that NIR-ICG imaging is a good diagnostic and screening test (p=0.643 and p=0.791, according to the Cohen kappa tests, respectively for the laparoscopic and robotic groups). **Conclusions:** The few differences observed did not seem to be clinically relevant, thus making the two procedures comparable in terms of the ability to visually detect endometriotic lesions. Further prospective trials are needed to confirm our results.

Keywords

endometriosis; near-infrared radiation; indocyanine green; minimally invasive surgery; endometriosis surgical treatment

Abbreviations:

NIR: near-infrared radiation

ICG: intravenous injection of indocyanine green

NIR-ICG: near-infrared radiation imaging after intravenous injection of indocyanine green

WL: white light

PE peritoneal superficial endometriosis

DIE deep infiltrating endometriosis

Key message

In women affected by advanced endometriosis, the 3D and 2D camera approaches with near-infrared radiation imaging after intravenous injection of indocyanine green have similar visual detection rates of lesions.

INTRODUCTION

The complete surgical removal of endometriosis lesions has been demonstrated to be effective in treating pain and subfertility, particularly in women with mild to moderate endometriosis.[1,2] Minimally invasive surgery is the preferred surgical approach because it is usually associated with less pain, shorter hospital stays and faster recovery, in addition to providing better cosmetic outcomes.[3-6]

Although endoscopy allows for magnification of the operative field, the identification of endometriosis implants is not always possible using white light, because some implants may be very small or hidden ('occult lesion').[7-8] Several authors have emphasized that the persistent growth of endometriotic implants is due to their invasive ability and angiogenic potential.[9] In this context, several studies have demonstrated that the use of intra-operative near-infrared radiation (NIR) imaging after intravenous injection of indocyanine green (ICG) highlights macro and micro-vascular anatomy and tissue perfusion, thereby enhancing the intra-operative visualization of neo-vascularized lesions in several conditions.[10-13] Neo-vascularized lesions usually ellicit a radial or circumferential pattern and consist of an immature and permeable vascular endothelium that permits easy diffusion of ICG in deep lesions.[14,15]

Recently, the Green-Endo trial showed a high rate of accuracy in the identification of endometriotic lesions using NIR-ICG during operative laparoscopy in symptomatic women with pelvic endometriosis.[16] However, intra-operative NIR imaging can be performed utilizing both conventional or robot-assisted laparoscopy. It has been postulated that robotic technical advances, which include tridimensional and high-resolution vision and integrated NIR camera, may provide better visualization of endometriotic foci than conventional laparoscopy, leading to improvements of mid- and long-term surgical outcomes.[17] There have been no studies comparing the diagnostic efficacy of intra-operative NIR-ICG imaging using a 2D or a 3D camera in women with endometriosis, however.

The aim of this study was to compare the detection rates of endometriotic lesions utilizing 3D NIR-ICG(R-NIR-ICG) with a matched group of patients employing 2D NIR-ICG(L-NIR-ICG) in symptomatic women with pelvic endometriosis. In addition, perioperative outcomes between the two groups were compared.

MATERIAL AND METHODS

This is a retrospective case-control study comparing perioperative outcomes of L-NIR-ICG (*Controls*) and R-NIR-ICG (*Cases*) in symptomatic women with pelvic endometriosis. Surgical procedures on the Controls were performed at the Department of Women's and Children's Health, Catholic University of the Sacred Heart, Rome, Italy, between January 2016 and March 2018 and were matched with *Cases*, treated during the same period, at the Department of Obstetrics and Gynecology - S.Orsola Hospital, University of Bologna, Italy (Figure 1).

To mitigate any differences of surgical technique, only women whose surgeons possessed abundant experience with laparoscopic and robotic endometriosis procedures were selected. Specifically, only two surgeons (one from each center) were employed. These surgeons each had an experience of more than 100 endometriotic laparoscopic procedures and had performed more than 50 endometriotic surgeries robotically. In addition, the surgeon of one center was present during the surgery being performed by the other surgeon, in order to ensure the use of the same methodology.

