Review Article

Indocyanine green (ICG)-guided lymphadenectomy during complete mesocolic excision of colorectal cancer: a narrative overview

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Objective: To review and discuss the rationale, technique and results of indocyanine green (ICG)-guided lymphadenectomy

Background: In recent years, more radical surgeries such as complete mesocolic excision with central vascular ligation and the Japanese D3 lymphadenectomy have been increasingly adopted as the optimal approach for colorectal cancer. These approaches share a specific focus on the extent of lymphadenectomy. While lymph node metastases are a major determinant of prognosis and a key factor for deciding further management, it has been recognized that the extent of lymphadenectomy, which in turns affect the number of lymph node harvested, might have a therapeutic effect with improved survival in patients with a higher number of dissected lymph nodes. However, individual variations of the lymphatic flow pattern, with possible extramesocolic diffusion, have been described for all colonic area, in particular for tumors of the hepatic and splenic flexures. In addition, the definition of the area to dissect, in particular the D3 area, is based on anatomical landmarks that might vary due to frequent vascular variants. Therefore, the possibility of directly visualize the regional nodal basin might increase the precision of an individualized lymphadenectomy. ICG is a fluorescent fluorophore that, after direct tissue injection, migrates in lymphatics and lymph nodes providing an intraoperative map of the tumor-specific draining area.

Methods: A through literature search was done to identify pertinent articles.

Conclusions: Although few studies exist, data indicate the potential of using this technique to guide the lymphadenectomy: complex surgical procedures seem facilitated and the extent of resection is tailored to include, in up to 34% of patients, lymph nodes that otherwise would not be harvested, resulting in a higher lymph nodes yield.

Keywords: Indocyanine green lymphatic mapping (ICG lymphatic mapping); indocyanine green fluorescence (ICG fluorescence); colorectal cancer; indocyanine green-guided lymphadenectomy (ICG-guided lymphadenectomy)

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Introduction

The principle of colon cancer surgery in patients with localized disease is *en-bloc* resection of the primary tumor with regional lymph nodes. In recent years growing knowledge have refined the concept of the optimal oncologic resection and most surgeons have adopted more aggressive approaches including complete mesocolic excision (CME) with central vascular ligation (CVL) (1,2), the Japanese D3 lymphadenectomy and extra-mesenteric lymph node dissection. CME is based on the same principle of TME surgery in the rectum and entails removal of an intact peritoneal and fascial-lined package of mesentery containing all potential routes of metastatic tumor spread. To ensure the complete lymph nodes removal in the central direction the technique of CME requires a central vascular tie. A similar concept underlies the Japanese D3 lymphadenectomy. According to the Japanese Society for Cancer of the Colon and Rectum (3), regional lymph nodes are classified as pericolic (i.e., along the marginal arteries and vasa recta of the colon), intermediate (i.e., along the colic arteries), and main (i.e., at the origin of each colic artery). The extent of lymphadenectomy is expressed with the D number: the term D3 applies to the type of lymphadenectomy wherein complete dissection of all three regional lymph node stations is performed. When comparing D3 specimens with CME specimens, both showed higher rates of the mesocolic plane surgery and long distances from the high vascular tie to the bowel wall (4).

The common denominator of these approaches is the focus on complete lymph node retrieval. Among the known prognostic factors, the presence of lymph node metastases has been established as the single most important prognosticator in both colon and rectal cancer and represents one of the constitutive components of the current TNM staging system. Although 12 lymph nodes have long been considered sufficient for an adequate staging, multiple evidence indicate that increasing the number of harvested lymph nodes from the regional basin not only provides a more precise prognostication but also improves patients' survival (5-9). Therefore, while lymph node yield is determined by numerous factors, many inherent to the patient, the tumor and the histopathological practice, the extent of lymphadenectomy to provide a curative intent resection remains crucial. Whatever the definition of lymphadenectomy (CVL or D3) the field of lymph node retrieval has been described based on vascular landmarks, even though intestinal vascular anomalies or aberrant vessels are relatively common (10-12) and the D3 area is not precisely defined, with terminology that has changed over time. In addition, while the lymphatic draining pattern is similar in many patients, numerous studies have shown individual variability as well as unusual patterns of extramesocolic diffusion such as in tumor of the right colic flexure through the Henle's trunk toward the gastroepiploic vessels or in patient with splenic flexure tumors to infrapancreatic or splenic hilum lymph nodes (13,14). Similarly, in tumor of the splenic flexure different and unpredictable lymphatic drainage roots within the mesentery are possible (14,15). Unfortunately, the individual lymphatic pattern is visually indistinguishable although a personalized surgery would be desirable. In recent years, several strategies have been investigated to intraoperatively visualize the anatomy of the lymphatics with some authors using this as a roadmap to guide the lymphadenectomy.

