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A New Vision in Endometriosis Surgery: The Impact of Near-Infrared Indocyanine Green Fluorescence Imaging

Mohamed Mabrouk[1*], Rami Saad[1], Sherif Mahgoub[2], Arvin Vashisht[1], Saikat Banerjee[2]

[1]University College London Hospitals.
[2] Cambridge University Hospitals.

Prof. Mohamed Mabrouk is a Consultant gynecologist and endometriosis surgeon at the University College of London Hospitals (UCLH), London, UK, Consultant gynecologist and endometriosis specialist at the Cleveland Clinic London (CCL), Director of Cambridge EndoCare Endometriosis Centre at the Spire Lea Hospital, Cambridge, UK, Adjunct Professor of Gynaecology at the University of Southern Denmark, Odense, Demark, Professor of Obstetrics and Gynaecology at Alexandria University, Egypt and Member of the Advisory Board of the European Endometriosis League (EEL)

Abstract

Background: Endometriosis, a chronic disease affects a substantial number of women worldwide and frequently necessitates surgery. The limitations of traditional laparoscopy, primarily due to the reliance on white-light imaging, might result in incomplete resection of lesions. NIR-ICG fluorescence imaging emerges as a significant innovation, offering improved visualization of endometriotic lesions and surrounding tissues.

Objective: This review evaluates the application and effectiveness of Near-Infrared Indocyanine Green (NIR-ICG) fluorescence imaging in the surgical management of endometriosis, with an emphasis on its utility in enhancing the visualization of critical anatomical structures.

Methods: This review collates data from a variety of studies that have employed NIR-ICG fluorescence imaging in endometriosis surgeries. It details the chemical properties and mechanisms of NIR-ICG, its application in enhancing lesion detection and resection, and its specific roles in visualizing ureters, facilitating nerve-sparing techniques, and ensuring the integrity of bowel surgery.

Results: NIR-ICG fluorescence imaging significantly enhances the visualization of deep infiltrating endometriotic lesions and other critical pelvic structures, thereby reducing the risk of intraoperative injuries. It facilitates more precise lesion excision, aids in preserving essential anatomical features, and improves assessment of tissue perfusion, which is crucial in surgeries that involve bowel resection.

Conclusion: NIR-ICG fluorescence imaging represents a pivotal advancement in the surgical treatment of endometriosis, contributing to improved surgical precision, reduced complication rates, and potentially lowering recurrence. Future research should aim to standardize the use of NIR-ICG in endometriosis surgery, explore its quantitative analysis capabilities, and evaluate long-term surgical outcomes to fully ascertain its clinical benefits and cost-effectiveness.

Keywords: Endometriosis, Near-Infrared Indocyanine Green, NIR-ICG fluorescence imaging, surgical management, ureter visualization, nerve-sparing surgery.

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Narrative Review

Introduction

Endometriosis is a prevalent and complex gynecological condition affecting millions of women globally, particularly those of reproductive age. Characterized by the presence of endometrial-like tissue outside the uterus, it can lead to symptoms ranging from chronic pelvic pain to infertility. This disease often affects multiple pelvic organs, including the ovaries, fallopian tubes, and bladder, complicating both diagnosis and management. Deep Endometriosis (DE) often necessitates surgical intervention. The key challenge in endometriosis surgery is the accurate identification and complete excision of lesions to minimize recurrence, which remains high, with rates of 30-50% within five years post-surgery (1).

Traditionally, endometriosis diagnosis and management have relied heavily on visual inspection during laparoscopy, often supplemented by histological confirmation. However, the limitations of white-light laparoscopy, such as its inability to distinguish subtle or deeply infiltrating lesions, contribute to incomplete lesion removal and high recurrence rates (2). The introduction of Near-Infrared Indocyanine Green (NIR-ICG) fluorescence imaging has significantly advanced the visualization and management of endometriosis by enhancing the contrast of vascular structures and lesions during surgery, thereby improving the surgeon's ability to accurately identify and excise endometriotic tissue.

This review aims to provide a comprehensive overview of the application of NIR-ICG in endometriosis surgery, emphasizing its role in improving visualization of ureters and other critical structures during complex pelvic surgeries. We discuss the mechanisms and properties of ICG, its role in ureteral visualization, its application in bowel and nerve-sparing surgeries, and the current evidence supporting its use. Future directions for ICG fluorescence imaging in endometriosis surgery and its potential to enhance surgical outcomes are also explored.

