Original Article

ICG-assisted D3 lymphadenectomy in right colectomy for cancer

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Background: The presence of regional lymph node (LN) metastasis is a strong negative prognostic factor in colorectal cancer (CLRC). Recent advances in surgical management of CLRC, such as complete mesocolic excision (CME) with central vascular ligation (CVL), are focused on quality of surgical specimen, including an increase of LN count, in order to obtain a better survival than standard surgery. The aim of the study is to verify if intraoperative real-time visualization of the lymph flow, using indocyanine green fluorescence imaging (ICG-FI), improves lymphadenectomy during laparoscopic right hemicolectomy for cancer, performed according to CME/CVL criteria.

Methods: This is a monocentric, non-randomized prospective pilot study. From January 2019 to October 2019 we analyzed data form 20 patients with right colon cancer who underwent laparoscopic resection with D3 lymphadenectomy fluorescence guided by means of intraoperative injection of ICG.

Results: A total of 20 patients undergoing laparoscopic right colectomy were enrolled: the mean operative time were 162 minutes. Median length of the anatomical preparation was 30 cm, the mean LN harvested was 30.65, the incidence of nodes metastasis was 55%. Nine patients underwent a change of therapeutic strategy based on intraoperative ICG-FI [8 for positive ICG-FI in superior mesenteric artery's (SMA's) nodes and 1 in the LNs of the middle colic artery (MCA)].

Conclusions: ICG-intraoperative lymphography gives additional intraoperative information about lymphatic flow during laparoscopic right colectomy for cancer and may lead to change, and sometimes extend, lymphadenectomy. Larger further randomized prospective trials are needed to validate this new technique.

Keywords: Indocyanine green (ICG); right side colon cancer; laparoscopic surgery; technology; lymphadenectomy; complete mesocolic excision (CME)

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Introduction

The principles of oncologic resection for colon cancer are based on primary tumor excision associated with blood supply and lymph node (LN) drainage (1). Resection of the tumor and its vessels are relatively standardized, while the extent of the mesenteric lymphadenectomy can be variable. This topic can affect the quality of specimen, the nodal yield and potentially the survival outcomes for the patient through under-staging (2).

From literature we know that the distribution pattern of LNs metastasis in resected specimens is extremely variable. The first metastatic node was found in the pericolic area outside 5 cm from the tumor in 18% of cases (3). Patients with cecal and ascending colon cancer had most frequently metastasis in the ileocolic LNs, while the LNs metastasis along the right branch of the middle colic artery (MCA)

occurred only in 6.1% of patients with cecal cancer (4). An adequate oncological resection requires a minimum of 12 nodes removed but there is recent evidence that shows how this is still a substandard LN yield (5,6). There are in literature several evidence that confirm how complete mesocolic excision (CME) perform more radical surgery with a larger mesenteric specimen resulting in a higher number of harvested LNs, improving survival outcomes compared to conventional colectomy (7). This is the result of higher central vascular ligation (CVL) that contains more LNs with CME than conventional surgery for colon cancer (8). In the JSCCR guidelines 2019 (9), the extent of LNs dissection for cancer is well described. For pTis, D1 dissection can be performed. For pT1–cT2 at least D2 dissection is necessary. From cT3 to Ct 4b, D3 lymphadenectomy is recommended. For an adequate D3 lymphadenectomy, in right colectomy, the lymphatic territory of the nodes central station around the AMS must be correctly removed (LN stations 213–223).

In recent years, indocyanine green (ICG) fluorescence imaging (FI) has been indicated as a surgical tool with increasing applications in colorectal surgery to guide lymphatic mapping and obtain a more precise oncologic resection (10). This information gained from this technology enables real-time decision making potentially changing the operative plan.

The aim of this study was to visualize lymphatic flow during right colectomy using ICG technology to analyze whether this method can modify the standard CME lymphadenectomy and can help to obtain a greater accuracy in lymphadenectomy. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/ales-20-62).

