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Technical Note

# Indocyanine green imaging to guide lymphadenectomy in laparoscopic distal gastrectomy - With vídeo

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ABSTRACT

Gastric cancer (GC) is one of the most lethal malignancies and Gastrectomy with D2 lymphadenectomy is considered the standard surgical treatment.

Adequate lymph node dissection is necessary for patients' prognosis, but D2 lymphadenectomy is technically demanding due to the complexity of anatomy, even more so if performed laparoscopically. The learning curve requires a high degree of training with a considerable number of cases and standardization of the technique.

Recently, Indocyanine Green (ICG) and Near-Infrared (NIR) Fluorescence Imaging have been presented as promising image-guided surgery techniques, providing real-time anatomy assessment and intra-operative visualization of blood flow, lymph nodes and lymphatic vessels. ICG fluorescence imaging has been studied in GC surgery, especially for real-time lymphatic mapping.

At present, we are conducting a prospective, open-label, single-arm clinical trial (Clinical trial - NCT03021200) to evaluate the feasibility and outcomes of ICG and NIR Fluorescence Imaging in GC surgery.

In this technical note, we present one approach to the use of this technique to guide lymphadenectomy in laparoscopic distal gastrectomy.

## 1. Introduction

Gastric cancer (GC) is the fourth leading cause of death in the world [1] and surgery remains the main curative option. Gastrectomy with D2 lymphadenectomy is considered the standard surgical treatment [2].

Lymphadenectomy is one of the main prognostic factors in GC and can significantly improve long-term survival [3]. Therefore, it is required that surgeons carry it out properly, with a high number of lymph nodes harvested. Due to the complex vascularization of the stomach, and anatomical variation [4], the subjective intraoperative definition of each lymph node station may be difficult. Thus, the learning curve to an adequate lymphadenectomy is challenging, even more, if performed laparoscopically.

As an example, the KLASS-02 a prospective multicenter study conducted to compare laparoscopic and open gastrectomy for advanced distal GC, standardized surgical skills and proficiency of surgeons who applied to join the trial. Only twelve surgeons (44.4 %) were qualified on initial evaluation and twenty-one (77.7 %) were qualified after re-evaluation [5].

In this context, image-guided surgeries have gained increased attention, allowing surgeons to visualize and identify real-time anatomy, with a high degree of accuracy [6,7]. One of the featured modalities is Indocyanine Green (ICG) and Near-Infrared (NIR) Fluorescence Imaging. By this technology, a fluorescence imaging system device (Spy Elite® Fluorescence Imaging System, Pinpoint® Endoscopic Fluorescence Imaging System or Firefly® Imaging System) provides identification of anatomical landmarks using NIR Technology and ICG, an injectable fluorescence dye.

ICG is approved for human use by the United States Food and Drug Administration (FDA). It is a sterile water-soluble tricarbocyanine dye that binds to plasma proteins [8] and emits maximal fluorescence at a wavelength of approximately $\geq$ 820 nm after NIR light stimulation. Then, using specifically designated scopes and cameras, the emitted ICG fluorescence is detected [9]. ICG can be administered intravenously, intra arterially, or topically. Through its bright fluorescence, even lymphatic vessels and lymph nodes in dense fat can be easily visualized

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[10]. ICG stability and degradation properties depend on several factors like ICG concentrations, solvent (water, methanol or plasma) and incubation temperature. In previous literature, ICG was stable for 3 days when diluted in water and stored at 4 °C in the dark, with a loss of 20 % of fluorescence intensity within this period, suggesting that ICG should be used within 1 or 2 days after dilution, under these conditions [11].

Tracer deposition can last for prolonged periods in the lymphatic vessels and lymph nodes (1–3 days), allowing both preoperative and intraoperative injection for lymphatic mapping [10]. Moreover, it does not require ionizing radiation and the infrared light is invisible to the human eye, without changing the appearance of the operative field [6,12]. These factors are the advantages of ICG fluorescence imaging compared to other methods like radioactive colloids or blue dye.

ICG fluorescence imaging has been studied to perform real-time lymph node navigation in GC surgery, with the assessment of the route of lymphatic drainage and identification of lymph node non-compliance [13]. In this technical note, we present one approach to the use of ICG fluorescence imaging to guide lymphadenectomy in laparoscopic distal gastrectomy.

## 2. Technique (video)

### 2.1. Patients

The technique is performed for patients with potentially resectable gastric adenocarcinoma eligible for surgery with curative intent and lymphadenectomy. Clinical staging is performed with chest, abdômen, and pelvis tomography, endoscopy, and laboratory tests.