Indocyanine Green (ICG): Mechanism and Properties

Historical Context and Development

Developed in the 1950s for medical diagnostics, particularly for cardiac output, liver function tests, and ophthalmic angiography, Indocyanine Green (ICG) has found extensive application due to its ability to fluoresce in the near-infrared (NIR) spectrum. Specifically, ICG emits fluorescence when exposed to light at approximately 806 nm, making it useful for imaging in various surgical fields (3). The NIR fluorescence emitted by ICG allows for deep tissue penetration, ideal for visualizing structures difficult to detect with standard imaging techniques.

Chemical Properties and Mechanism of Action

ICG is a water-soluble tricarbocyanine dye that binds to plasma proteins upon intravenous administration and is rapidly cleared from the bloodstream by the liver, with a half-life of about 3-4 minutes, being excreted unchanged into the bile(4). The pharmacokinetics of ICG make it suitable for dynamic imaging during surgeries as it provides real-time visualization of vascular structures and tissue perfusion with minimal background fluorescence.

The fluorescence mechanism of ICG involves the absorption of photons under NIR light, leading to electron excitation. These electrons return to their ground state by emitting light at a longer wavelength, a process known as fluorescence. This emitted fluorescence can be captured by specialized NIR imaging systems, providing surgeons with enhanced contrast between different tissues, particularly vascularized and non-vascularized areas, which is advantageous in endometriosis surgery where differentiating between endometriotic lesions and healthy tissue is challenging (5).

Application of ICG in Endometriosis Surgery

Challenges in Endometriosis Surgery

Endometriosis, particularly DE, presents significant surgical challenges due to its propensity to involve multiple pelvic organs, leading to complex anatomical distortions that complicate both diagnosis and surgical treatment. Traditional laparoscopy, while effective, is limited by its reliance on white-light imaging, which often fails to detect subtle or deeply infiltrating lesions, contributing to high recurrence rates post-surgery (6).

- **ICG in Ureteral Visualization**

Ureteral Endometriosis: A Complex Surgical Challenge

Ureteral endometriosis affects about 0.1% to 1% of women with endometriosis and can lead to severe complications such as hydronephrosis and potential loss of kidney function if not managed properly. The ureters, being long, narrow structures that traverse the pelvis, are particularly susceptible to injury during pelvic surgeries, especially when endometriotic lesions involve or obscure them (7). The risk of iatrogenic ureteral injury during gynecologic surgeries is a significant concern, with reported rates varying from 0.1% to 10% depending on the surgery's complexity and the surgeon's experience (8).

ICG in Ureteral Visualization

ICG fluorescence imaging has emerged as a crucial tool in enhancing the safety and efficacy of surgeries involving the ureters by providing real-time, enhanced visualization of these structures, helping surgeons to clearly distinguish them from surrounding tissues. This enhanced visualization is particularly beneficial in severe endometriosis cases, where anatomical distortions are significant.

In a study by Park et al., the use of ICG for intraoperative ureteral visualization significantly reduced the risk of ureteral injuries during complex laparoscopic procedures for endometriosis. The study demonstrated that ICG, when administered intravenously, allows for the ureters to be clearly identified within minutes, thereby facilitating safer dissection and minimizing the likelihood of accidental damage (9). The adoption of ICG fluorescence imaging in such surgeries has been widely recognized as a major advancement in improving surgical outcomes.

Injecting ICG via a ureteric catheter through cystoscopy represents a safe, straightforward, and reproducible method for enhancing ureter visualization during surgery. (Figure 1a,1b). Centini et al. demonstrated that the systematic use of intraureteral ICG prior to deep endometriosis surgery is safe and significantly reduces the length of ureterolysis and operative time, making it a valuable addition to surgical protocols (10).

Further studies have explored the integration of ICG with robotic-assisted surgery. In one such study, Guan et al. illustrated the advantages of using ICG to guide the dissection of the ureters during robotic-assisted laparoscopic surgery for ureteral endometriosis. The researchers reported a noticeable decrease in ureteral injuries and post-operative complications, underscoring the utility of ICG in enhancing the safety of complex pelvic surgeries (11).

