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Current Status of Indocyanine Green Tracer-Guided Lymph Node Dissection in Minimally Invasive Surgery for Gastric Cancer

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ABSTRACT
With the rapid development and popularization of laparoscopic and robotic radical gastrectomy, gastric cancer (GC) surgery has gradually entered a new era of precise minimally invasive surgery. The era of precision medicine has put forth new requirements for minimally invasive surgical treatment of patients with GC at different disease stages. For patients with early GC, avoiding surgical trauma caused by excessive lymph node (LN) dissection improves quality of life while pursuing radical treatment of the tumor. In patients with advanced GC, systematic LN dissection can be achieved without increasing surgical complications. With the successful application of indocyanine green (ICG) fluorescence imaging technology in minimally invasive surgical instrumentation in recent years, researchers have found that ICG fluorescence imaging yields good tissue penetration and can identify LNs in fat tissue better than other dyes. Therefore, whether ICG fluorescence imaging technology can guide surgeons in performing safe and effective LN dissection has attracted much attention. The present review discusses the clinical applications and research progress of ICG tracer-guided LN dissection in patients with GC.

Keywords:
indocyanine green; gastric cancer; minimally invasive surgery; precision medicine; lymph node.

Background

Gastric cancer (GC) is the sixth most frequent malignancy and ranks third among tumor-related mortality worldwide [1]. Curative treatment of GC depends on operation-centered, comprehensive treatment. Simultaneously, complete resection of the tumor and radical lymphadenectomy are key points of the operation. Since Kitano et al. [2] first described laparoscopic distal gastrectomy in Japan in 1994, after more than 20 years of development[3,4], minimally invasive gastrectomy has been widely implemented in clinical practice. With advances in minimally invasive instrumentation and the development of minimally invasive technology in recent years, minimally invasive GC surgery has gradually entered the era of precision medicine. Therefore, accurate definition of the scope of lymph node (LN) dissection in early GC and ensuring the thoroughness of LN dissection in patients with advanced GC have become the focus of discussion in the field of minimally invasive gastrectomy. Individualized radical lymphadenectomy is becoming the goal of every surgeon performing minimally invasive procedures. Over the past several years, the emergence of indocyanine green (ICG) near-infrared (NIR) fluorescence imaging has provided a more feasible solution to the above problems [5-7].

Principle of ICG Fluorescence imaging technology

ICG is the only NIR contrast agent approved for a small number of surgical indications by the Food and Drug Administration and European Medicines Agency[8]. ICG is excited by external light at a wavelength range of 750–810 nm and emits NIR light at a wavelength of approximately 840 nm [9]. ICG injected locally around GC is absorbed by the lymphatic system and binds to albumin, eventually returning to the blood system with drainage of the lymphatic system. Due to the slow transport of the lymphatic system, ICG can persist for prolonged periods [10]. ICG fluorescence imaging technology is based on the above principles using special imaging equipment to track drainage of the lymphatic vessels and LNs. Because the rate of uptake of ICG varies among different tissues, it can effectively distinguish lymphoid tissue from perigastric vessels, fat, pancreas, and other tissues during surgery.

Development of ICG fluorescence imaging technology

As early as the beginning of the 21st century, Hiratsuka et al. [11] reported, for the first time, the application of an ICG LN tracing technique in sentinel LN biopsy for early GC in open surgery. Initially, sentinel LNs were identified only by the naked eye to determine whether they were stained by ICG. With the development of fluorescence imaging equipment, some centers have performed related studies investigating ICG fluorescence imaging of sentinel LN biopsy in open GC surgery [12,13]. However, due to the subjectivity of naked eye discrimination and the need for additional imaging equipment, it remains difficult to popularize ICG fluorescence imaging technology in open GC surgery. After 2010, with the successful integration of ICG fluorescence imaging technology in laparoscopic and robotic equipment [14], researchers have found that ICG fluorescence imaging provides better tissue penetration and signal stability than other dyes (such as 99m technetium-labeled tin colloid and isosulfan blue dye, among others) [6,7]. Therefore, based on the unique high-definition camera display system and clear magnification effect of minimally invasive equipment, ICG fluorescence imaging-guided sentinel LN biopsy and LN dissection has the characteristics of in vivo and real-time imaging. Perigastric LNs can be observed in a closer and more physiological condition, LNs can be mapped more accurately, and lymphadenectomy can be performed in real time (*Figure 1*). Minimally invasive radical gastrectomy guided by ICG fluorescence imaging has become a new area of exploration. To further standardize applications of ICG fluorescence imaging technology in the field of minimally invasive GC surgery, our center performed the first prospective, randomized, controlled study (FUGES-012) of ICG tracer-guided LN dissection during laparoscopic radical gastrectomy in patients with GC [15] from November 2018 to July 2019. That study aimed to promote the standardization of NIR imaging in the laparoscopic resection of GC and to establish a reference for the application of fluorescence imaging in the radical resection of digestive tract cancers.