### 2.2. ICG preparation

The dye solution is made by diluting 25 mg of ICG in 10 mL of distilled water, to a final concentration of 2.5mg/mL.

### 2.3. ICG endoscopic injection

At the time of the surgery, 0.2 mL of the ICG solution is injected into the submucosal layer at four points around the lesion (0.8–1 mL), using an endoscopic injection needle.

### 2.4. Procedure

The patient is placed in a supine position, in the reverse Trendelenburg position, with legs abducted. The surgeon stays between the legs and surgical assistants by the patient's side.

A 5-trocar technique is used. The first 10 mm trocar is placed supraumbilically by the open method and a 12 mmHg pneumoperitoneum is established. The other four trocars are placed as follows: 12mm trocar in the left lateral abdomen and 5 mm trocars in the epigastric area, right lateral abdômen, and left upper quadrant.

All adhesions are released and the Hepatogastric and Gastrocolic ligaments are sectioned for access to the retro cavity and complete visualization of the perigastric lymph node chains. After visually confirming the absence of metastasis, the patient receives intraoperative ICG endoscopic injection, which allows an adequate localization of the lesion and definition of the surgical margins in suspected cases.

If there is an intention to identify the sentinel lymph node (SL), the fluorescein diffusion is observed for 5 min with the Fluorescence system. Once the SL is identified, it is collected together with the corresponding lymph node basin and sent for pathological analysis separately.

The surgery proceeds in the usual way (gastrectomy with D2 lymphadenectomy) and the Fluorescence system is activated simultaneously along with it, always checking the route of lymphatic drainage, quality of lymphadenectomy, and identification of residual lymph nodes in the dissected area.

After releasing the greater curvature and the left gastroepiploic vessels, the dissection is continued clockwise with the identification of the pancreatic head and duodenum. The right gastroepiploic vessels are clipped, sectioned and lymph node station 6 is removed. This video presents a case where a lymph node in station 6 would be left behind without the use of ICG fluorescence imaging.

Next, the gastroduodenal artery is dissected towards the common hepatic artery, and lymph node station 8a is cleared. The surgery proceeds to the supra pyloric region and hepatic hilum. Stations 12a, 9, and 11p are removed. Finally, the left gastric artery is clipped and sectioned, clearing lymph node station 7. For distal gastrectomy, stations 1 and 3 are also dissected from the lesser curvature and removed with the specimen.

After the end of the lymphadenectomy, the Fluorescence system is activated again, for final control. All residual non-resected lymph nodes are collected and sent for analysis separately.

If there is any doubt about vascularization, the ICG solution can be injected intravenously in a dose of 3.75–7.5 mg bolus to assess the blood supply. The perfusion of the stomach will be visualized and evaluated through the Fluorescence system, with the stomach being sectioned in an area of well-perfused tissue.

## 3. Discussion

In this technical note, we presented one approach to the use of ICG fluorescence imaging to guide lymphadenectomy during a laparoscopic distal gastrectomy. The video demonstrated a case where the application of the ICG technology was essential for the performance of an adequate lymphadenectomy.

The clinical application of NIR fluorescence imaging and ICG is wide-ranging [12]. It is described for SL node mapping (e.g. skin cancer [14], breast cancer [15], colorectal cancer [16], GC [10,17], cervical cancer [18], vulvar cancer [19]), tumor imaging (liver cancers [20]), identification of vital structures (bile ducts [21]), perfusion evaluation (vascular perfusion of anastomoses [22], and flaps in reconstructive surgery [23,24]).

NIR low scattering, low absorption and low autofluorescence characteristics provide deeper tissue penetration with great potential to identify critical anatomical structures [6,12,25]. Additionally, the ICG provides better sensitivity and depth penetration when used together with NIR technology, being also a safe vital dye with very rare reports of hypersensitivity reactions and minimal toxicity [26].

Currently, the use of ICG fluorescence imaging in GC [9] is the detection of SL [27,28], visualization of blood flow [29,30], localization of the tumor [9], and determination of the lymphadenectomy range [13,31].

Due to the complex vascular anatomy and lymphatic drainage around the stomach, lymphadenectomy remains a challenge for surgeons, especially with new surgeons' learning curve and minimally invasive techniques. In these circumstances, the application of ICG and NIR fluorescence imaging have been studied to perform real-time lymph node navigation to achieve adequate lymphadenectomy.