Aim of this article is to describe the rationale, technique and results of indocyanine green (ICG)-guided colorectal lymphadenectomy.

A literature search using the PubMed and MEDLINE databases from database inception to 31 January, 2021, was done to identify pertinent articles. The following search terms "indocyanine green", "ICG", "Near-Infrared (NIR) Fluorescence", "colorectal", "cancer", "lymph node", "lymphatic mapping", "lymphadenectomy", and "Surgery", were used in various combinations. In addition, a search of major databases collecting trials from all over the globe (ClinicalTrial.gov, EU Clinical Trials Register, EudraCT, International Clinical Trials Registry Platform-WHO, ISRCTN Registry, Global Clinical Trials Data, EORTC Clinical Trials Database, Japan Registry of Clinical Trials-jRCT; last access February 3, 2021) (search terms "indocyanine-green", "ICG" and "colorectal") was performed to identify ongoing studies on this topic.

We present the following article in accordance with the Narrative Review reporting checklist (available at https://dx.doi.org/10.21037/ls-21-5).

Rationale for the use of ICG

ICG is a water-soluble, tricarbocyanine dye that, after intravenous injection, binds tightly to plasma proteins, of which albumin is the principal carrier (95%), and remains confined in the intravascular compartment until elimination. ICG is extracted from the plasma almost exclusively by the hepatocytes, with a plasmatic half-life of 150–180 seconds, and is excreted unchanged entirely into the bile after

15–20 min. ICG is a fluorophore, i.e., a chemical compound that upon light excitation absorbs light energy and re-emits a light at a longer wavelength. The ICG spectral absorption is from 790 to 805 nm. Therefore, use of a near-infrared (NIR) light source is necessary to excite the ICG molecules which in turns emit a fluorescent signal at 835 nm captured from a dedicated optical system and displayed on the screen of a laparoscopic or robotic equipment. ICG can be used for fluorescence imaging, which is emerging as a major contributor to intraoperative decision making and surgical guidance. Considerable published evidence, including several meta-analyses and large clinical trials, exists proving the safety of ICG with the only cautionary note for possible adverse reaction in patients with iodine or shellfish allergies. Therefore, its safety profile greatly facilitates its diffusion in the daily practice (16).

Several applications of ICG fluorescence in cancer surgery have been described. In particular, it has been used to define the lymphatic pattern in patients with breast cancer, gastric cancer and melanoma (17-19). Studies have shown that, if injected directly in tissue, ICG migrates in lymphatic vessels and in lymph nodes, where it deposits into macrophages (20) and can provide information about organs' lymphatic draining basin. In the past years, in patients with colorectal tumors, ICG, as well as other dyes or radiotracers, have been used mostly to identify the "sentinel nodes" to be extensively analyzed for micrometastases and isolated tumor cells' identification with the scope of fully staging the resected tumor. However, few manuscripts report the use of lymphatic mapping to guide the extent of lymphadenectomy. With this purpose, ICG-fluorescence is emerging as the preferred operative modality.

ICG-guided lymphadenectomy: technique and results

A fluorescent lymphatic mapping can be obtained by either submucosal or subserosal ICG administration. While intraoperative subserosal peritumoral injection has been frequently used, this approach has some limitations. First, accurate subserosal injections might be complex especially in minimally invasive surgeries and an inadvertent direct puncture of the tumor might be at risk of intraperitoneal tumor spillage. Second, authors have reported a frequent ICG intraperitoneal leakage from injured lymphatic vessels, not seen after preoperative endoscopic injection (19). This leak translates into a widespread distribution of bright ICG fluorescence covering over the surgical field and making further ICG-guided surgical procedure difficult. Third, in patients undergoing ICG guided sentinel node mapping for gastric cancer the mean number of fluorescent nodes was significantly higher in the preoperative ICG injection group than in the intraoperative subserosal ICG injection group (19). Therefore, the preoperative endoscopic route of injection appears more appealing. In these patients, ICG diffuses into the draining nodes where it remains for 24/48 hours. Although there is no evidence on the optimal dose of ICG and timing of injection, most investigators have adopted a similar protocol for endoscopic administration (21-23). To ensure sufficient time for the dye to migrate towards all lymph nodes, a total of 0.2–1.2 mL of an ICG solution (dilution: 2.5 mg of ICG/mL of sterile water) is injected endoscopically in the peritumoral area between 3–5 hours to 1–2 days before surgery. At our institution, a standardized protocol is utilized: it dictates the endoscopic injection, through a 22-gauge needle, of 3 mg of ICG at the dilution of 2.5 mg/mL into the four cardinal points around the tumor. Submucosal injection does not contemplate a preemptive submucosal lift to avoid the risk of excessive ICG dilution. We routinely perform the endoscopic ICG injection 24 hours before surgery since in patients in whom injection is performed the same day of surgery, the fluorescent signal has been reported to be weak (22).

