

Early results of fluorescence lymphatic mapping for right colon cancer: a case-matched study

Murat Şen¹, Ahmet Tuncay Yılmazlar¹, Deniz Sığırlı², Özgen Işık¹

¹Department of General Surgery, Bursa Uludağ University School of Medicine, Bursa, Turkey; ²Department of Biostatistics, Bursa Uludağ University School of Medicine, Bursa, Turkey

ABSTRACT

Objectives: The complete mesocolic excision (CME) technique has been described to improve the surgical outcomes of colon cancer. Collecting more lymph nodes is one of the goals of CME. In our study, indocyanine green (ICG) injection was applied to the anterior and posterior walls at certain levels of the right colon. The aim of this study is to determine the impact of lymphangiography in right colon cancer surgery.

Methods: The data of patients were analyzed who underwent colectomy surgery between 1.1.2018-1.1.2022 and using our mapping technique. A case-match study was performed at a ratio of 1:2 (Study group [group S; n=10], Control group [group C; n=20]). Case-matched criteria were age +/-10, T stage +/-1, and tumor location.

Results: There were no differences in terms of age, the American Society of Anesthesiologists score, tumor location, tumor T and N stages, and pathological markers affecting prognosis between the groups. Although 10% of intraoperative complications were seen in group C, it was not statistically significant (P=0.540). After lymphangiography, lymph nodes containing ICG were detected in the resection site and these lymph nodes were sent to pathology in separate containers. Considering the number of lymph nodes sent separately, it was determined that significantly more lymph nodes were sent in the group S (P=0.001).

Conclusions: We have shown that the ICG mapping can be applied safely in the surgical treatment of right colon cancer.

Keywords: Colonic neoplasms, Indocyanine green, lymphatic metastasis, fluorescence lymphatic mapping

Colorectal cancer is the third most common cancer worldwide. Nodal involvement is one of the crucial factors affecting survival, as 5-year survival can range from 90% in early disease to 10% in metastatic disease [1]. To improve outcomes, the complete mesocolic excision (CME) technique was identified [2].

Fluorescence imaging (FI) technology makes intraoperative lymphangiography and lymphatic mapping possible. Several studies demonstrate that

peritumoral indocyanine green (ICG) injection makes lymphatic flow and lymph nodes visible in the mesocolon [3, 4]. However, pure peritumoral injection of ICG may not be sufficient for demonstrating whole lymphatic drainage of the right colon, and lymphatic flow and mapping may not be reliable since lymph vessels might be blocked by tumoral cells.

The present study aimed to investigate the effect of intraoperative lymphangiography used in right colon cancer surgery on the number of lymph nodes

Corresponding author: Murat Şen, MD., PhD.
Phone: +90 224 295 20 40. E-mail: muratsen.dr@gmail.com

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collected intraoperatively, the number of lymph nodes left in the patient (especially D3 lymph nodes) after removal of the resected right colon, and the total number of collected lymph nodes. We also aimed to determine the impact of ICG lymphatic mapping on postoperative complications and its effects on short-term oncological outcomes.

METHODS

Patient Selection and Data Collection

After obtaining Institutional Review Board approval (approval number 2022-6/19) patients who underwent elective right hemicolectomy due to right colon cancer between 1.1.2018 and 1.1.2022, since the lymphatic mapping technique with ICG became available in Bursa Uludag University School of Medicine General Surgery Department, were included in the study.

Data of patients older than 18 years old who had tumors in the right colon, including the cecum and hepatic flexure during the preoperative colonoscopy, and whose histopathological diagnosis was adenocarcinoma, were accessed via patient charts. Computed tomography imaging (thorax and abdomen) was performed for metastasis screening in all patients preoperatively. Patients with metastases on tomography images and patients whose imaging findings had a tumor localization in the colon other than the right colon were excluded from the study. Patients who underwent emergency surgery due to obstruction, bleeding, or perforation and patients with distant organ metastases were excluded from the study. Since there is no laparoscopic fluorescence imaging equipment in our center, cases who underwent laparoscopic right hemicolectomy were excluded from the study. Additionally, patients who were found to have a colon tumor outside of the right colon during surgery were excluded from the study.