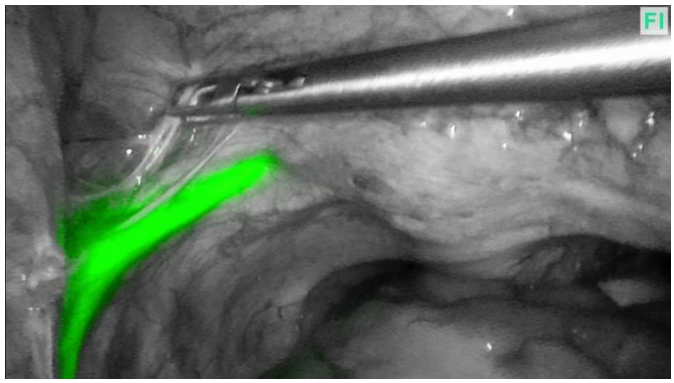

Figure1a. ICG in Ureteral Visualization

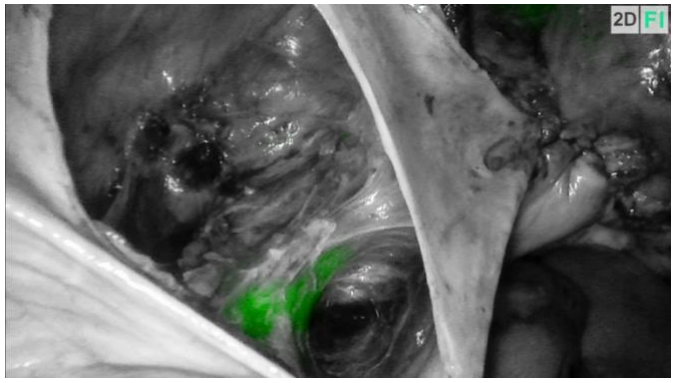

Figure1b. ICG in Ureteral Visualization

Another pivotal study by Raimondo et al. examined the ICG fluorescence imaging for evaluating ureteral perfusion during surgery for ureteral endometriosis. This research involved the intravenous administration of ICG to visualize the ureters and assess their vascularity in real time. This method not only facilitated the safe dissection of the ureters but also provided valuable insights into the adequacy of blood supply to the ureters post-dissection, which is critical for preventing ischemic complications. The authors concluded that ICG fluorescence imaging should be regarded as an adjunct in surgeries involving ureteral endometriosis due to its capability to enhance visualisation and improve surgical outcomes (12).

- **ICG in Bowel Endometriosis: Assessing Bowel Perfusion**

Bowel Endometriosis and the Surgical Challenge

Endometriosis affecting the bowel, particularly the rectosigmoid colon, is one of the most challenging manifestations of the disease. Bowel endometriosis occurs in approximately 5% to 12% of women with the condition and often necessitates complex surgical interventions, including bowel resection. The primary surgical challenge lies in ensuring adequate blood supply to the resected bowel segment, as poor vascularization can lead to significant complications such as anastomotic leakage (12).

ICG in Bowel Perfusion Assessment

The use of ICG fluorescence imaging to assess bowel perfusion during surgery has been a significant development in minimizing the risks associated with bowel resections for endometriosis. ICG allows surgeons to visualize the blood flow within the bowel in real-time, thereby assessing the viability of the tissue before completing an anastomosis.

Seracchioli et al. were among the first to demonstrate the effectiveness of ICG fluorescence angiography in reducing anastomotic leakage rates in patients undergoing bowel resection for endometriosis. Their study showed that by using ICG, surgeons could accurately identify well-perfused bowel tissue, guiding the resection and ensuring a healthy anastomosis (13). This technique has been supported by a systematic review and meta-analysis conducted by Pang et al., which found that the use of ICG fluorescence angiography significantly reduced the incidence of anastomotic leakage in colorectal surgeries (14).

Bourdel et al. extended this application of ICG by using it in laparoscopic rectal shaving procedures for deep infiltrating endometriosis. Their study found that ICG was instrumental in preventing complications such as fistula formation by providing real-time visualization of the tissue's vascularity, ensuring that only well-perfused tissue was left intact (15). This application of ICG has become increasingly important in complex surgeries involving the bowel where the risk of complications is high.

Another study by Raimondo et al. explored the use of ICG in assessing the vascular patterns of the rectosigmoid colon during surgery for bowel endometriosis. The study found that ICG provided critical insights into the vascularity of the bowel, which informed surgical decision-making and improved postoperative outcomes (16). The authors concluded that ICG fluorescence imaging is a valuable tool in bowel endometriosis surgery, particularly in cases requiring complex resections.

