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Endoscopic fluorescent lymphography for gastric cancer

Fluorescence for gastric cancer

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Abstract

Lymphography by radioisotope or dye is a well-known technique for visualizing the lymphatic drainage pattern in a neoplastic lesion and it is in use in gastric cancer. Indocyanine green (ICG) more recently has been validated in fluorescent lymphography studies and is under evaluation as a novel tracer agent in gastric cancer. The amount and dilution of ICG injected as well as the site and the time of the injection are not standardized. In our unit, endoscopic submucosal injections of ICG are made as 0.5 mg in 0.5 mL at four peritumoral sites the day before surgery (for a total of 2.0 mg in 2.0 mL). Detection instruments for ICG fluorescence are evolving. Near-infrared systems integrated into laparoscopic or robotic instruments (near-infrared fluorescence imaging (known as NIFI) have shown the most promising results. ICG fluorescence recognizes the node that receives lymphatic flow directly from a primary tumor. This is defined as the sentinel lymph node, and it has a high predictive negative value at the cT1 stage, able to reduce the extent of gastrectomy and lymph node dissection. ICG also enhances the number of lymph nodes detected during extended lymphadenectomy for advanced gastric cancer. Nevertheless, the practical effects of ICG use in a single patient are not yet clear. Standardization of the technique and further studies are needed before fluorescent lymphography can be used extensively worldwide. Until then, current guidelines recommend an extensive

lymphadenectomy as the standard approach for gastric cancer with suspected metastasis.

Key Words: Indocyanine green; Fluorescence; Lymphography; Sentinel lymph node; Gastric cancer; Lymphadenectomy

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Core Tip: Endoscopic injection of indocyanine green (ICG) the day before surgery is a simple technique that could increase the number of lymph nodes recovered during lymphadenectomy for advanced gastric cancer. In addition, ICG-guided sentinel lymph node detection could reduce unnecessary extensive lymphadenectomy and the amount of gastric resection in early gastric cancer. However, further research is needed to confirm its usefulness in both scenarios. Currently, D1/D2 lymphadenectomy remains the standard of care for gastric cancer with suspected metastasis. Our review explores this topic in depth and provides practical information for the endoscopic use of ICG.

INTRODUCTION

Lymphography dates back to the 1950s when the first studies were carried out[1]. The term 'sentinel lymph node' (SLN) was originally used in 1960[2]. A sentinel node is defined as the node that receives lymphatic flow directly from a primary tumor. The beneficial effects of SLN detection were first published by Morton *et al*[3] in 1992. They injected isosulfan blue vital dye in a melanoma, with the aim to select and evaluate neoplastic infiltration to the first lymph node (LN). They demonstrated that if there was no metastasis in the SLN, then metastasis would also be absent in the downstream LNs, thus avoiding unnecessary lymphadenectomy. SLN navigation surgery is a widely accepted technique for malignant melanoma[3] and breast cancer[4]. Several tracer agents have been studied over the past 70 years[1,5-7] and are used for the

detection of lymphatic drainage in several digestive surgical settings[8,9]. Studies of lymphatic drainage in gastric cancer have been carried out only relatively recently[10]. The primary outcomes in these studies was an increase in LN harvest[11] and in detection of SLNs[12].

Historically, a radioisotope (RI) technetium-99 tracer combined with a blue dye was injected endoscopically into the gastric submucosa around the tumor the day before surgery. The radioactivity of the LN was measured during surgery using a hand-held gamma probe[5,13]. This technique has a high detection rate and accuracy[14]. A meta-analysis based on 46 reports that included 2684 patients with gastric cancer using RI and/or dye showed sensitivity, detection rate, negative predictive value and positive predictive value of 87.8%, 97.5%, 91.8% and 38.0%, respectively[15]. The disadvantages of RI are expensive cost and the requirement of a radioactivity-controlled area. While this technique is considered the gold standard, it is rarely performed outside of Eastern Countries, currently.