Methods

This is a prospective, non-randomized, monocentric pilot study. It was prospectively designed and all patients provided informed consent before the procedure. Internal institutional review board approval was obtained. The study is conformed to the provisions of the Declaration of Helsinki (as revised in 2013).

From January 2019 to October 2019 we prospectively analyzed 20 patients with diagnosis of right colon cancer and treated by videolaparoscopic right hemicolectomy CME/D3 lymphadenectomy guided by Fluorescence and intraoperative subserosal injection of ICG. All cases were performed by a single skilled, laparoscopic colorectal surgeon. We include in this study patients aged between 18 and 75 with diagnosis of cecal, ascending and right flessure tumor, preoperative staging T2, T3, T4, any N and M0. All patients had a clear histologic diagnosis of colon cancer (confirmed by endoscopy and computed tomography imaging). We only included patients with a performance status of 0–2, adequate cardiac, renal, pulmonary and bone marrow function. Exclusion criteria were: patients with transverse colon cancer, synchronous colorectal cancer (CLRC) or other tumors, distance or locoregional metastases detected with CT scan, allergy or history of adverse reaction to ICG, iodine or iodine dyes.

In all cases lesion was preoperatively marked with black ink. Surgical resection was performed within 4 weeks from diagnosis. All patients underwent laparoscopic right hemicolectomy with CME and CVL with intraoperative real-time visualization of the lymph flow using ICG-fluorescence lymphangiography.

Surgical technique

Under general anesthesia, the patient was placed in supine position. After pneumoperitoneum Veress technique, four ports were placed (one 12 mm-port 2 cm near to umbilicus for a camera, another 12 mm port in the left upper quadrant and two 5 mm working ports in left lower, and right lower quadrants). The patient was placed with a 20° tilt to the left side so that the small bowel fell toward the left quadrants. After exact tumor's localization, ICG (Verdye 5 mg/10 mL) was injected in subserosal layer at the four cardinal points of the lesion according to an internal standardized procedure (first, injection of 2 mL of air through a 23 Gauge needle in order to have a delamination of the subserosal tunic from the muscular tunic and subsequent injection of 1 mL of ICG repeated for four injections). Any ICG leakage has been removed by gauze soaked in 0.9% sterile physiological solution (partial hydrophilicity of the substance) to eliminate any intra-abdominal contamination of ICG that would mask the effective lymphatic drainage. Lymph flow was observed using the near-infrared camera system 40 minutes after injection (laparoscopic NIR camera system by Karl Storz). Then a medial to lateral dissection was performed according to oncological principles.

First pedicle of ileocolic vessels was identified, isolated and sectioned at their roots, separately. Then superior mesenteric vein (SMV) was identified and LN dissection along right side was performed, with high section of right colic vessels, if present, and section of right branch of middle

Table 1 Clinical characteristics

	N/mean	Range %
Patients	20	–
Age (mean)	63.6	30–76
Sex		
Male	10	50
Female	10	50
Performance status		
0	8	40
1	9	45
2	3	15
Tumor location		
Cecum	5	25
Ascending colon	11	55
Hepatic flexure	4	20

Table 2 Results

	N/mean	Range %
Mean operative time (min)	162	115–215
Mean blood loss (mL)	87.5	50–200
Patient with drain	4	20
Conversion	0	0
Hospital stay (days)	5	3–11
Morbidity (Clavien-Dindo classification)		
Grade I	2	10
Grade II	2	10
Grade IIIA	0	0
Grade IIIB	1	5
Grade IV	0	0
ICG toxicity (cases)	0	0
LN count (mean)	30.65	20–64
Metastases	16.86	55
Modified lymphadenectomy after ICG	9	45
Extra SMA lymphadenectomy	8	89
Extra MCA lymphadenectomy	1	11
Extra LN removed	3	2–5
Number positive	0	–
Length of resection (cm)	30	21–44
Resection margin closest (cm)	9.3	7.8–14.6
Stage (TNM classification)		
IIA	7	35
IIB	1	5
IIC	1	5
IIIA	1	5
IIIB	7	35
IIIC	3	15

ICG, indocyanine green; LN, lymph node; SMA, superior mesenteric artery; MCA, middle colic artery.