The most relevant clinical data regarding the outcomes of this procedure are derived from a 1:2 matched case-control study (25 patients undergoing fluorescence imaging-guided laparoscopic surgery versus 50 undergoing conventional laparoscopic surgery) (21) and from a case-series analysis of 50 patients (22). Both studies focused on patients undergoing right colectomy with CME and/or D3 lymphadenectomy. In all patients, the procedure of lymphatic mapping was successful with intraoperative visualization of fluorescent nodes. Interestingly, with the exception of one case, fluorescent lymph nodes were observed in the D3 area, along the superior mesentery vessels, highlighting the potential for a precise definition of the lymphatic flow pattern. In addition, in 32% of patients (8 out 25) in the study of Park (21) and in 34% of patients (17 out 50) in the study of Petz (22) lymph nodes outside the standard lymphatic basin were identified and removed with either a "berry-picking" technique or with extension of the *en-bloc* dissection area to the left of the superior mesenteric artery or to the gastroepiploic vessels. *Figure 1* depicts a representative case treated at our institution in which fluorescence permitted to identify a lymph node on

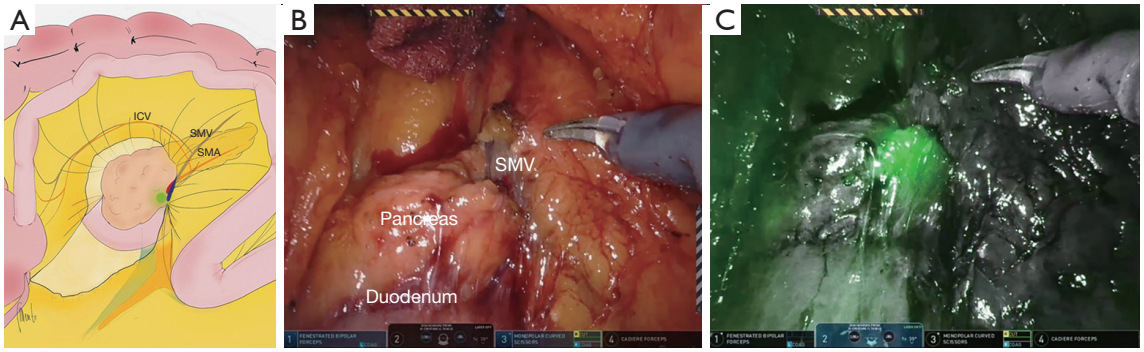

Figure 1 Sketch of the surgical field (A) and corresponding intraoperative pictures under white (B) and near-infrared (C) light of a patients undergoing robotic right colectomy with complete mesocolic excision and D3 lymphadenectomy with a bottom-to-up approach. With NIR light a fluorescent node is visualized on the uncinate process of the pancreas (the green dot represented in A) that was not visible under normal white light. SMV, superior mesenteric vein; SMA, superior mesenteric artery; ICV, ileocolic vessels; NIR, near-infrared.

the uncinate process of the pancreas that otherwise would not have been distinguished nor removed. Noteworthy is also the fact that proponents of this technique observed that with ICG-guidance the lymphadenectomy of the intricate D3 area was facilitated as compared to cases performed without ICG (21,22,24). As a consequence, a high median of 34 and 41 lymph nodes were harvested in the series of Petz (22) and Park (21), respectively. In a direct comparison with the control group undergoing surgery without ICG-guidance, Park *et al*. (21) demonstrated a significant increase of the total number of lymph nodes retrieved with IGC-guidance (41 *vs.* 30, P=0.021), as well as of the number of lymph nodes retrieved from the D3 area (14 *vs.* 7, P<0.01). After controlling for possible confounding factors with multivariate analysis, ICG-guidance remained an independent predictor of the number of removed lymph nodes either total number or D3 nodes. None of the studies reported complications related to the use of ICG or to the extension of the field of lymphadenectomy, suggesting that ICG-guided lymphadenectomy is a safe procedure. Our personal experience confirms the safety of this approach. Since November 2018 we have performed 108 colorectal resections with ICG-guided lymphadenectomy using the da Vinci Xi® robotic platform: none of the patients had procedure's related complications (unpublished data).