Exclusion criteria included women less than 18 years, and greater than 50 years of age; history of allergy to compounds similar to ICG (e.g., iodides); pregnant or breastfeeding women; women actively participating in another study; and the presence of medical conditions that would preclude general anesthesia or surgery. Prior to surgery, demographic features were collected, and pain symptoms (chronic pelvic pain, dysmenorrhea, dyspareunia, dysuria, dyschezia), were assessed utilizing the visual analogue scale (VAS). The severity of endometriosis was delineated using the intraoperative classification revised by the American Society for Reproductive Medicine (rASRM).[18] Preoperative evaluation included physical examination and standardized imaging (Ultrasound or MRI).

The Olympus ICG Imaging System Prototype (Olympus Winter and Ibe GmbH KuehnstraßeHamburg, Germany) based on the Visera Pro System® (custom camera head, modified light source, and modified camera control unit; Olympus Europa Holding GMBH, Wendenstrasse Hamburg, Germany) and a special laparoscopic lens optimized for infrared transmission used for NIR imaging were employed during surgery on the control group. The specific imaging system used was kindly provided to our institution by Olympus Winter and Ibe GmbH (Kuehnstraße Hamburg, Germany). For the *Cases group*, the Firefly Imaging System,

installed on the da Vinci Xi robotic system (Intuitive Surgical Inc., Sunnyvale, CA, USA), was used.

The ICG used for the intraoperative intravenous injection was ICG Pulsion®, (PULSION Medical Systems SE, Feldkirchen, Germany), routinely used in clinical management.

Surgical Procedure

The abdomen and pelvis were inspected using direct laparoscope/robotic visualization under white light (WL) conditions. Adhesiolysis was then performed, exposing the torus uterinum and the ovarian fossae, followed by freeing up of the bowel from eventual retro-cervical nodule attachment. All suspected areas were classified as either peritoneal superficial endometriosis (PE) or deep infiltrating endometriosis (DIE). All suspected PE was classified as white and black lesions and documented with their associated anatomic location. Suspected DIE lesions were also noted, along with their anatomical location (retro-cervical, vaginal, rectosigmoid, urinary bladder lesions).

After the administration of 0.25 mg/kg ICG intravenously, the NIR imaging was initiated 15-30 minutes later in order to permit washout of ICG and its accumulation in the third space of neovascularized areas (Figure 2 and Figure 3).

All suspected endometriotic lesions (PE and DIE) were tabulated, reporting their aspect during WL and NIR-ICG imaging. In addition, a random control biopsy was obtained from negative peritoneum visualized with WL and NIR- ICG that was at least two cm away from any suspected peritoneal endometriotic lesion. Lesions of the rectosigmoid up to three cm were treated with more conservative techniques, such as shaving and discoid resection. Segmental resection was indicated for rectosigmoid lesions greater than three cm and/or in cases of multiple lesions, lesions that involved more than 40% of the intestinal circumference, and lesions that were deeper than the submucosal layer or were associated with bowel obstruction.

Surgical data

In both groups operative time, estimated blood loss, necessity for blood transfusion, length of hospital stay, American Society of Anaesthesiologists (ASA) score, the number and type of surgical procedures, and peri-operative complications were assessed.. The perioperative complications were classified according to the Dindo-Clavien classification system as minor (grades I–II) or major (grades IIIA and IIIB–IV).[19]

Pathology

We identified a "pathologic" lesion as a site of florid endometriosis or a site of related chronic inflammation according to histopathologic criteria defined elsewhere.[20,21] The criteria for interpreting the histological findings were agreed upon prior to surgery. However, all cases were discussed jointly at the end of the study.

Statistical analyses

Randomization was not employed in this study. The surgical approach utilized depended on the availability of the surgeon and/or the operating room with robot. Because of the nonrandomized nature of the study design and the possible allocation biases arising from the retrospective comparison between groups, we performed a propensity-matched analysis. Propensity-matched comparison attempts to estimate the effect of a treatment by accounting for possible factors (e.g., constitutional variables) that predict receiving the treatment. Propensity-matched comparison aims to reduce biases arising from different covariates. A propensity score was developed through a multivariable logistic regression model.