colic vessels along the left border of SMV. At the end of the lymphadenectomy the absence of additional fluorescent LNs was checked using the near-infrared camera system. The gastrocolic trunk identification is necessary to perform an adequate lymphadenectomy but due to several anatomic variations, the identification is essential to prevent vascular injury. Now a complete mobilization between embryological plane was performed. The Told's plane between the posterior right side mesocolon fascia and Gerota's fascia is gently dissected and the second portion of the duodenum with pancreatic head is exposed. The colon was transected with adequate tumor-free resection margins. Intracorporeal side to side stapled anastomosis was performed. In three patients the anastomosis was manually packaged.

We analyzed data from operative time, blood loss, hospital stay, surgical morbidity according with Clavien-Dindo classification (11). On specimen we analyze LN count, length of resection, resection margin, TNM stage. Statistical analyses were performed using NCSS (Windows edition 2014).

Results

A total of 20 right colon cancer patient were enrolled. The clinical characteristics are reported in *Table 1*. The tumor was located in cecum (25%), ascending colon (55%) and hepatic flexure (20%). Mean operative time was 162 (range, 115–215) minutes, and no intraoperative complications occurred; no patient was converted laparotomically (*Table 2*). In 9 patients we modified lymphadenectomy based on intraoperative ICG fluoroscopic mapping: 8 patients removing extra nodes from the superior mesenteric artery (SMA) (213/223 station) and 1 patient extra nodes from

MCA (222 station) (*Table 2*).

All patients underwent intracorporeal anastomosis and in three patients the anastomosis was manually packaged. Abdominal drainage was positioned in 20% of the patients and was removed on average on the 2nd post-operative day.

Median length of specimen was 30 (range, 21–44) cm, the average free margin, closest to the lesion was 9.3 (range, 7.8–14.6) cm. The mean number of nodes was 30.65 (range, 20–64), the incidence of nodes metastasis was 55%. Patients with fluorescence-modified lymphadenectomy had an average of three LNs more than other patients. These nodes were negative on pathologic assessment. Final pathological staging was: 35% IIA, 5% IIB, 5% IIC, 5% IIIA, 35% IIIB and 15% of patients was stage IIIC.

Mean hospital stay was 5 days. Most patients had an uneventful recovery (75%). According to Clavien-Dindo classification, Grade I complication occurred in 10% of patients (fever), Grade II, ileus, in 2 patients (10%), Grade IIIB in 5% of patients (anastomotic bleeding) (*Table 2*). No patient showed toxicity or allergic reactions to ICG. No patient was admitted to hospital 30 days after admission.

Discussion

The broad range of vascular anatomical variation in right colon are the most common cause of difficulty performing CVL and consequently lympadenectomy.

The SMV is the most important anatomical landmark in D3 for the right colon nodes dissection (12). In order to help the surgeon during nodes dissection, intraoperative real-time lymph flow mapping with ICG-FI was adopted. The present study investigated laparoscopic D3 lymphadenectomy in right hemicolectomy with intraoperative real-time visualization of the lymph flow using ICG-FI.

Several reports describe the feasibility of ICG lymphography in right-side colon cancer (13,14) Theoretically this method can lead to obtain a more precise LNs dissection and more accurate LN staging improving in long-term survival outcomes.

We demonstrate that this procedure is safe and reproducible and does not increase operative time compared to literature data [162 *vs.* 158–176 (range) min] (13,15,16). No intraoperative complications were reported. An increased rate of removed LNs has been observed in patients undergoing this surgical strategy, compared to the removed LNs following right hemicolectomy with CME without the use of fluorescence (17). In our study, LN metastases (N+) were found in 55% of patients although the positivity of the LNs was not related with the number of LNs removed (P=0.07).

The surgical strategy is safely reproducible with minimal cost increase and no complications toxicity-related. With the standard CME we perform a standardized extended lymphadenectomy without being able to discriminate which is the specific lymphatic drainage involved in tumor. This happens because the anatomical variability, in terms of lymphatic drainage, seems to be high in the right sections of the colon and closely correlated to the tumor position.