During the study period, 198 colon cancer surgeries were performed in our center. Sixty-four of these were right colon cancer surgeries. ICG mapping method was applied to 10 patients who fell within the inclusion criteria. Twenty control patients were selected based on matching criteria.

A study group (group S) of 10 colon cancer patients underwent lymphatic mapping with ICG during right hemicolectomy surgery. These patients were

case-matched in a 1:2 ratio with 20 right colon cancer patients (group C) who were operated on without using the lymphatic mapping technique. Case-match criteria were age ± 10 , T stage ± 1 and same tumor location. Additionally, no significant difference was detected in terms of biological factors of the tumors between the two groups (lymphovascular invasion, perineural invasion, mucinous component, tumor budding, tumor grade, and differentiation).

In group S, 3 (30%) patients had tumors in the cecum, 3 (30%) patients had tumors in the ascending colon, and 4 (40%) patients had tumors in the hepatic flexure. Similarly, 6 (30%) of the patients in the group C had tumors located in the cecum, 6 (30%) in the ascending colon, and 8 (40%) in the hepatic flexure.

In both patient groups, age, gender, American Society of Anesthesiologists (ASA) score, tumor location, T stage, mucinous component, grade, venous/vascular invasion, lymphatic and perineural invasion, tumor budding, N stage, total and metastasized lymph node counts, operation times, intraoperative and postoperative complications, distant metastasis developed in the follow-up, mortality during the follow-up period and survival times were examined. Additionally, total, and metastasized lymph node counts those sent separately after intraoperative fluorescence imaging in group S were examined.

Surgical Technique and ICG Lymphatic Mapping

Indocyanine green (DID Indocyanine Green Inj, Dongindang Pharmaceutical CO., LTD, Gyeonggi-do, Korea) and SPY Elite laser angiographic system (Stryker Corp/Novadaq Technologies, Kalamazoo, MI, USA) imaging system was used in this study.

The patients who were taken to the operating room were placed in a supine position under general anesthesia, and a laparotomy was performed with a median incision. The lateral peritoneal attachments of the right colon were separated by sharp dissections, and the posterior wall of the colon was made visible. Before applying ICG, a concentration of 2.5 mg/mL was obtained and 8 mL solution (20 mg-ICG) was applied subserosal to 8 different points with a 26-gauge needle tip, as 1 mL per injection site. The application points were chosen as 6 points, the anterior and posterior walls of 3 different localizations, namely the cecum, the midpoint of the ascending colon, and the hepatic flexure. Additional 1 ml injections were made at two

different peritumoral points. Thus, eight different injection points were determined as standard (Fig. 1).

Mobilization of the right colon was achieved by proceeding from the avascular embryological plane between the visceral and parietal planes. Next, initial imaging was performed to ensure that ICG was draining into the lymphatics and lymph nodes of the right colon mesentery (Fig. 2).

After this initial imaging central ligation of vascular structures was performed. Then, the right hemicolectomy was completed in a way that the integrity of the right colon mesentery was preserved. For tumors located at the hepatic flexure, the middle colic artery and vein were high ligated. The gastroepiploic omentum was included in the sample. D3 lymph nodes were not removed in the study group. A second fluorescence imaging was performed just before the ileotransversostomy anastomosis was created to identify whether there were any ICG-positive and fluorescent

lymph nodes in the right hemicolectomy resection area, especially D3 lymph nodes. All tissues found to retain ICG in the surrounding fatty tissues were excised under immunofluorescence imaging. All excised tissues were sent in a separate pathology container. Afterward, using a surgical stapler, the surgery was terminated by creating a side-to-side anisoperistaltic ileotransversostomy anastomosis.

Postoperative surgery-related complications were scored using the Clavien-Dindo classification.