Age, body mass index, pre-operative symptoms and stage of disease were included in the model. To maximize the power of the study, women undergoing robotic surgery were matched 1:1.3 with controls undergoing laparoscopic surgery using a caliper width ≤ 0.1 standard deviations of the logit odds of the estimated propensity score. A detailed description of propensity matching is described elsewhere.[22,23]

WL has been the gold standard imaging technique for detecting endometriosis. The statistical method for scoring each laparoscopic/robotic feature has been previously described.[16] Sensitivity, specificity, and accuracy were compared using the McNemar test and Cohen's kappa. The diagnostic performances of WL and NIR-ICG were calculated per patient, as well as per lesion. Univariate analysis was performed to verify any difference between the two groups. Univariate analysis included χ^2 analysis or Fisher's exact test when appropriate for categorical variables and the Student t test and Mann-Whitney test when appropriate for continuous variables. Differences between the groups were considered statistically significant at $p < 0.05$ (95% confidence interval). The NCSS statistical software program, version 11.0 (NCSS Statistical Software, Kaysville, UT, USA), was used.

Ethical approval

The study was approved by Institutional Review Board (Protocol Number: CICOG-31-10-18/181).

RESULTS

No statistically significant differences were observed between cases and controls preoperatively, as shown in Table 1. All women were clinically stage III/IV according to the revised American Society for Reproductive Medicine and underwent NIR-ICG both robotically or laparoscopically according to described technique.[16] Perioperative outcomes are shown in Table 2. No differences were noted in terms of estimated blood loss. A higher percentage of resection of retrocervical/vaginal and uterosacral ligament nodules in the laparoscopic group with respect to robotic group was observed. Conversely, a significant higher discoid resection was performed in the Cases group than in the Controls. The operative time, calculated from the beginning of the intraperitoneal procedure to skin closure, did not differ between groups.

Intra- and postoperative complications were evaluated in all women. No procedures required conversion to laparotomy. No differences in postoperative complications were observed between the two groups (Table 2). In the early postoperative period (<30 days), only two (4.2%) major complications were observed, one in each group: one woman (5.0%) experienced intestinal stenosis requiring mechanical dilatation after discoid excision in the *Cases* group, and the other woman (*Controls* group) showed vaginal dehiscence that required post-operative resuturing. Minor post-operative complications consisted of one urinary tract infection in the *Cases* group and two in the *Controls* group, (Table 2). The median time to discharge from the hospital was postoperative day four in the Cases group (range, 3–5) and postoperative day three (range,3–4) in the Controls group (p=0.08) (Table 2).

The NIR-ICG procedures were successfully performed in all women. The suspected lesions identified with both methods (WL and NIR-ICG) were 116 in the Controls group (2D) and 70 in the Cases group (3D) (Table 3). Among them, 16 of 116 controls (13.8%) and 12 of 70 cases (17.1%) were identified utilizing only NIR-ICG imaging and collected as occult endometriotic lesions (p=0.536). As neo-vascularized tissue, the occult lesions were identified as DIE only in the Controls group, whereas, in the robotic cases, more than half of them (7 of 12) were identified as

peritoneal white lesions (Table 3). The clinical impact of the removal of occult endometriosis, especially of superficial lesions, could not be evaluated.

Considering NIR-ICG imaging only, 93 laparoscopic and 68 robotic suspected lesions were identified. Of these, 97.8% (91/93) and 100% had pathologic confirmation (true positive) in the Control and in the Case group, respectively (p=0.223). However, among 100 and 58 suspected lesions for endometriosis found with WL imaging by laparoscopy and robot respectively, 20 of 100 (20%) and 2 of 58 (3.4%) lesions confirmed at pathology were not visualized with NIR-ICG imaging (p=0.003). The overall NIR-ICG lesion identification showed positive predictive value of 97.8%, negative predictive value of 82.3%, a sensitivity of 82.0%, and a specificity of 97.9% for the Control group (Table 3). In the Cases group, a positive predictive value of 100%, negative predictive value of 97.1%, sensitivity of 97.1%, and specificity of 100% were observed, confirming NIR-ICG imaging as a good diagnostic and screening test (p=0.643 and p=0.791, according to the Cohen kappa tests, respectively for laparoscopic and robotic group).

McNemar test revealed that although the NIR-ICG imaging failed with respect to WL at the peritoneal lesions in the Controls group, it was more effective at the level of DIE (i.e.: detecting eight occult Periureteral/Ovarian lesions) and for the white lesion, in the control and case group, respectively (Table 3, Supporting Information Table S1).