INDOCYANINE GREEN AS A LYMPHATIC TRACER

Indocyanine green (ICG) is gaining status as the most utilized tracer in surgical practice. ICG is a sterile water-soluble tricarbocyanine dye that rapidly binds to plasma proteins and is subsequently drained by the lymphatic system. The visualization of ICG is difficult for the naked eye when observed in human tissue. However, when excited by near-infrared light at 700–900 nm, ICG emits fluorescence at a wavelength of approximately 820 nm and is easily visualized by various devices[16-18].

ICG submucosal (SM) or subserosal (SS) injection is virtually free of adverse effects. Although, rare cases of anaphylactic shock have been reported (0.05%-0.4%)[19]. Several methods of ICG mapping exist; they include, naked eye observation under white light (by Hiratsuka[12] and Ichikura[10]), infrared light observation (IREE; by Nimura[18]), infrared ray laparoscopic system (IRLS; by Takahashi[20]), and near-infrared fluorescent imaging (NIFI; by Kusano[16] and others). Of note, Hiratsuka's method is no longer used, largely due to its poor contrast, while Nimura's IREE and Takahashi's IRLS have fallen out of use due to the devices being commercially

unavailable but they are still generally considered excellent techniques. Only ICG fluorescent mapping (NIFI) is currently performed.

ICG was evaluated in surgical management of gastric cancer in order to guide selective lymphadenectomy in intraoperative SLN identification as well as comprehensive lymphadenectomy by increasing the number of total and metastatic LNs retrieved during gastric surgery. Feasibility of ICG lymphography by NIFI was demonstrated in open[11], laparoscopic[21] and robotic surgeries[22]. Surgeons are able to switch between white light, near-infrared light and a composite vision. Technical details were published by Zhu *et al*[23].

RATIONALE FOR LN STAINING IN GASTRIC CANCER

According to the European Society for Medical Oncology gastric cancer treatment guidelines 2022[24], D1 lymphadenectomy limited to perigastric LNs and those along the left gastric artery is recommended for early tumors (cT1) that do not meet the criteria for endoscopic resection. However, only 20% of T1 tumors have lymphatic involvement, and this approach resulted in overtreatment for most patients[24,25]. Furthermore, D2 lymphadenectomy with removal of additional LNs along the hepatic artery, splenic artery and coeliac axis is frequently performed in cT1 gastric cancer due to the difficulty of excluding micrometastases. This has a negative effect on morbidity and quality of life[26-28]. The number of LNs harvested during surgery for advanced gastric tumors was associated with correct staging and better prognosis[29-31]. However, extensive lymphadenectomy is a demanding procedure that carries a high risk of tissue or vascular injury. Therefore, detecting SLN draining in early (cT1) gastric tumors and facilitating the detection of LN in advanced gastric cancer would be beneficial and accepted in the clinical setting[11,29,32,33].

ICG FLUORESCENCE FOR SLN DETECTION IN GASTRIC CANCER

A pioneer study was conducted by Hiratsuka *et al*[12] and demonstrated that after peritumoral ICG injection SLN status was able to be visually defined with 100% sensitivity in a T1 group (44 patients) and 88% sensitivity in a T2 group (29 patients).

The authors concluded that SLN status could predict the presence of lymphatic metastasis with a high degree of accuracy, especially in patients with T1 gastric cancer.