Scarce data exist on the potential benefit in patients undergoing resection for tumors of the left colon or rectum. We report herein our experience in 56 patients operated on during the past 2 years, with 40 of them enrolled within a prospective observational study (GREENLIGHT Trial approved by the Ethical Committee of the Candiolo Cancer Institute, FPO-IRCCS, protocol number 363/2018). All patients [31 male and 25 female, median age 63 years (range, 44–88 years)] underwent robotic left colectomy (n=23) or anterior rectal resection (n=33) with partial or total mesorectal excision (TME) based on the distance of the tumor from the anorectal junction. All 56 patients had a high tie of the superior mesenteric artery. ICG-fluorescence lymphatic mapping was intraoperatively visualized with the Firefly™ vision modality and used to guide the extent of lymph nodes retrieval. Fluorescent lymph nodes outside the field of standard lymphadenectomy were observed in 17 (30.4%) patients. All these nodes (median 2; range, 1–5) were excised with the "berry-picking" technique. *Figure 2* depicts the anatomical sites of nodes outside the standard lymphadenectomy field. No complications were registered as a consequence of the additional node retrieval.

Use of ICG lymphatic mapping has been also investigated in patients with mid-low rectal cancer and suspected lateral pelvic lymph node (LPLN) metastases with the aim of defining whether it might facilitate the complex surgical procedure of lateral pelvic node dissection (LPND) (25). In a series of 42 consecutive patients, 12 patients underwent LPND with ICG-fluorescence guidance after preoperative transanal submucosal ICG injection (dose 4 mL, 0.1 mg/mL) into four sites on the anal side of the tumor. In all patients a fluorescent mapping of the LPLNs was visualized after completion of the rectal resection with TME. In these patients the number of LPLNs harvested was significantly higher than that obtained after LPND without ICG-guidance (11.5±5.9 *vs.* 7.1±4.8) suggesting that ICG might improve the accuracy in detecting small or occult lymph

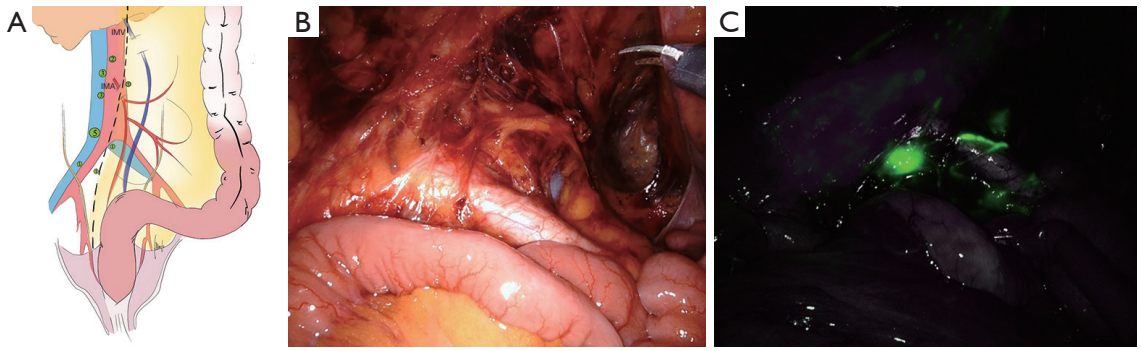

Figure 2 Sketch and intraoperative pictures of the surgical field showing the position of fluorescent nodes outside the standard field of lymphadenectomy during resection of tumors of the left colon and rectum. (A) The green dots are positioned in anatomical sites of fluorescent nodes identified outside the standard field of lymphadenectomy which is indicated with the dotted black line; the number inside each green dots is the number of patients who had showed fluorescent nodes in that anatomical position; (B,C) intraoperative pictures under white (B) and near-infrared (C) light showing a fluorescent node on the right of the aorta at the origin of the iliac artery. IMV, inferior mesenteric vein; IMA, inferior mesenteric artery.

nodes thus enhancing the radicality of the procedure. In fact, in the non-ICG group, 2 out of 30 patients developed an early recurrence in residual lymph nodes at the level of the distal left internal iliac artery and in the left obturator foramen, respectively. The authors concluded that the use of ICG might provide a significant advantage in LPND due to better distinction between lymph nodes and non-lymphatic soft tissues thereby also better preserving of blood vessels and nerves in difficult anatomical areas.