Chen et al. [13] conducted a prospective randomized clinical trial to investigate the safety and efficacy of ICG NIR tracer-guided imaging during laparoscopic D2 lymphadenectomy in GC patients. They randomized 266 patients with potentially resectable gastric adenocarcinoma (clinical tumor stage cT1-cT4a, N0/+, M0), 133 underwent ICG tracer-guided laparoscopic gastrectomy and 133 underwent conventional laparoscopic gastrectomy. ICG significantly improved the number of lymph node dissections and reduced lymph node noncompliance. It did not increase perioperative complications suggesting that ICG NIR tracer-guided imaging can be performed for routine lymphatic mapping during laparoscopic gastrectomy.

Fluorescent lymphography using ICG and NIR imaging for lymph node navigation was also studied in robotic gastrectomy. Similar results, with more lymph nodes retrieved and reduced lymph node noncompliance, were found with fluorescent imaging [32].

Currently, a large-scale prospective phase III trial (SENORITA TRIAL) [33] is ongoing in Korea to compare Laparoscopic sentinel node navigation surgery (LSNNS) versus standard Laparoscopic gastrectomy with lymph node dissection for early GC. The dual-tracer method (ICG and radiolabeled human serum albumin) is been used for LSNNS. Short-term surgical outcomes revealed a comparable rate and severity of postoperative complications between the groups, indicating that LSNNS is feasible and safe [34].

Limitations of the NIR fluorescence imaging include the availability of specific technology in the operating room (NIR imaging systems and intraoperative endoscopy), which increases the cost and surgical time. Furthermore, ICG is a non-targeting fluorescence agent, with rapid degradation under certain circumstances (light and high temperatures) and non-specificity for cancer [25,26,35]. Concerning the ICG-guided lymphadenectomy in GC, the diffusion of the dye can induce the dissection of nodes outside the D2 territory causing contamination of the lymphadenectomy without oncological benefit. A long-term follow-up is needed to evaluate this outcome [13].

Despite the limitations above, ICG fluorescence imaging is a promising tool, allowing real-time image-guided surgery with wide application in GC. Future perspectives are on the development of targeted fluorophores with higher specificity for tumors, including small molecules, peptides, and antibodies [36]. The increased sensitivity and specificity for cancer tissue will increase the ability of the surgeon to perform a more precise surgery.

Along with it, future clinical trials with specific evidence-based indications and standardized techniques are needed to implement this technology in the cancer surgical routine.

At present, we are conducting a prospective, open-label, single-arm clinical trial (Clinical trial - NCT03021200) to evaluate the applicability of ICG and NIR Fluorescence Imaging in GC surgery. The main outcomes will be the accuracy of the method in the identification of SL and the feasibility to guide lymphadenectomy. This video represents our standardized technique for lymphadenectomy guidance.

## Funding

The study is financed by PRONON (National Oncology Care Support Program by Brazilian Ministry of Health)and is registered online (Plataforma Brasil - CAAE: 56687616.5.0000.0065 - Clinical trial - NCT03021200).

## Declaration of competing interest

The authors declare that there is no conflict of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amsu.2021.102657.

## Sources of funding

The study is financed by PRONON (National Oncology Care Support Program by Brazilian Ministry of Health) and is registered online (Plataforma Brasil - CAAE: 56687616.5.0000.0065 - Clinical trial - NCT03021200).

## Ethical approval

The study was approved by the Hospital's Ethics Committee and is registered online (https://plataformabrasil.saude.gov.br, CAAE 56687616.5.0000.0065).

## Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

## Author contribution

Erica Sakamoto: edited the video, drafted the initial manuscript, discussed the results and contributed to the final manuscript. Marcus Fernando Kodama Pertille Ramos: carried out the operative procedure, edited the video, discussed the results and contributed to the final manuscript. Andre Roncon Dias: carried out the operative procedure, discussed the results and contributed to the final manuscript. Adriana Vaz Safatle-Ribeiro: performed the endoscopic procedure, discussed the results and contributed to the final manuscript. Bruno Zilberstein: supervised and commented on the manuscript, discussed the results and contributed to the final manuscript. Sergio Carlos Nahas: supervised and commented on the manuscript, discussed the results and contributed to the final manuscript. Ulysses Ribeiro-Junior: supervised and commented on the manuscript, discussed the results and contributed to the final manuscript.

## Registration of research studies

1. Name of the registry: Laser Fluorescence in Cancer Surgical Treatment
2. Unique Identifying number or registration ID: NCT03021200
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): https://clinicaltrials.gov/ct2/show/NCT03021200?term=NCT03021200&draw=2&rank=1

## Guarantor

Erica Sakamoto.

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