DISCUSSION

The goal of surgery in women suffering from endometriosis, regardless of the approach, is the removal of endometriotic foci in order to eliminate disease and its associated symptoms, as well as to prevent recurrence that occurs in 20% to 50% of women at two and five years, respectively.[24,25] The use of NIR-ICG imaging technology associated with a 2D or 3D approach was of value in identifying "occult" endometriosis.[16,26]

Only a few studies performed with small case series have been published that describe the potential benefits of NIR-ICG imaging in the visual detection of peritoneal and deep endometriosis during laparoscopic/robotic resection.[16,26,27] Furthermore, a recently published case series proposed the novel concept of employing indocyanine-green fluorescent-guided surgery in the removal of rectovaginal endometriosis in those patients with DIE, allowing for the preservation of healthy tissue.[24] To our knowledge, ours is the first case-control study comparing the visual detection rate of 3D vs. 2D NIR-ICG in women suffering advanced endometriosis.

The data show that utilizing the NIR-ICG scope enabled visual identification of a greater number of lesions, as well as of histologically confirmed endometriosis lesions, compared with the conventional WL technique, in the hands of experienced gynecologic surgeons. However, the employment of NIR-ICG vision alone did not identify 20% and 3.4%, respectively, of pathological lesions using a 2D and 3D camera. This result suggests that the NIR-ICG vision technique cannot replace WL vision, especially with a 2D camera, but, instead, could be a valid tool to complement the standard vision technique, in order to better identify and eradicate otherwise unseen endometriosis.

All suspected occult lesions were confirmed by pathological exam after removal. Although laparoscopy and histologic examination remain the gold standard of diagnosis for endometriosis, the NIR-ICG technology has proven to be a valid tool which facilitates the intra-operative recognition of endometriotic lesions, as demonstrated by the statistical test performed in comparison with WL ($p = 0.617$ and $p = 0.643$ according to the McNemar and Cohen kappa tests respectively for Controls, $p = 0.157$ and $p = 0.791$ according to the McNemar and Cohen kappa tests respectively for Cases, Table 3).

Moreover, our findings suggest that some endometriotic lesions are more challenging to visualize and resect using the standard scope technique. A higher discrepancy was observed in the control group between the use of NIR-ICG vision and WL vision in regards to periureteral/ovarian lesions, where the sensitivities enhanced from 38.4% to 92.3%, respectively (data not shown). In the Cases group, on the other hand, the main difference between the two video-systems was demonstrated for white superficial lesions, where the sensitivities improved from 50.0% to 100% (Table S1). In the future, the use of NIR-ICG vision, regardless of endoscopic approach, might allow the complete excision of endometriotic lesions without compromising surrounding healthy tissue, in addition to avoiding damage to ovaries and ureters, thus preventing infertility and urologic dysfunction.

The limitations of the present study include i) the retrospective nature of the study, ii) the higher percentage (~90%) of advanced endometriosis (stages III and IV according to the revised American Society for Reproductive Medicine criteria), iii) different vision technologies employed in the two groups, iv) the use of two different institutions with their respective surgeons performing either all of the Control patients or all of the Cases.

Although the retrospective nature of this study could be a weakness, the standardization of the pre-operative selection of women, the surgical strategies employed, and the post-operative

management of patients added conformity to this study. Both hospitals are referral centers for the treatment of women with advanced stages of endometriosis. Nevertheless, enrollment of women with advanced endometriosis did not exclude the need for the use of NIR-ICG, in order to identify occult lesions.

Although it has been reported by some authors that the use of the 3D surgical scope improves depth perception and enhances intra-operative visualization of lesions compared with the use of the conventional 2D scope, there have been no large scale or long-term studies published to support these findings. [17,28,29] While the future availability of new technologies, such as the new platform of the Da Vinci-SP Robot (Intuitive Surgical, Sunnyvale, CA, USA), the new generation of the 3-dimensional high-definition laparoscopic vision system,[28] and further refinement of articulated instruments, might lead to better surgical outcomes, it will be increasingly difficult to highlight any slight difference between 2D and 3D NIR-ICG.

CONCLUSION

Although the role of NIR-ICG in endometriosis remains to be definitively established, compelling data from retrospective and prospective series support its role in this clinical setting as a confirmatory diagnostic test for endometriosis, for both the 2D and 3D approach.
Larger prospective studies, such as the Gre-Endo 2 study, just beginning in our institutions for this purpose, are warranted in order to validate and confirm these encouraging preliminary results.