- **ICG in Nerve-Sparing Surgery for Deep Infiltrating Endometriosis**

The Importance of Nerve Preservation in Endometriosis Surgery

Deep Infiltrating Endometriosis (DE) often involves the infiltration of endometriotic lesions into areas with a high density of nerves, such as the sacral plexus and hypogastric nerves. Surgical excision of these lesions is challenging because it requires careful dissection to remove the lesions while preserving the autonomic nerves that are crucial for bladder and bowel function. Nerve damage during surgery can result in significant morbidity, including bladder dysfunction, sexual dysfunction, and chronic pelvic pain.

ICG-Assisted Nerve-Sparing Techniques

ICG fluorescence imaging has been employed to enhance the visualization of nerves during DE surgeries, thereby facilitating nerve-sparing procedures. The technique involves the intravenous administration of ICG, which, when viewed under NIR imaging, highlights the autonomic nerves and surrounding tissues, allowing for more precise dissection.

Kanno et al. reported the successful use of ICG in nerve-sparing surgery for DE. By enhancing the visualization of the pelvic autonomic nerves, ICG allowed the surgical team to more accurately distinguish between diseased and healthy tissues, thus preserving nerve function while ensuring complete excision of endometriotic lesions (17). This approach has been associated with improved postoperative outcomes, including reduced rates of bladder and bowel dysfunction.

In a subsequent study, Raimondo et al. explored the use of ICG in nerve-sparing surgery for endometriosis, particularly in cases involving the sacral plexus. The study found that ICG significantly improved the surgeon's ability to identify and preserve the sacral nerves, which are often at risk during extensive pelvic dissections. The authors recommended the routine use of ICG in nerve-

sparing surgeries for DE, particularly in cases where the preservation of nerve function is critical for maintaining quality of life (18).

Another important study by Kanno et al. highlighted the utility of ICG in robotic-assisted nerve-sparing surgery for DE. The study demonstrated that ICG fluorescence imaging allowed for the precise identification and preservation of critical nerve structures during complex pelvic dissections, reducing the risk of postoperative nerve-related complications (19). The use of ICG in this context represents a significant advancement in the surgical management of DE, where the preservation of nerve function is paramount.

- **ICG for Visualizing Endometriotic Implants**

Challenges in Identifying Endometriotic Lesions

Endometriotic implants can vary widely in appearance, ranging from subtle, non-pigmented lesions to deeply infiltrating nodules. This variability makes it challenging for surgeons to accurately identify and excise all affected tissues using conventional white-light laparoscopy. Incomplete excision of endometriotic lesions is a significant cause of symptom recurrence and the need for repeat surgeries.

ICG for Enhanced Lesion Visualization

ICG fluorescence imaging has proven to be an effective tool in enhancing the visualization of endometriotic implants during surgery. By highlighting the vascular structures associated with endometriotic tissue, ICG allows for more precise identification and excision of lesions, reducing the likelihood of recurrence.

Levey et al. first demonstrated the use of ICG in differentiating between endometriotic lesions and surrounding healthy tissue during robotic-assisted laparoscopy. The researchers found that ICG significantly improved the identification of lesions that were not visible under conventional white-light imaging, leading to more complete excision and better postoperative outcomes (20). This study highlighted the potential of ICG to improve the thoroughness of endometriosis surgeries, particularly in cases where lesions are difficult to visualize.

Cosentino et al. further explored the diagnostic accuracy of ICG in identifying both visible and occult endometriotic lesions. Their study demonstrated that while ICG is highly effective in enhancing lesion visibility, it should complement traditional imaging techniques rather than replace them entirely. The authors concluded that ICG fluorescence provides additional information that can improve the thoroughness of lesion excision, potentially reducing recurrence rates (21).

Additionally, Vizzielli et al. conducted a comparative study on the effectiveness of ICG fluorescence imaging versus traditional white-light laparoscopy in identifying endometriotic lesions. The study found that ICG significantly improved the surgeon's ability to detect non-pigmented and deeply infiltrating lesions that were missed during white-light laparoscopy. However, the study also emphasized the need for combining ICG with other imaging modalities to achieve the most accurate and comprehensive surgical outcomes (22).