Two meta-analyses regarding the diagnostic value of ICG for SLN detection in gastric cancer were published in 2018. In the first, Skublenky *et al*[34] included 643 patients from 10 studies conducted with IREE or NIFI detection devices; among them, 513 (79%) were cT1 patients. Pooled sensitivity and specificity of ICG fluorescence for SLN detection was 87% and 100%, respectively. Metastatic SLNs were retrieved in 18.7% of the enrolled patients. IREE demonstrated a higher diagnostic odds ratio, sensitivity and identification rate than NIFI. In the second meta-analysis, He *et al*[35] included 13 studies conducted with IREE, IRLS or NIFI devices. Significant heterogeneity among the included studies was found for sensitivity (from 50% to 100%) and for specificity (from 60% to 100%). There was also significant publication bias. An interesting subgroup analysis demonstrated that sensitivity for T1 was much higher than T2-T3. Intraoperative IGC injection was compared with preoperative injection. The sensitivity of the intraoperative injection subgroup was slightly lower than the preoperative injection subgroup (98% *vs* 99%). SM injections were compared to SS injections. The pooled sensitivity of the SM injection subgroup was considerably higher than that of the SS injection subgroup (98% *vs* 40%). NIFI also showed a lower sensitivity rate than either IREE or IRLS. Finally, when the ICG concentration of 5.0 mg/mL was compared to a diluted ICG concentration of 0.5 mg/mL or 0.05 mg/mL, the sensitivity of the former was lower than that of the latter (83% *vs* 98%); this was explained as due to a reduction of ICG fluorescence intensity with the higher concentration (*i.e.* the "quenching effect"). A comprehensive evaluation of effects of various ICG concentrations for SLN detection was conducted by Kinami *et al*[36].

The clinical application of sentinel node biopsy for gastric cancer must still overcome the problem of rapid intraoperative diagnosis of micrometastasis in the SNL. To reduce the rate of false negative findings, Miwa *et al*[37] suggested "en bloc" dissection of blue dye-stained perigastric SLN according to defined basins in their pilot study. The subsequently identified the SLN at the back table in the surgical suite (*ex vivo*). This method was termed "lymphatic basin dissection" and is now regarded as the standard method for SLN navigation surgery. A decade after that study, a

landmark multicenter research project by Kitagawa *et al*[14] demonstrated that lymphatic basin dissection with RI+ dye was able to detect the SLN in 97.5% of patients (n = 387/397). The accuracy of nodal evaluation for metastasis was 99% (n = 383/387). There were only four false-negative SLN biopsies, and in all patients with a false-negative intraoperative pathologic diagnosis the metastatic spread was limited to either the SLNs or within the SLN basins. To further limit false negative SLNs, it was suggested that only < 4-5 cm diameter T1 neoplasms be focused on. Another suggestion was to perform nucleic acid amplification, reverse transcription-polymerase chain reaction or immunohistochemistry in association with the intraoperative rapid (hematoxylin and eosin) pathology examination.

Kinami *et al*[38] described the algorithm for SLN navigation surgery conducted with ICG fluorescence detected by NIFI. The SLN detection is performed first, followed by lymphatic basin dissection, *ex vivo* identification and biopsy of the SLN(s), and intraoperative rapid pathology. If a metastatic SLN is detected, then a standard gastrectomy with nodal dissection up to D2 is performed; if the SLNs are diagnosed negative, then the extent of gastrectomy is reduced and function-preserving curative gastrectomy is applied (Figure 1).

Oncological effectiveness of the lymphatic basin dissection method for SLN detection has been demonstrated, along with its ability to prolong survival better than total gastrectomy and extensive LN dissection[38]. Importantly, function-preserving curative gastrectomy is safe and well tolerated[39,40] (Figure 2).

ICG FLUORESCENCE FOR LN DETECTION AND MAPPING IN GASTRIC CANCER

An increase of LN detection by ICG fluorescence *vs* white light has been confirmed in most of studies. Mean retrieval increases have varied from 7.9 LNs/patient[41] to 12.0 LNs/patient[42] and 13.7 LNs/patient[22]. The effects of ICG were also evaluated in a pooled analysis from two randomized controlled trials (FUGES-012 and FUGES-019 studies)[43]. Data from 514 patients showed a significantly increased mean number of LNs retrieved (an increase of 7.9 LNs/patient) in the ICG group compared to the non-ICG group. The sensitivity of fluorescence imaging for detecting all metastatic LN

stations was 86.8%. The negative predictive value was 92.2% for non-fluorescent LN stations. Regardless of gastrectomy type, the diagnostic accuracy for detecting all metastatic LN stations in the D1 and D2 lymphadenectomy for cT1-cT2 disease reached 100%. Kim *et al*[44] demonstrated that the activation of near-infrared fluorescence increased the detection of LN after a standard lymphadenectomy. A recent meta-analysis demonstrated that ICG was able to increase the mean number of harvested LNs by 6.93 LNs/patient (40.33 *vs* 33.40)[45].