Statistical Analysis

The normal distribution of the data was tested with the Shapiro-Wilk test. While quantitative variables with normal distribution are given with mean±standard deviation, variables without normal distribution are passed with median (minimum-maximum) values. Mann-Whitney U test was used to compare quantitative variables between two independent groups. Pear-

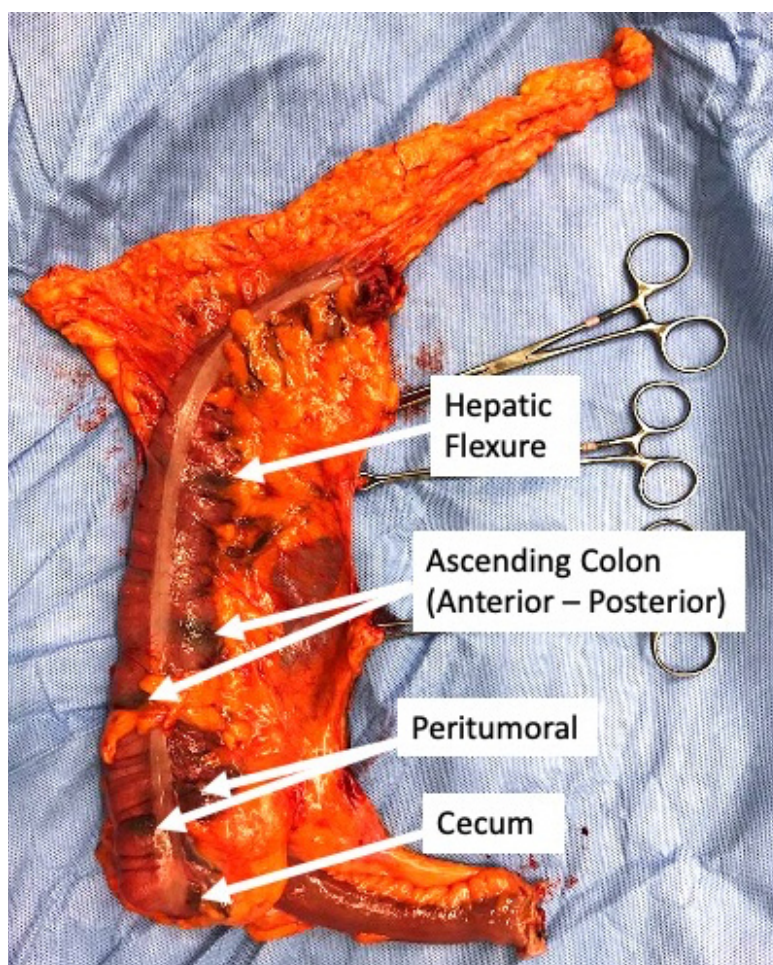


Fig. 1. Subserosal indocyanine green application points seen in right hemicolectomy specimen.

son chi-square, Fisher's exact chi-square, and Fisher-Freeman-Halton tests were used to compare categorical variables between groups, and categorical variables were given with frequency and percentage values. The significance level was accepted as $\alpha=0.05$. Statistical analyzes were performed using the IBM SPSS Statistics version 23 package program.

RESULTS

The number of female patients was significantly higher in the group S, which was mapped with ICG. There was no significant difference between the two groups regarding age and ASA Class (Table 1).

The median operative time was 60 minutes (60-190 minutes) in the group S, and the median was 75 minutes (60-195 minutes) in the group C. There was no significant difference between the two groups regarding operative time ($P=0.948$).

There was no significant difference between the two groups regarding tumor stages and pathological factors with prognostic importance which are mucinous component, grade, tumor budding, lymphatic invasion, perineural invasion, and venous/vascular invasion (Table 2).

The median number of lymph nodes in the main pathology specimen were 34 (10-70) in the group S, and the median number metastatic lymph nodes were 0 (0-5). In group C, the median number of total lymph nodes were 38.5 (12-56), and the number of metastatic lymph nodes were 0 (0-4). There was no statistically significant difference between the two groups regarding the total and metastatic lymph node numbers included in the main piece ($P=0.983$ and $P=0.713$, respectively).