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Legends to Tables and figures:

Table 1. Baseline characteristics.

Table 2. Surgical Procedures and Intraoperative data.

Table 3. Comparison between the two different surgical near-infrared radiation imaging after intravenous injection of indocyanine green (NIR-ICG) approaches (robotic vs. laparoscopic).

Figure 1. Study design and selection process

Figure 2. The laparoscopic operating field shown in (A) WL imaging and in (B) NIR-ICG imaging.

Figure 3. The robotic operating field shown in (A) WL imaging and in (B) NIR-ICG imaging

Supporting information legend

Table S1. Comparison between the two different surgical NIR-ICG approaches (robotic vs. laparoscopic) for each surgical site.

Table 1. Baseline characteristics.

Variables	Total (N, %)	Cases (n, %)	Controls (n,%)	p value
All cases	47 (100)	20 (43.0)	27 (57.0)	
Age, y (range)	37 (31-42)	37 (31 - 42)	37 (31 – 42)	0.906
Body mass index (range)	19 (19 - 24)	21 (19 - 22)	22 (21 - 24)	0.121
Previous delivery	16 (34.0)	6 (30.0)	10 (37.0)	0.758
Prior surgery for endometriosis	18 (38.3)	6 (30.0)	12 (44.4)	0.374
Pre-Operative Symptoms (median VAS)(range)				
Dysmenorrhea	8 (8-10)	8 (8-10)	9 (8-10)	0.650
Dyschezia	7 (6-8)	7 (6-8)	7 (7-8)	0.896
Dysuria	8 (7-10)	8 (7-10)	8 (7-10)	0.857
Dyspaurenia	7 (6-8)	6 (5-7)	7 (5-8)	0.347
Chronic pelvic pain	7 (5-8)	4 (3-6)	7 (5-8)	0.277
Stage[a]				
Stage I (minimal)	0	0	0	-
Stage II (mild)	6 (13)	3 (15)	3 (11)	0.693
Stage III (moderate)	16 (34)	6 (30)	10 (37)	0.758
Stage IV (severe)	25 (47)	11 (55)	14 (52)	0.831

[a]According to American Society for Reproductive Medicine (rASRM) [18]

VAS: Visual analogue scale

Table 2. Surgical Procedures and Intraoperative data.

Surgical procedure	TOTAL (n,%)	Cases (n,%)	Controls (n,%)	p value
Ovarian cysts removal	20 (42.6)	9 (45.0)	11 (40.7)	0.770
Peritoneal removal	26 (55.3)	14 (70.0)	12 (44.4)	0.137
Retrocervical nodule removal	26 (55.3)	5 (25.0)	21 (77.8)	0.0001
Vaginal nodule removal	10 (21.3)	1 (5.0)	9 (33.3)	0.019
Utero-sacral ligament nodule removal	21 (44.7)	3 (15.0)	18 (66.7)	0.0001
Rectal nodule shaving	11 (23.4)	6 (30.0)	5 (18.5)	0.358
Resection and anastomosis of sigma-rectum	6 (12.8)	2 (10.0)	4 (14.8)	0.625
Resection and anastomosis of sigma-rectum plus loop ileostomy	6 (12.8)	4 (20.0)	2 (7.4)	0.201
Discoid resection of bowel	4 (8.5)	4 (20.0)	0	0.015
Other procedures (appendicectomy, salpingectomy, ureteral stent placement, bladder surgery)	16 (34.0)	8 (40.0)	8 (29.6)	0.541
Estimated blood loss (mL)[a]	100 (50-250)	125 (50-250)	100 (50-225)	0.595
Operative Time (min)[a]	150 (118-185)	170 (140-208)	146 (118-196)	0.051
Intraoperative complications	0	0	0	-
Conversion to laparotomy	0	0	0	-
Minor post-operative complications[b]	3 (6.3)	1 (5.0)	2 (11.1)	0.738
Major post-operative complications[b]	2 (4.2)	1 (5.0)	1 (3.7)	0.827