Clinical relevance

In patients with colorectal cancer the presence of lymph node metastases is a major determinant of prognosis and a key factor for deciding further management, particularly adjuvant therapy. Although the AJCC-UICC TNM staging system recommends examination of a minimum of 12 lymph nodes for adequate staging, several studies have demonstrated a positive correlation of greater number of harvested lymph nodes with improved survival (6,26-28). This observation revitalizes the unsolved debate on whether lymphadenectomy is directly therapeutic or whether it simply provides prognostic and staging information. Indirect evidence for a therapeutic benefit of lymphadenectomy can be inferred from studies focusing on lymph node count. The most compelling ones come from the secondary analysis of data from The Intergroup Trial INT-0089 that showed, in patients with N2 disease, a 5-year overall survival increase from 51% to 71% if >35 lymph nodes were retrieved compared to <35, with an absolute 22% improvement in 5-year disease-free survival (from 48% to 69%) (26). Since all patients had at least 4 metastatic lymph nodes, better staging and stage migration cannot entirely explain the results, implying a curative component of the lymphadenectomy.

With these premises, in recent years more extensive surgeries, including CME, CVL, D3 lymphadenectomy and extra-mesenteric lymph node dissection, have been progressively implemented worldwide in an effort to ensure more appropriate cancer-directed treatments. This aggressive surgical approach enables maximal lymph node yield for precise cancer staging and maximal clearance of all draining lymph nodes, in particular the central mesocolic lymph nodes. Pathological analyses of the metastatic pattern in the regional lymphatic basin have demonstrated that right-sided tumors spread to central mesocolic nodes in 1–22% of cases, while a slightly inferior proportion of ≤12% is observed in patients with left-sided colon cancers (29). Noteworthy is the observation that up to 9% of patients have central "skip metastases", e.g., the presence of positive lymph nodes in the D3 area with negative D2 lymph nodes, with differences in reported frequencies mostly depending on the methodology for N+ detection, i.e., routine histology versus use of immunohistochemistry or molecular technique (reverse transcription polymerase chain reaction) (29). Although the debate on the appropriate extent of lymphadenectomy, in particular whether or not to include the D3 area, is still open, growing evidence support the removal of the entire lymphatic basin including the

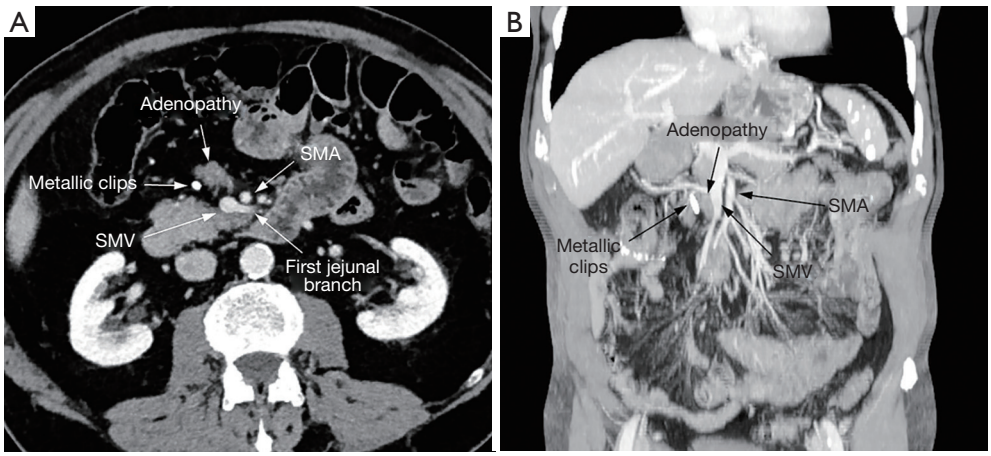

Figure 3 Computed tomography scan images (A: axial; B: MIP reconstruction) showing a recurrent lymph node metastasis in front of the superior mesenteric vein close to the metallic clips used to secure the ileocolic vessels. The patient undergone right colectomy with lymphadenectomy for a pT3 pN1a (1 LN+/13) adenocarcinoma of the cecum followed by adjuvant chemotherapy interrupted for a severe allergic reaction during the 2nd cycle; after 3.5 years he developed this lymph node recurrence that was surgically resected. At 2 years the patient is disease free. SMA, superior mesenteric artery; SMV, superior mesenteric vein; MIP, maximum intensity projection.

central nodes in cN+ and cT3-4 N0 patients (30).