Some studies observed an increased number of metastatic LNs detected by ICG[46], but a meta-analysis did not confirm this[45]. This may be due to metastatic LNs not staining or the presence of lymphatic vessels that are blocked. ICG does not have preferential uptake in metastatic LN, and frequently the overall percentage of fluorescent LNs and the percentage of metastatic fluorescent LNs are similar[44]. In addition, the number of LNs stained by ICG is small compared with the total number of LNs excised and often less than 60%[41,22,43].

The ability of ICG to visualize the anatomy of gastric lymphatic drainage was specifically evaluated in patients with advanced gastric cancer who underwent extended D2 lymphadenectomy[11]. During surgery, ICG was injected in 11 patients along the greater and lesser curvatures of the anterior surface of the stomach. ICG stained only 37.8% LNs (260 of 687) removed by D2 lymphadenectomy. ICG globally stained 30 of 75 (40.0%) metastatic LNs. In 4 out of 8 cases (50.0%), ICG signals were detected in all metastatic LN stations. Overall, ICG stained 21 of 28 metastatic LN stations (75.0%).

CONTROVERSIES FOR ICG USE IN GASTRIC CANCER

The usefulness of ICG fluorescent lymphography in gastric cancer remains controversial. A standardization of ICG concentration and method of injection is lacking. Several studies have proposed various dilutions of injected ICG. Dilutions vary from 5 mg/mL[16], 1.25 mg/mL[47], 0.5 mg/mL[40], and 0.05 mg/mL[11,48]. SM endoscopic preoperative injection and SS or SM intraoperative injection have been compared. Preoperative injection was observed to increase the number of detectable LNs for some authors[49], while others found that it did not increase the number of

detectable LNs[50]. Taken together, these results suggest that preoperative ICG injection the day before surgery may facilitate comprehensive mapping of lymphatic drainage, and an increased concentration of ICG is likely needed for intraoperative injection[34,47,49]. Further research is warranted to definitively answer these questions.

The theory that the absence of metastasis in the SLN corresponds to an absence of metastasis in downstream LNs may not apply to gastric cancer due to the complexity of the lymphatic system of the stomach. It is difficult to accurately visualize the connections between the perigastric lymphatic network and the location of every single LN, which can lead to micrometastases or skip metastasis detection[10, 51-53]. The number of false negative SLNs has been shown to gradually increase from T1 to T3 gastric cancer[54] due to lymphatic obstruction by massive cancerous infiltration[43]. Kitagawa *et al*[14] suggested that SLN navigation surgery should only be performed on cT1 gastric cancer due to the higher risk of false negatives in cT2 gastric cancer.

SLN detection may avoid the need for an extended lymphadenectomy and limit the area of gastrectomy and preserving the pylorus or allowing a segmental gastrectomy. However, it has been reported that the patient's quality of life following laparoscopy-assisted pylorus-preserving gastrectomy is equivalent to that following laparoscopy-assisted distal gastrectomy[55]. Similarly, it was reported that patients who received a D3 lymphadenectomy showed no significant difference in quality of life compared to patients who received a D1 lymphadenectomy[56].

A multicenter study by Miyashiro *et al*[57] (Group multicenter trial JCOG0302) published in 2014 was prematurely suspended due to high false negative SLN detection. However, the authors concluded that false negative SLNs were a consequence of inadequate histological detection (only one slide and hematoxylin and eosin staining) and not due to ICG performance. A meta-analysis showed that the sensitivity of immunohistochemistry plus hematoxylin and eosin was superior to use of hematoxylin and eosin alone (0.99 *vs* 0.77)[35]. Unfortunately, the use of immunohistochemistry in clinical practice would likely be demanding.