Hospital Stay(#day)[a]	4 (3-4)	4 (3-5)	3 (3-4)	0.08

Variable	Surgical approach	WL visualization	NIR-IGC visualization	Overall visualization[a]	NIR-IGC Sensitivity (%)	NIR-IGC Specificity (%)	McNemar Test	Cohen's kappa	C-OcL[b]
Peritoneal Lesion	***Cases***	27	32	34	94.1	100	0.179	0.858	7
	Controls	20	7	20	41.2	100	0.003	0.609	0
Deep Infiltrating Lesion	***Cases***	31	36	36	100	100	0.062	0.928	5
	Controls	80	86	86	89.4	97.7	0.361	0.832	16
Overall	***Cases***	58	68	70	97.1	100	0.157	0.791	12
	Controls	100	93	116	82.0	97.9	0.617	0.643	16

[a]Data are shown as median and interquartile ranges (25–75)

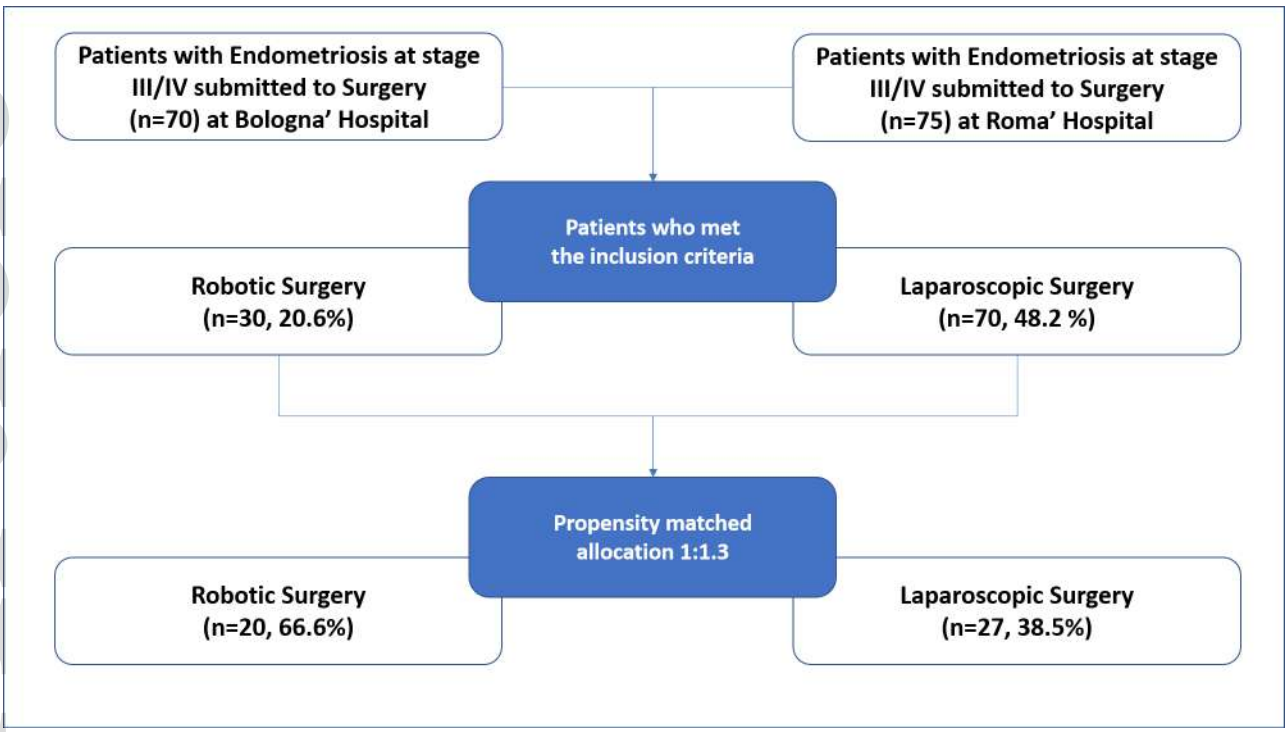
[b]According to Dindo-Clavien classification.[19]

Table 3. Comparison between the two different surgical near-infrared radiation imaging after intravenous injection of indocyanine green (NIR-ICG) approaches (robotic vs. laparoscopic).

WL, white light.