While a number of reports have demonstrated that variations exist in the individual lymphatic flow pattern, even in extramesocolic lymph nodes, the exact definition of the area to dissect, in particular the D3 area, is not precisely defined, and terminology has changed over time (3,31). The boundaries of the lymphadenectomy areas are usually described using anatomical structures, namely arteries and vein to be either ligated at their origin or dissected (respective examples are the ileocolic vessels and the anterior surface of the superior mesenteric vein in D3 lymphadenectomy for a tumor of the cecum). In recent years the concept of precision medicine, aiming at generating knowledge and optimizing treatment strategies that take individual variability into account, has been dramatically improved. Within this context, the concept of precision image-guided surgery is emerging as a potential strategy to improve the quality of oncological resections and to reduce the risks of iatrogenic injuries (32,33). ICG-fluorescence lymphatic mapping, which provides an intraoperative visualization of the anatomy of the individual lymphatic draining basin, brings the surgeons into this new era. Data from available studies indicate first that preoperative endoscopic injection of ICG permits in almost all patients to visualize the tumor's draining lymph nodes up to the D3 area. Second, 30–34% of patients' fluorescent nodes are found outside the area that would have been dissected without the aid of fluorescent mapping. These data are consistent with those reported by Saha *et al*. (34) who changed in ~22% of patients [in 24 out of 104 (23.1%) patients with right colon cancer and in 18 out 87 (20.7%) patients with left colon cancer], the extent of the operation beyond the field of standard resection margin due to the intraoperative evidence of aberrant drainage after subserosal blue dye injection. Interestingly, in this large series, in 19 out of 192 patients (9.9%) lymph node metastases were found in aberrant locations and in 2 patients aberrant lymph nodes were the only pathologically positive nodes. Third, all authors reported the ease of performing under the ICG fluorescence guidance the lymph node dissection of the intricate D3 area draining the right colon or of the lateral pelvic region. This, in turn, resulted in a higher number of lymph nodes harvested in the studies of Park *et al*. (21) and of Zhou *et al*. (25).

Overall, the presented data suggest that the fluorescence guidance helps surgeons to achieve a radical, potentially curative resection. As others (35), we have observed patients who had received a supposed radical lymph node dissection at primary surgery but later developed isolated metastases in central nodes (D3 area) and underwent curative re-resection (35). *Figure 3* depicts one of these cases: the patient was reoperated with complementary lymphadenectomy around the superior mesenteric vessels. The history of these individual cases reinforces the concept that a

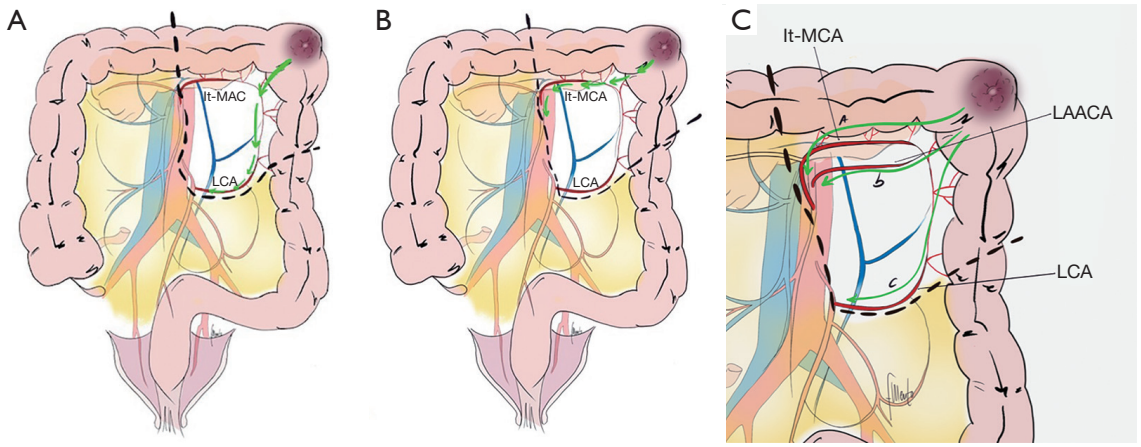

Figure 4 Splenic flexure drainage pathways indicated by green arrows. (A) Main pathway toward the left colic artery (LCA); (B) main pathway toward the left branch of the middle colic artery (lt-MCA); (C) in patients in whom there exists the left accessory aberrant colic artery (LAACA) 3 routes indicated by the letters a, b and c are identified. The black dotted line indicates the boundaries of the D3 area based on the principles of the Japanese Society for Cancer of the Colon and Rectum.