The median total lymph node number was calculated as 39.5 (14-56) in 12 patients with hepatic flexura tumors (4 patients in group S versus 8 patients in group C). The number of lymph nodes with metastasis detected in the main piece was 0 (0-5). The number of lymph nodes sent separately after resection was 0 (0-4).

After the specimen was taken out in group C, suspicious rest lymph nodes were excised in 2 (10%) patients and sent in a separate pathology container. In the group S, fluorescent lymph nodes were detected in the resection site by the second FI performed in 9 patients. These lymph nodes were sent to pathology in separate containers. While the number of lymph nodes sent separately was 0 (0-5) in the group C, the median was 1 (0-5) in the group S. It was determined that signifi-

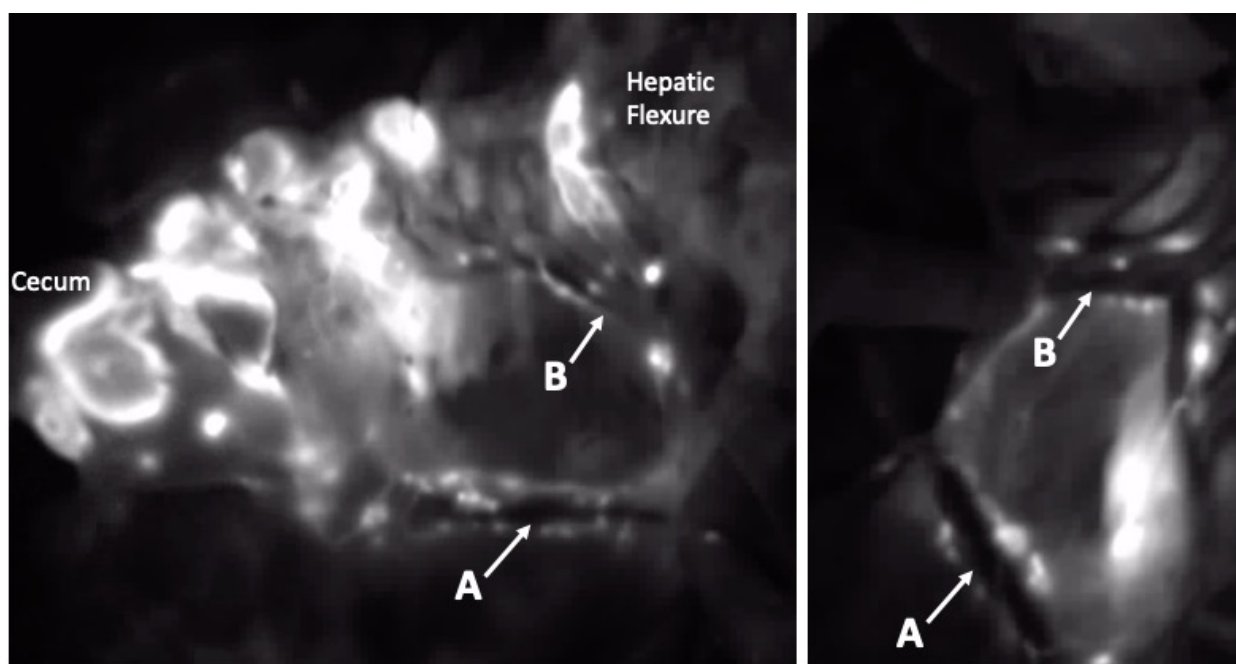


Fig. 2. Lymph nodes around the ileocolic pedicle (A) and right colic vessels (B) visible on the posterior and anterior faces of the mesentery in the first imaging performed after ICG injection.

Table 1. Demographic variables and ASA class

		Group S	Group C	P value
Sex, n (%)	Male	4 (40)	16 (80)	0.045
	Female	6 (60)	4 (20)	
Age (years), median (min-max)		59 (36-76)	66.5 (28-78)	0.214
ASA class, n (%)	ASA 1	3 (30)	6 (30)	> 0.99
	ASA 2	7 (70)	14 (70)	

ASA = American Society of Anesthesiologists, Group S = Study group, Group C = Control group

cantly more lymph nodes were sent separately in the group S (P=0.001). In both groups, no metastatic lymph nodes were detected in the lymph nodes sent separately (Table 3).