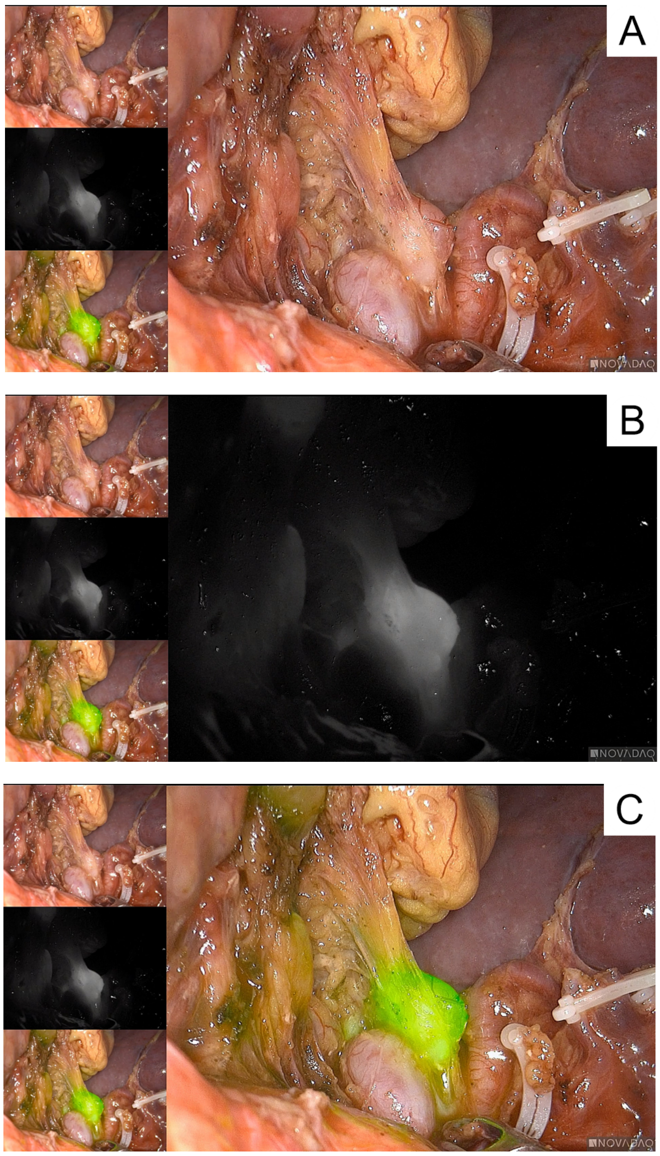

Figure 1:
Indocyanine green (ICG) tracer-guided lymph node (LN) dissection.
A. Natural light mode.
B. Near-infrared mode.
C. Green fluorescence mode.

Application of ICG tracer-guided LN dissection in early GC

Traditionally, the treatment of early GC was based primarily on standard open gastrectomy and LN dissection. Due to the low rate of LN metastasis in early GC (0–10.6%) [16,17], advances in surgical instrumentation and surgical concepts, endoscopic treatment, rescue surgery after failure of endoscopic treatment, and minimally invasive radical surgery, represented by laparoscopic and robotic gastrectomy, have become the main theme of early GC treatment [13]. Some investigators have proposed that sentinel LN navigation surgery is an "accurate operation" under the guarantee of radical surgery based on the distribution and biopsy of sentinel LNs. Only metastatic LNs are dissected to avoid excessive LN dissection, reduce complications, preserve function, and improve quality of life in patients with early GC. However, due to the complexity of gastric lymphatic reflux and the jumping metastasis of GC, the application of sentinel LN navigation surgery in the field of GC remains controversial [18]. Among them, in addition to defining indications for sentinel LN dissection, accurate identification of sentinel LNs is also the focus of surgeons. In recent years, several studies [14,19,20] have confirmed that ICG is safe and feasible for mapping sentinel LNs in GC surgery, and that ICG fluorescence imaging technology has the advantages of intuitiveness, high sensitivity, and signal stability, which have gradually replaced the previous radiolabeled tin colloid and blue dye. Based on a previous report by Hiratsuka et al. [11], Japanese surgeons immediately performed the Japan Clinical Oncology Group multicenter trial JCOG0302 [21]. However, that trial was suspended due to its high false-negative rate. It should be noted that ICG was subserous injected in open surgery, without using fluorescence imaging, and the histopathological diagnosis rate was not high. Shoji et al [18] combined ICG submucosal injection with sentinel LN navigation biopsy in laparoscopic radical resection for early GC, and improved the method of intraoperative sentinel LN biopsy using a one-step nucleic acid amplification assay that can identify the expression of epithelial protein CK19 within 30 minutes. This compensates for shortcomings of low sensitivity and the time-consuming process of hematoxylin and eosin staining of frozen biopsy samples, and significantly reduces the false-negative rate. We believe that with the development of imaging technology, drug administration regimens, and detection technology, the application of ICG fluorescence imaging technology in sentinel LN biopsy and function-preserving surgery for early GC can be more secure.