complete lymph nodes removal is mandatory to achieve the highest probability of survival for the patient. The direct visualization of the draining nodes with ICG fluorescence appears to be an excellent aid in achieving a complete node dissection. Although the most evidence is derived from patients undergone right colectomies, the advantages of ICG fluorescence guidance might be of utmost importance also in patients with tumors of the splenic or hepatic flexures. Splenic flexure is a critical site because tumors in this location are in the middle of two vascular territories, e.g., between the middle colic artery through its left branch (lt-MCA) and the left colic artery (LCA) with multiple lymphatic drainage roots, including extramesocolic nodes along the lower edge of the pancreatic body and tail or the splenic hilum (13,14,36). Using intraoperative subserosal injection of ICG, Watanabe *et al*. (36) studied the direction of lymphatic flow from splenic flexure tumors in 31 patients. They recognized different patterns schematized in *Figure 4* according to the presence (in 61% of patients) or absence (in 39% of patients) of the left accessory aberrant colic artery (LAACA) which originates from the superior mesenteric artery more proximally to the middle colic artery, at the inferior border of the pancreas. In patients in whom the LAACA was not present, the prevalent direction of the lymphatic flow was along the LCA (*Figure 4A*) in 68% of patients and along the lt-MCA (*Figure 4B*) in 31% of cases. Interestingly no case exhibited a lymph flow in both the LCA and lt-MCA areas. When the LAACA was present 3 different patterns where observed: along the LAACA (route B in *Figure 4C*) in 33% of cases, along the LAACA and the lt-MCA (routes A + B in *Figure 4C*) in 25% of patients, or along the LAACA and the LCA (routes B + C in *Figure 4C*) in the remaining 42%. Since no systematic data nor clear unequivocal indication exist on the proper extent of lymphadenectomy/site of vascular ligation, in patients with these tumors, understanding the individual lymph flow direction might help deciding the more appropriate operative procedure. Similarly, it has been shown that, in patients with hepatic flexure colon cancer, an extramesocolic lymphatic diffusion to infrapyloric and gastroepiploic nodes is possible. In past years resection of these nodes used to be a routine practice at specialized institutions in Japan. However due to the rarity of proven metastasis in this area, which ranges between 2% and 9% (29), at present inclusion of this node station in the field of lymphadenectomy is recommended only in cases of clinically suspected metastases. Use of IGC fluorescence might refine this indication by showing the territory of potentially involved lymph nodes. In patient in whom fluorescence is clearly visualized in this area, resection of infrapyloric and gastroepiploic nodes can be considered because of the potential to remove nodes harboring micrometastases or isolated tumor cells.

At present most manufacturers of laparoscopic or robotic equipment have developed optics systems with NIR light reflecting the growing interest of the surgical community toward the use of NIR-fluorescence imaging that, nowadays, should be part of the routine practice in different fields of surgery (16). Technology is also rapidly evolving and is now possible to have the NIR-fluorescence images

Table 1 Advantages of the ICG-lymphatic mapping with fluorescence-guided lymphadenectomy

Individualized definition of the single patient lymphatic anatomy that permits identification, in 30–34% of cases, of draining nodes outside the standard field of lymphadenectomy
Intraoperative definition of the type of node dissection in patients with variable lymphatic pattern (e.g., patients with tumor of the splenic flexure) and/or with potential extramesocolic diffusion (e.g., patients with tumor of both the hepatic and splenic flexure)
Easy dissection of the D3 area in patients undergoing right colectomy
Visualization of the lymphatic map seems to increase the number of harvested lymph nodes, providing a better staging and, potentially, the removal of all regional nodes harboring micrometastases or isolated tumor cell
The real-time visualization of the lymphatic map during CME and CVL may help to prevent iatrogenic rupture of the lymph vessels and/or lymph nodes with consequent tumor spillage

ICG, indocyanine green; CME, complete mesocolic excision; CVL, central vascular ligation.

superimposed to the surgical field observed in white light. Whether technical specification of different optics systems might affect the sensitivity of intraoperative detection of fluorescent lymphatic mapping remains unknown, it is reasonable that any equipment may offer an adequate view of the lymphatic pattern.