In group S, 7 (70%) patients were N0, 3 (30%) patients were N2a; in group C, 14 (70%) patients were N0, 3 (15%) patients were N1a, 1 (5%) patient was N1b and 2 (10%) patients were N2a. There was no significant difference between the two groups regarding the N stage (P=0.387).

No intraoperative complications developed in the

group S. In group C, there were 2 patients reported intraoperative bleeding from the branches of superior mesenteric vein (right colic vein and the gastrocolic trunc), and bleeding were controlled by surgical intervention. There was no significant difference between the two groups regarding intraoperative complications (P=0.54). Complications experienced in the postoperative period were categorized using the Clavien Dindo Classification as described in the study method section. Accordingly, 9 (90%) patients in group S, who underwent lymphatic mapping with ICG, were in

Table 2. Tumor stages and pathological factors with prognostic importance between two groups

		Group S n (%)	Group C n (%)	P value
Tumor stage	T1	1 (10)	0 (0)	0.251
	T2	1 (10)	1 (5)	
	T3	8 (80)	19 (95)	
Mucinous component	Yes	3 (10)	7 (35)	> 0.99
	No	7 (70)	13 (65)	
Grade	1	1 (33.3)	0 (0)	0.365
	2	1 (33.3)	5 (45.5)	
	3	1 (33.3)	6 (54.5)	
Tumor budding	Yes	6 (60)	8 (40)	0.442
	No	4 (40)	12 (60)	
Lymphatic invasion	Yes	3 (30)	5 (25)	> 0.99
	No	7 (70)	15 (75)	
Perineural invasion	Yes	1 (10)	3 (15)	> 0.99
	No	9 (90)	17 (85)	
Venous/vascular invasion	Yes	1 (10)	2 (10)	> 0.99
	No	9 (90)	18 (90)	

Group S = Study group, Group C = Control group

Clavien Dindo class 1, and 1 (10%) patient was in class 2. Ten (50%) patients in group C were in the Clavien Dindo 1 group, 8 (40%) patients were in the Clavien Dindo 2 group, 1 (5%) patient was in the Clavien Dindo 3 group, and 1 (5%) patient was in the Clavien Dindo 4 group (Table 4). There was no significant difference between the two groups in terms of postoperative complications (P=0.171).

There were no patients in both group who developed local recurrence during the follow-up period. There was no significant difference between the two groups regarding distant metastasis at follow-up (P=0.3). The mean postoperative follow-up time was calculated as 21.3±10.72 months. There were no mortalities in two groups. The median survival was 23.5 months (1-36 months) in the group S and 24.5 months (range: 4-37 months) in the group C, and there was no significant difference between the two groups (P=0.846).

DISCUSSION

In the present study, we have shown that ICG and lymphatic mapping techniques can be safely applied in the surgical treatment of right colon cancer and selective D3 lymph node dissection may be possible.

Colorectal cancer is one of the most common malignant tumors [5]. More than one million people worldwide are diagnosed with colorectal cancer each year, and about half of this number die from colorectal cancer [6]. Nodal involvement is one of the crucial factors affecting 5-year survival. Standardized techniques have been developed for maximum lymph node removal during colectomy. The Complete Mesocolic Excision (CME) technique defined by Hohenberger *et al.* [2] was developed by being inspired by the Total

Mesorectal Excision (TME) technique, which is a rectal resection technique previously described by Heald [7].

In the standardized right hemicolectomy+CME technique for right colon cancers, ligation of the ileocolic vessel and, if any, right colic vessel(s) at the origin is recommended. For tumors in the transverse colon and both flexures, it is recommended to tie the middle colic artery at its root and to include the lymph nodes in this area in the specimen [2].