Although endoscopic resection can result in a radical effect in some early GCs, approximately 10% of patients experience LN metastasis after endoscopic resection [22]. Therefore, according to the condition of postoperatively resected specimens, some patients still need to undergo further rescue LN dissection. Recently, Roh et al. [23] reported that ICG fluorescence lymphography successfully visualized all draining LNs after endoscopic treatment, with very high sensitivity and negative predictive value for detecting metastatic LNs. Therefore, ICG fluorescence-guided LN dissection could be an alternative to systematic lymphadenectomy during additional surgery after endoscopic treatment.

For early GC, minimally invasive radical gastrectomy, including laparoscopic and robotic D1 + or D2 radical gastrectomy, has become one of the main recommended treatments [16,24]. In terms of LN navigation in early GC, Tae-Han Kim et al. [25] reported that, among 43 cases of laparoscopic radical resection for early GC, the application of ICG increased the detection rate of LNs, especially in the infrapyloric region. In a prospective, single-arm study, Kwon et al. [26] reported that ICG tracing increased the number of LNs retrieved in patients with early GC and achieved complete LN dissection compared with a historical control group .

Application of ICG tracer-guided LN dissection in advanced GC Application of ICG tracer-guided LN dissection in advanced GC

Previous studies have shown that within the prescribed range of dissection, the more LNs dissected, the better the long-term survival of patients with GC [27-30]. Increasing the number of LN dissections and the number of positive LNs retrieved were highly significant to accurate patient staging and the choice of adjuvant treatment. Therefore, for advanced GC, it is important to thoroughly and effectively dissect perigastric LNs during surgery. In principle, D2 lymphadenectomy is indicated for advanced GC[16]. Presently, however, LN dissection is often performed under the naked eye according to the surgeon's experience. Due to the complex anatomy of the perigastric vessels and fascia, the complicated characteristics of laparoscopic and robotic instrument operation, especially in patients with high body mass index, how to harvest a sufficient number of LNs efficiently and accurately without increasing complications remains a significant challenge for surgeons, especially for those newly trained. Because ICG can emit NIR light at a wavelength of 840 nm after being excited, the penetration depth of the enhanced fluorescence is between 0.5 cm and 1 cm [31]. High-resolution signals are collected using high-definition laparoscopy, and the outline and boundaries of perigastric LNs can be displayed clearly in real-time under fluorescence imaging, which helps guide surgeons in performing LN dissection within the prescribed range more confidently, calmly, and accurately. However, previous studies remain controversial as to whether ICG fluorescence imaging can increase the number of LNs dissected during minimally invasive GC surgery. Cianchi et al. [32] reported that the application of ICG tracer-guided LN dissection in robotic gastrectomy has similar short-term efficacy and postoperative complication rate as traditional robotic surgery and can harvest more LNs. However, Lan et al. [33] found that, compared with the non-ICG group, the ICG group did not increase the total number of dissected LNs. These inconsistent results, however, may be explained by the selection bias inherent in retrospective investigations and the different inclusion/exclusion criteria and varying injection methods, time, and concentration(s) of ICG used across studies. Therefore, in addition to adopting strict prospective randomized controlled methods to select patients and ensure that the basic characteristics of patients were comparable, for the standardized use of ICG, the FUGES-012 study adopted unified and strict standards for preoperative injection, intraoperative photography and postoperative LN sorting, and recorded them by video or photographs. Through previous exploration, we found that, compared with intraoperative subserous injection of ICG, preoperative endoscopic submucosal injection is easier to control and saves time, and it is not easy to cause intraoperative leakage to the operative field or mistakenly inject vessels during the operation. In the FUGES-012 study, a modified intention-to-treat analysis included 258 patients with clinical T1-4a GC (ICG group, n = 129; non-ICG group n = 129). The results showed that the average number of total LN dissections in the ICG group was significantly higher than that in the non-ICG group (50.5 vs. 42.0; P < 0.001). The postoperative recovery process and the 30-day incidence of complications were similar between the two groups. Further hierarchical analysis revealed that regardless of whether distal or total gastrectomy was performed, the average number of total LN dissections in ICG group was significantly higher than that in non-ICG group (distal gastrectomy, 49.2 vs. 39.8; total gastrectomy, 52.1 vs. 43.1; P < 0.001). The results were published in JAMA Surgery [15]. At the same time, JAMA Surgery commissioned an invited commentary by Professor Marco G. Patti from the University of North Carolina (Capel Hill, NC, USA) [34]. He commented that the study was important for surgeons in Western countries and suggested that ICG should be routinely performed in GC surgery due to its simplicity and effectiveness.