[a]Overall visualizations= all the lesions visualized with the combination of WL and NIR-ICG

[b]C-OcL= confirmed pathologic lesion resected trough NIR-IGC not observed in WL



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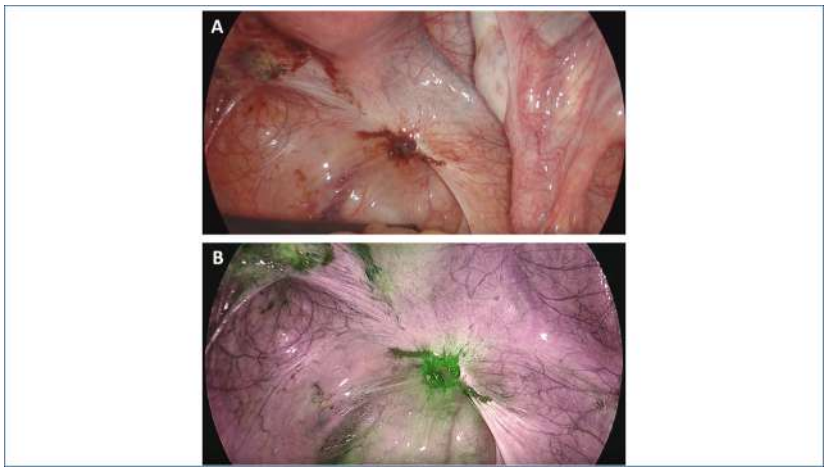

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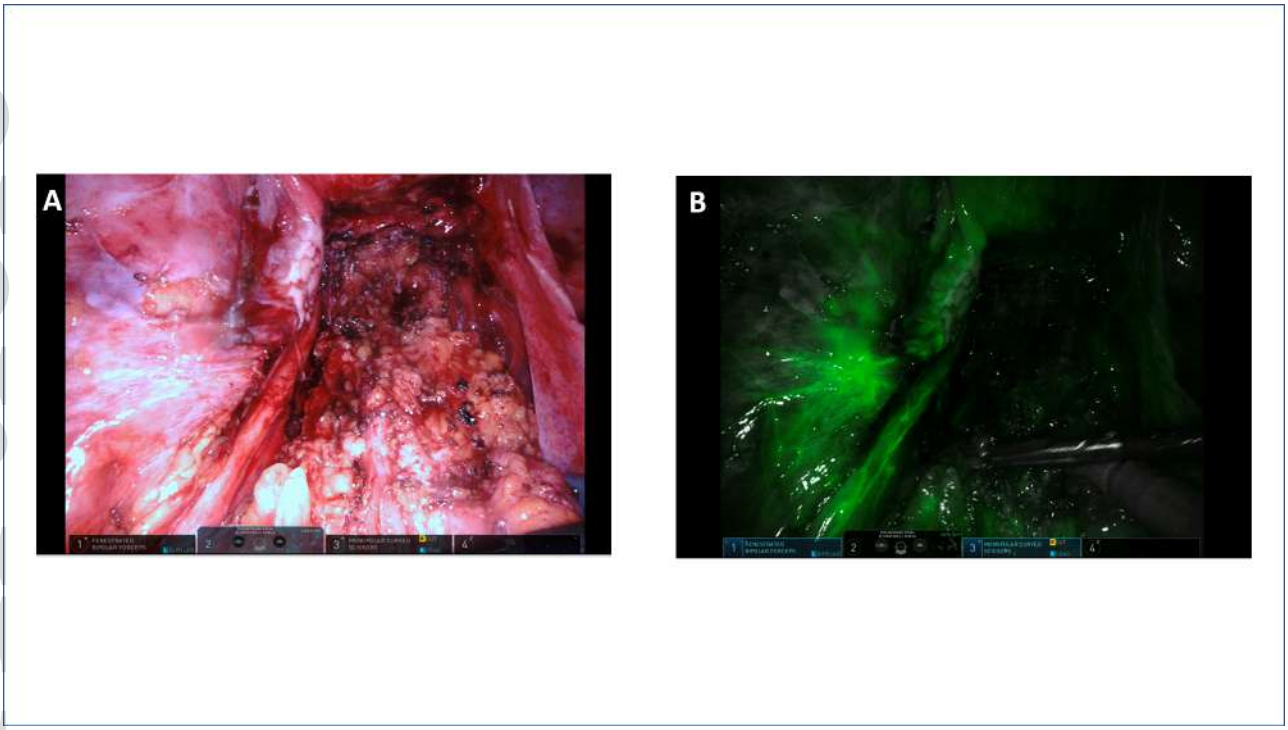

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