Collecting more lymph nodes is one of the goals of the CME technique. Studies have proven that the number of lymph nodes collected in colon cancer surgery is directly proportional to the prognosis [8-10]. These studies have shown the importance of developing new methods to collect more lymph nodes in colon cancer surgery.

Hohenberger *et al.* [2] stated in his original article that the CME technique reduces the local recurrence rate and increases survival. However, the limits of lymphadenectomy in colon cancer surgery are among the most debated issues today. The superiority of the CME technique over conventional right hemicolectomy in terms of survival has been demonstrated in several retrospective studies [11, 12]. These studies have been criticized for examining patients over a long period (>20 years), comparing patients operated by surgical teams with different experiences, different responses to adjuvant chemotherapeutic drug regimens developed by patients, and retrospective design.

No randomized controlled study comparing the CME technique with conventional right hemicolectomy operations exists [13]. Two meta-analyses in this area have shown that CME has no superiority over conventional right hemicolectomy [14, 15].

Many studies criticize the CME technique because of longer operative times, increased intraoperative complications (especially vascular injury), and in-

Table 3. Number of lymph nodes sent with and separately from the main piece

Variables	Group S (n = 10)	Group C (n = 20)	P value
Number of main piece lymph nodes (total)	34 (10-70)	38.5 (12-56)	0.983
Number of main piece lymph nodes (with metastases)	0 (0-5)	0 (0-4)	0.713
Number of lymph nodes sent separately	1 (0-5)	0 (0-5)	0.001

Group S = Study group, Group C = Control group

creased rate of autonomic nerve damage [13, 16, 17]. All these discussions encourage research on new techniques that can provide similar local recurrence and survival results by reducing the intraoperative complication rate brought by the CME technique. The central premise of our study is this argument.

Although there was no significant difference in our study, 10% of vascular injuries were observed in group C, and no intraoperative complications were observed in group S, which supports this finding.

Studies showed that intraoperative lymphangiography makes lymph nodes in the mesocolon visible in colon cancer surgery [3, 4]. However, in these studies, it was seen that lymphangiography was performed to show possible spread areas of the tumor by injecting only into the peritumoral area. Since we think that the peritumoral lymphatic pathways may be involved with tumor cells and may prevent the spread of indocyanine green, in addition to the peritumoral area, six more submucosal indocyanine greens were applied as standard to three different anatomical points in the right colon to show the entire lymphatic mapping of the right colon.

In our study, in the group S, there is a phase in which the residual lymph node tissues in the resection area are visualized with ICG and excised separately. The number of additionally excised lymph nodes in the S group was significantly higher than in the C group ($P=0.001$). This superiority of sampling more lymph nodes is one of the strengths of mapping with ICG.

Our center is one of the reference centers in its region for the surgical treatment of colorectal cancer. However, since intraoperative indocyanine green and lymphatic mapping can be applied to limited patients and this study was conducted in a single center, the number of patients is small.

Limitations

Two major limitations of these study are its retrospective nature and limited number of patients. Not reporting long- term results may be another weak point. However, describing a new surgical technique gives this study its clinical value. This study was planned as a preliminary study to test the applicability of the technique. We believe that if our study is continued with a longer observation period and larger number of cases, it may make a difference in oncological results.

CONCLUSION

In conclusion, we have shown that ICG and lymphatic mapping techniques may be safely applied in the surgical treatment of right colon cancer without prolonging the operation time. With the second imaging performed in our study, we showed that the limits of lymphadenectomy may be extended with the fluorescent lymph nodes that remained in the resection area by avoiding intraoperative complications. Thus, selective D3 lymph node dissection may be possible, avoiding vascular injury, which is a fundamental problem of CME.

Authors' Contribution

Study Conception: ÖI, ATY; Study Design: ÖI; Supervision: ÖI, ATY; Funding: N/A; Materials: MŞ; Data Collection and/or Processing: MŞ, ÖI; Statistical Analysis and/or Data Interpretation: ÖI, DS; Literature Review: MŞ, ÖI; Manuscript Preparation: MŞ, ÖI and Critical Review: ÖI, ATY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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