There is little data regarding the effects of neoadjuvant therapy on ICG fluorescence. The histological fibrotic changes following chemotherapy may represent

a possible limitation of ICG dissemination in the lymphatic system. Therefore, the intraoperative identification of peritumoral LNs may be impaired[41].

Finally, it is accepted that ICG fluorescence increases the number of LNs harvested, but the clinical utility is debatable because detection of metastatic LNs did not increase. In addition, an ICG-guided lymphadenectomy is not feasible due to the low percentage of LNs stained. Park *et al*[11] demonstrated in a series of patients with advanced gastric cancer that ICG detected only 37.8% of the total LNs and only 37.5% of metastatic LN stations were retrieved. This was likely due to obstruction of lymphatic vessels.

ICG FLUORESCENCE FOR GASTRIC CANCER: A WESTERN PERSPECTIVE

The incidence of gastric cancer in western countries is roughly 17%-25% of the incidence in East Asia[58]. Consequently, the experience of Western surgeons, with the exception of a few referral centers, may not be comparable to that in East Asia. In general, the experienced Asiatic surgeons believe that lymphatic mapping is unnecessary if accurate LN dissection and careful harvesting are performed. In advanced gastric cancer, however, mapping with ICG fluorescence could increase the quality of LN dissection in less experienced western centers and this must be considered.

The technique of ICG for SLN detection in gastric cancer is complex and requires training for at least 30 procedures[14]. Unfortunately, the opportunity to learn the SLN navigation surgery technique in Western countries is compromised by the fact that only a reported 20% of gastric cancers in the West are T1 at diagnosis compared to 50% in East Asia[59].

Historically, western surgeons have less experience with extensive lymphadenectomy for gastric cancer because DII lymphadenectomy became a standard of action only after the follow-up results from the Dutch D1D2 trial were released[60]. As a consequence, western schools of surgery had less experience with LN mapping and SLN navigation surgery techniques prior to the recent widespread use of ICG. This explains why Eastern surgeons consider ICG to be a mere reintroduction of yet another tracer for gastric surgery, whereas for Westerners it represents an

entirely new experience.

Another obstacle encountered when ICG was introduced in gastric cancer was the lack of clear guidance from the literature regarding the best dilution of ICG for the laparoscopic system. Also, since proprietary devices are obviously evolving, the latest version of the Olympus laparoscopic system, the Visera Elite III (Olympus Europa SE & Co.KG, Hamburg, Germany), which was acquired by our unit uses a different technique for NIFI from its predecessor, the Visera Elite II, and likely requires a higher dilution of ICG; we will explore this in the future. In the East, this issue was overcome by the considerable experience of surgeons who have structured customized techniques over the years; it could be the same for western surgeons as they continue increasing their practice. Although there are many useful indications online in the International Society for Fluorescence Guided Surgery (ISFGS) documents[61] our personal experience has led to cautious consideration for gastric cancer because the optimal dilution has not been well defined yet. We advocate that in the future, the ISFGS (https://isfgs.org/) in collaboration with laparoscopic equipment companies will define the best ICG dilution for each proprietary device.

ICG USE FOR GASTRIC CANCER IN CLINICAL PRACTICE

In our surgical unit, ICG fluorescence detection is still primarily performed by video-angiography with the Olympus Visera Elite II. This detection technology is based on the use of two optical filters located, respectively, in the light source and the proprietary ULTRA infrared optics. These filters cut certain frequencies in the light spectrum that allow the system to detect light emission in the near infrared (NIR), a wavelength range from 800 nm to 2500 nm. The filter in the light source blocks the red component of visible light, allowing blue-green and infrared light to pass through, hitting the tissue and being reflected (the infrared is partly reflected and partly penetrates the tissue, reaching the ICG molecules that emit fluorescence). At this point, the filter in the laparoscopic optics blocks the infrared reflection while allowing the blue and green visible light components and fluorescence to pass through, and thereby enabling the two viewing modes (partial white light fluorescence and pure fluorescence) (Figure 3).