- **ICG in Reproductive Outcomes Post-Endometriosis Surgery**

Impact on Fertility and Pregnancy Outcomes

Endometriosis is a leading cause of infertility, with up to 50% of women with the condition experiencing difficulty conceiving. Surgical management of endometriosis aims not only to alleviate symptoms but also to improve fertility outcomes. However, the impact of endometriosis surgery on fertility is complex and influenced by factors such as the extent of disease, the presence of adhesions, and the skill of the surgeon.

Role of ICG in Improving Reproductive Outcomes

ICG fluorescence imaging has been proposed as a tool to improve reproductive outcomes post-endometriosis surgery by enhancing the thoroughness of lesion excision and minimizing the risk of adhesions. The enhanced visualization provided by ICG allows for more complete excision of endometriotic tissue, which is crucial for restoring normal pelvic anatomy and improving fertility.

In a study by Coccia et al., the use of ICG fluorescence imaging during endometriosis surgery was associated with improved reproductive outcomes compared to traditional white-light laparoscopy. The study found that women who underwent ICG-assisted surgery had higher pregnancy rates and lower recurrence rates of endometriosis-related infertility (23). The authors attributed these findings to the more thorough excision of endometriotic lesions achieved with

ICG, which reduced the likelihood of persistent or recurrent disease affecting fertility.

Furthermore, a retrospective analysis by Ferrero et al. examined the reproductive outcomes of women who underwent ICG-assisted laparoscopic surgery for ovarian

endometriomas. The study reported a significant improvement in pregnancy rates and a reduction in the time to conception among women treated with ICG fluorescence imaging compared to those who underwent standard laparoscopy (24, 25). The study suggested that the enhanced visualization of ovarian tissue provided by ICG allowed for more precise excision of endometriomas while preserving healthy ovarian tissue, thus improving ovarian function and fertility.

Future Directions and Research Needs

Despite the promising results associated with ICG fluorescence imaging in endometriosis surgery, several areas require further research to optimize its use and establish its role as standard practice in surgical management.

Quantitative Analysis of ICG Perfusion

One potential development area is the quantitative analysis of ICG perfusion levels during surgery. While current applications of ICG rely on qualitative assessment of fluorescence, developing systems for quantitative analysis could provide more objective criteria for surgical decision-making. For example, quantitative perfusion metrics could help determine the optimal resection margins in bowel surgery or assess the adequacy of nerve preservation in DIE surgeries.

Comparative Studies Across Different Stages of Endometriosis

Comparative studies exploring variations in ICG uptake across different stages of endometriosis could also provide valuable insights into the disease's progression and the effectiveness of ICG at different points in the disease course. Such studies could help identify specific biomarkers associated with ICG uptake in endometriotic tissue, potentially leading to more targeted and personalized surgical interventions.

Longitudinal Studies on Long-Term Outcomes

Longitudinal studies are essential to assess the long-term outcomes of patients undergoing ICG-guided surgeries, including recurrence rates, quality of life, and reproductive outcomes. These studies would provide critical data on the durability of surgical outcomes achieved with ICG and help establish evidence-based guidelines for its use in endometriosis surgery.

Cost-Effectiveness Analysis

Finally, a comprehensive cost-effectiveness analysis of ICG fluorescence imaging in endometriosis surgery is needed. While the initial costs of adopting ICG technology may be high, the potential savings from reduced recurrence rates, fewer repeat surgeries, and improved fertility outcomes could make it a cost-effective option in the long run. Such an analysis would be valuable for healthcare providers and policymakers in making informed decisions about the integration of ICG into standard surgical practice.

Conclusion

ICG fluorescence imaging represents a significant advancement in the surgical management of endometriosis, offering substantial improvements in lesion visualization, surgical precision, and patient outcomes. The ability of ICG to enhance the visualization of critical structures such as ureters, nerves, and endometriotic implants addresses several key challenges in endometriosis surgery, reducing the risk of complications and recurrence.

While the current evidence strongly supports the integration of ICG into surgical protocols for endometriosis, further research is needed to optimize its use and fully establish its efficacy and cost-effectiveness. The development of quantitative analysis systems, comparative studies across different stages of the disease, and longitudinal studies on long-term outcomes will be crucial in advancing the use of ICG in endometriosis surgery.

As surgical techniques continue to evolve, the incorporation of ICG fluorescence imaging holds the potential to significantly improve the quality of life for patients suffering from this debilitating condition, offering hope for better management and outcomes in the future.

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