Many unsolved questions remain. Dose, number of ICG injection and time of administration need to be standardized. In addition, it will be important to clarify whether tumor invasion leads to lymphatic vessel obstruction. In fact, while some authors report a complete fluorescent-marked lymphatic area also in the presence of lymph node metastases, indicating that the fluorescent lymphatic flow is consistent with lymph node metastasis (21,23), others have postulated that lymph node metastases might change the lymphatic flow (23,24), thus reducing the value of fluorescence in precisely determining the draining area downstream to the occluded lymphatics. Overall, more robust data to support the benefit of this technique need to be generated. The search of ongoing study resulted in identification of only 3 registered trials: the first one from UK (ClinicalTrials.gov Identifier: NCT03204994) investigates pelvic lymph node mapping in patients with rectal cancer (completion date 8/01/2018); the second from China (ClinicalTrials.gov Identifier: NCT04207489) aims at defining related factors that affect the imaging effect (ongoing); the third from Japan (jRCTs031200195) is designed to determine whether the tumor location can be detected intraoperatively—primary endpoint—with a secondary endpoint evaluating the possibility that regional lymph nodes have luminescent properties (ongoing).

Despite some uncertainties, the theoretical premises and available evidence on the use of ICG guided lymphadenectomy, summarized in *Table 1*, are a solid base for further research. At present, fluorescent mapping can be used to better define the central boundaries of lymphadenectomy or to extend nodes retrieval to extramesenteric stations. Whether the intraoperative visualization of the lymphatic flow might reduce the extent of lymphadenectomy will be an area of future investigation.

Future perspectives

ICG has intrinsic limitations such as limited photostability, a moderate fluorescence quantum yield and rapid aggregation in physiological environments. To overcome these drawbacks ICG has been vectorized with different nanoparticles resulting in increased circulation time, better biodistribution and *in vivo* availability. Whether these improvements might result in a better visualization of the lymphatic map need to be proved. Similarly, if a prolonged or increased fluorescence can be obtained, one might postulate that injection of this new IGC nanoparticles can be performed either >24/48 hours or immediately before surgery with a proper, detectable lymphatic mapping. This will be an area of investigation.

The surface of the most recent third-generation nanoparticle, that guarantees an immune system escape, can be also functionalized by grafting onto the surface, biological ligands that recognize specific targets. Use of tumor-specific ligands, such as antibodies, creates ICG nanoparticles for active tumor targeting that might expand the possible applications of fluorescence imaging. Few experimental studies are available in the setting of colorectal cancer. Kolitz-Domb *et al.* (37) synthesized a proteinoid-poly (L-lactic acid) copolymer covalently conjugated to an anti-CEA antibody. The authors showed that encapsulation of the ICG within this nanoparticle improved its photostability by

avoiding leakage and photobleaching while achieving specific colon tumor detection in experimental chicken embryo and mouse models. A different strategy to obtain an active tumor targeting is ICG complexation, i.e., direct conjugation of ICG with cancer-specific ligands. Many authors had successfully conjugated ICG with antibodies creating activatable NIR probes. In fact, ICG loses its fluorescence when bound to the antibody but regains its fluorescent properties once it is chemically separated from the antibody which occurs after cell binding and internalization. One of the most frequently used antibodies is panitumumab, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody which has been shown, in a model of colorectal cancer, to have excellent target-specific uptake, with minimal liver retention *in vivo* (38). However, many studies are needed to define which strategy might be superior (ICG-Ab nanocomplex versus ICG-Ab complex) and if the theoretical benefits will be confirmed in the clinical setting.

Conclusions

ICG-guided lymphadenectomy is emerging as a new technique that facilitates performing complex procedures such as D3 lymph nodes retrieval during right colectomy and provides information regarding individual patient lymphatic pattern the permits the surgeon to tailor the extent of resection including node stations that otherwise would not be harvested. The focus on lymphatics is in line with principles expressed by Moynihan in his manuscript "The surgical treatment of cancer of the sigmoid flexure and rectum" dating 1908: "…*The surgery of malignant disease is not the surgery of organs, it is the anatomy of the lymphatic system.*" (39). Therefore, while we are convinced that this approach should be implemented in the routine clinical practice, we are also aware that many efforts will have to be made to provide more robust scientific data.

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Footnote

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