ICG is commercially available in 25 mg or 50 mg vials and is with saline-free water diluted in most studies. In our unit, endoscopic SM injection is performed the day before surgery. We inject four boluses, each containing 0.5 mg/0.5 mL of saline-free water, *via* a sandwich technique. An example of the visual effects of endoscopic injection are shown in Figure 4. Figure 5 illustrates the methods of dilution and injection.

ICG LYMPHOGRAPHY FOR GASTRIC CANCER: WHAT'S NEW

Theoretically, if all SLNs were histologically negative for cancer metastases, then endoscopic mucosal resection (EMR)/endoscopic submucosal dissection (ESD), instead of gastrectomy, may be appropriate for the curative resection of cT1 early gastric cancer that is outside the EMR/ESD criteria. Feasibility and performance of ICG staining after ESD was studied by Roh *et al*[62]. In their study, SLN-guided lymphadenectomy by ICG fluorescence was evaluated in 98 out of 290 patients who underwent gastrectomy after a non-curative ESD requiring standard lymphadenectomy according to the existing guidelines. ICG stained 8 out of 9 metastatic SLNs. The sensitivity was 88.9%, the negative predictive value was 99.9%, and the positive predictive value was 0.3%. The sensitivity and negative predictive value for detecting SLN metastasis by ICG was 100% if we considered the lymphatic stations because all metastatic stations were detected by at least one SLN stained with ICG. However, only 66% of LNs were stained by ICG, and only 9/4671 metastatic LNs were retrieved. The data are encouraging, but need further confirmation because there are concerns that some metastatic LNs may not be detected.

The SENORITA trial[63] is ongoing. This randomized controlled trial enrolled 580 patients and is confirming the usefulness of SLN navigation surgery for cT1 patients who do not meet the criteria for EMR/ESD. The trial is evaluating whether laparoscopic stomach-preserving surgery with SLN detected by ICG fluorescence achieves similar oncologic outcomes and improved morbidity compared to a standard gastrectomy with D1/D2 lymphadenectomy. Preliminary data have demonstrated that the organ-preserving surgery was performed in 81.4% of patients, and postoperative complications occurred in 15% of those patients. The SENORITA 2

phase II trial[64] is comparing laparoscopic SLN navigation surgery to laparoscopic standard gastrectomy in patients with early gastric cancer after endoscopic resection.

The combination of laparoscopic SLN biopsy and EMR/ESD for cT1 early gastric cancer is a very attractive novel minimally invasive approach. Non-curative EMR/ESD curative and subsequent laparoscopic limited gastrectomy or full-thickness endoscopic resection combined with SLN navigation surgery has the potential to become the standard minimally invasive surgery for patients with early gastric cancer.

CONCLUSION

ICG fluorescent lymphography is an attractive and feasible option in gastric cancer surgery. Endoscopic SM injection of ICG the day before surgery is a simple and effective approach. Alternatively, intraoperative SS staining is feasible. ICG staining increases LN visualization and increases the number of LNs retrieved during surgery. Currently, ICG staining is encouraged in cases of D1-D2 lymphadenectomy because it has been shown to facilitate LN dissection and to increase the number of LNs harvested. However, ICG staining does not increase the number of metastatic LNs retrieved. ICG-guided SLN navigation surgery is a promising technique to reduce unnecessary extensive lymphadenectomy and gastric resection in patients with cT1. It may also be useful after a non-curative ESD.

However, further research worldwide and technique standardization are necessary to confirm the utility of ICG staining of SLNs. Current studies typically have small sample sizes, and there is a large number of studies from Asia, which has different experience from other areas due to the higher prevalence of gastric cancer in Asia. Another challenge is the low sensitivity of ICG staining of LNs that are not retrieved, which represents a potential risk of metastasis and prevents an exclusively ICG fluorescence-guided LN dissection. At this time D1/D2 lymphadenectomy remains the standard of care for patients with gastric cancer with suspected cancer cell metastasis.

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