The ICG lymphatic mapping may help the surgeon to remove a target lymphatic tissue that improve accuracy of staging and reducing unnecessary extended lymphadenectomies associated with high rate of intraoperative complications. Major limitations of this study are small number of patients, a lack of randomization, and of an oncological follow-up. We conclude that a tailored lymphadenectomy guided by ICG fluorescence in patients with right colon cancer may improves the reliability, specificity and accuracy of lymphadenectomy.

Conclusions

During laparoscopic right colectomy for cancer ICG-intraoperative lymphography gives additional intraoperative informations about lymphatic flow and may lead to change and sometimes extend lymphadenectomy. Larger further randomized prospective trials are needed to validate this new technique.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by internal institutional ethics board and informed consent was taken from all the patients.

References

1. Lynch ML, Brand MI. Preoperative evaluation and oncologic principles of colon cancer surgery. Clin Colon Rectal Surg 2005;18:163-73.
2. Cai Y, Cheng G, Lu X, et al. The re-evaluation of optimal lymph node yield in stage II right-sided colon cancer: is a minimum of 12 lymph nodes adequate? Int J Colorectal Dis 2020;35:623-31.
3. Tan KY, Kawamura YJ, Mizokami K, et al. Distribution of the first metastatic lymph node in colon cancer and its clinical significance. Colorectal Dis 2010;12:44-7.
4. Park IJ, Choi GS, Kang BM, et al. Lymph node metastasis patterns in right-sided colon cancers: is segmental resection of these tumors oncologically safe? Ann Surg Oncol 2009;16:1501-6.
5. Betge J, Harbaum L, Pollheimer MJ, et al. Lymph node retrieval in colorectal cancer: determining factors and prognostic significance. Int J Colorectal Dis 2017;32:991-8.
6. Morikawa T, Tanaka N, Kuchiba A, et al. Predictors of lymph node count in colorectal cancer resections: data from US nationwide prospective cohort studies. Arch Surg 2012;147:715-23.
7. Hohenberger W, Weber K, Matzel K, et al. Standardized surgery for colonic cancer: complete mesocolic excision and central ligation--technical notes and outcome. Colorectal Dis 2009;11:354-64; discussion 364-5.
8. Liang JT, Lai HS, Huang J, et al. Long-term oncologic results of laparoscopic D3 lymphadenectomy with complete mesocolic excision for right-sided colon cancer with clinically positive lymph nodes. Surg Endosc 2015;29:2394-401.
9. Hashiguchi Y, Muro K, Saito Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol 2020;25:1-42.
10. Macina S, Boni L, Della Porta M, et al. What is the added value of intraoperative indocyanine-green in right colectomy for cancer? Ann Laparosc Endosc Surg 2019;4:52.
11. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187-96.
12. Ye K, Lin J, Sun Y, et al. Variation and treatment of vessels in laparoscopic right hemicolectomy. Surg Endosc 2018;32:1583-4.
13. Spinoglio G, Petz W, Borin S, et al. Robotic right colectomy with complete mesocolic excision and indocyanine green guidance. Minerva Chir 2019;74:165-9.
14. Kobiela J, Bertani E, Petz W, et al. Double indocyanine green technique of robotic right colectomy: introduction of a new technique. J Minim Access Surg 2019;15:357-9.
15. Galizia G, Lieto E, De Vita F, et al. Is complete mesocolic excision with central vascular ligation safe and effective in the surgical treatment of right-sided colon cancers? A prospective study. Int J Colorectal Dis 2014;29:89-97.
16. Kanemitsu Y, Komori K, Kimura K, et al. D3 lymph node dissection in right hemicolectomy with a no-touch isolation technique in patients with colon cancer. Dis Colon Rectum 2013;56:815-24.
17. Bertelsen CA, Kirkegaard-Klitbo A, Nielsen M, et al. Pattern of colon cancer lymph node metastases in patients undergoing central mesocolic lymph node excision: a systematic review. Dis Colon Rectum 2016;59:1209-21.

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