Laparoscopic or robotic radical resection of GC has been widely performed all over the world owing to its minimally invasive advantages. However due to the difficulty of laparoscopic or robotic D2 LN dissection, performing minimally invasive D2 LN dissection in a standardized and efficient manner has become focus of attention for many surgeons. To objectively evaluate the quality of D2 LN dissection, Japanese investigators have proposed the concept of "LN noncompliance" [35]. Several studies have considered the LN noncompliance rate as a quality control index of D2 radical surgery for GC [36-39]. Even when standard D2 radical resection is performed, the LN noncompliance reported in the literature still fluctuates between 43.2% and 81.6%. Several previous clinical trials also reported a high LN noncompliance rate. The LN noncompliance rate of D2 LN dissection in a Dutch trial[36] was as high as 81.6%. The D2 LN noncompliance rate in the COACT1001 study from Korea was 47% in the laparoscopic distal gastrectomy group and 43.2% in the open distal gastrectomy group [37]. The LN noncompliance rate of D2 LNs in the CRITICS study was 58.9%[38]. A previous retrospective study performed at our center [40] revealed that the LN noncompliance rate in the laparoscopic distal gastrectomy group was 50.9% and 59.8% in the laparoscopic total gastrectomy group . In the FUGES-012 study, through ICG tracing, the LN noncompliance rate in patients who underwent laparoscopic distal gastrectomy and those underwent laparoscopic total gastrectomy in the ICG group was 23.9% and 41.4%, respectively, which was significantly lower than that reported in previous studies. Therefore, the application of ICG tracer-guided LN dissection in laparoscopic radical resection of GC will help to reduce LN noncompliance. For advanced GC, it is recommended that ICG fluorescence imaging be routinely performed to guide laparoscopic or robotic radical GC surgery, and to guide the surgeon to harvest more LNs and improve the LN noncompliance rate.

Limitations and prospects

Due to the lack of survival data, whether ICG fluorescence imaging-guided LN dissection in minimally invasive GC surgery can improve the long-term prognosis of patients with GC still needs to be confirmed in multicenter, long-term, follow-up studies. There are still some limitations to the application of ICG fluorescence-imaging-guided LN dissection. First, when ICG imaging indicates LNs beyond the scope of LN dissection (such as no.13, 14v, or 16a) in patients undergoing D1 + or D2 LN dissection, it is unclear whether the surgeon needs to dissect the fluorescent LNs. In the FUGES-012 study, No.14v LN exhibited fluorescence during the operation and was dissected and submitted for pathological examination. Interestingly, the rate of LN metastasis in patients with fluorescent No.14v was as high as 33.3%, which was significantly higher than reported in previous studies [41,42]. To clarify, it is suggested that future studies investigate guiding controversial No.14v dissection through ICG imaging. Second, the LN indicated by ICG fluorescence only shows that the LN receives lymphatic reflux from the tissue around the tumor and cannot accurately identify metastatic LNs. The accuracy reported in the literature is approximately 62.2–97.2%. At the same time, some false-negative rates have been reported, in which fluorescence was absent in the LN; however, postoperative pathological examination revealed the presence of metastasis, the incidence of which was 46.4–60.0% [13,21,32]. This inaccuracy may have been due to large-scale cancer invasion of lymphatic vessels or LNs blocked by cancer cells. In this case, ICG fluorescence was not detected in the metastatic LNs [43]. We believe that through rigorous development of clinical practices and technological innovations, the accuracy of this technology will improve. For example, ICG can be combined with targeting marker molecules, which can successfully identify metastatic cancer cells and specifically identify metastatic LNs. We look forward to further exploring indications for ICG fluorescence imaging that can accurately indicate metastatic LNs through prospective multicenter studies in the future.

Conclusions

In conclusion, ICG fluorescence imaging is an emerging new method in the era of precision treatment in minimally invasive surgery, and provides a more stable signal, more obvious background contrast, and deeper penetration depth than other contrast agents. This technology is recommended as an effective method for sentinel LN mapping and LN dissection navigation in minimally invasive surgery for GC. The application of ICG tracer-guided LN dissection is helpful in completing D1+ or D2 LN dissection in laparoscopic and robotic radical gastrectomy, and to perform more precise LN dissection in function-preserving surgery. Novices of minimally invasive radical gastrectomy and experienced surgeons can benefit from ICG fluorescence imaging.

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Contributors

QZ, QYC, JXL, JWX, PL, CHZ, CMH conceptualized and designed the study, acquired, and analyzed data, interpreted the study results, drafted and revised the manuscript.

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Competing interests

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Availability of data and materials

Further information is available from the corresponding author on reasonable request.

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Not applicable.

Provenance and peer review

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