Original Article

Case series on the use of the indocyanine green fluorescence real-time imaging technique for lymph node sorting in patients undergoing radical esophagectomy

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Background: There is a clear correlation between accurate postoperative lymph node staging and the survival prognosis of patients. This study aimed to explore the application and value of indocyanine green (ICG) fluorescence real-time imaging technology in lymph node sorting during radical esophagectomy for esophageal cancer.

Methods: From August 2022 to June 2023, the specimens of 66 patients who underwent esophageal cancer resection with lymph node dissection were examined. Among them, 12 cases of *ex vivo* esophageal specimens underwent secondary lymph node sorting using ICG fluorescence real-time imaging technology after conventional lymph node sorting, while the remaining 54 cases underwent conventional lymph node sorting.

Results: A total of 329 lymph nodes were detected in the 12 patients with an average of 29.75±9.19 nodes per patient. Lymph node metastasis was detected in five patients, of whom, three were diagnosed as N1 (N refers to regional lymph nodes, N1: involves 1 to 2 regional lymph node metastases), and two were diagnosed as N2 (N refers to regional lymph nodes, N2: involves 3–6 regional lymph node metastases). Following the ICG injection of 12 patient specimens, lymph nodes were re-detected in 6 patients of them (above we stated 12 patients), yielding a detection rate of 50%. In total, 17 lymph nodes were detected. There was a statistically significant difference in the total number of lymph nodes detected before and after the injection of ICG (P=0.02). Among the other 54 patients, an average of 34.06±15.66 lymph nodes were detected. There was no statistically significant difference in the total number of lymph nodes detected between the two groups (P=0.21).

Conclusions: The use of ICG fluorescence real-time imaging technology facilitate lymph node identification in resected specimens and will become a powerful technique for precise staging in esophageal cancer treatment.

Keywords: Indocyanine green (ICG); fluorescence real-time imaging technology; radical esophagectomy; lymph node sorting; case series

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Submitted Nov 09, 2024. Accepted for publication Dec 19, 2024. Published online Dec 28, 2024.
doi: 10.21037/jtd-2024-1939
View this article at: https://dx.doi.org/10.21037/jtd-2024-1939

Introduction

Esophageal cancer is one of the most common malignancies of the digestive tract (1). The current treatment for esophageal cancer primarily involves surgery as part of a comprehensive approach. The pathological staging of esophageal cancer post-surgery significantly influences the choice of treatment strategies, and the survival prognosis of patients. There is a clear correlation between the number of metastatic lymph nodes in pathological staging and patient prognosis (2,3).Therefore, accurately identifying and clearing suspect lymph nodes to improve the accuracy of lymph node staging is crucial in the treatment of esophageal cancer (4,5).

Indocyanine green (ICG) is the most commonly used fluorescent tracer in clinical practice (6). ICG is characterized by its strong fluorescence properties and excellent tissue permeability. Using ICG, near-infrared visual fluorescence imaging technology has been widely applied to detect small nodules in the lung, sentinel lymph nodes in malignant tumors, and intersegmental planes in sublobar resections, and to detect thoracic ducts and chylous leaks. It is also used to assess blood flow perfusion to prevent anastomotic fistulas (7).

Highlight box

Key findings

- The application of indocyanine green (ICG) fluorescence real-time imaging technology has improved the detection rate of lymph nodes after esophageal cancer surgery.

What's known and what's new?

- Lymph nodes may be missed by traditional lymph node sorting methods.
- After the administration of ICG, the specimens were re-sorted, and among all the newly detected lymph nodes, there were no metastatic lymph nodes, but the number of non-metastatic lymph nodes detected increased.

What is the implication, and what should change now?

- As a supplement to conventional lymph node visual and tactile sorting, ICG real-time imaging technology could help doctors to more accurately identify the location and number of lymph nodes, and make more accurate predictions about patient survival.

Traditional lymph node sorting relies mainly on the visual and tactile senses of the sorter, which can lead to missed detections. Currently, no studies, domestically or internationally, have examined the use of ICG-guided lymph node sampling in *ex vivo* specimens. This study aimed to explore the application of ICG fluorescence real-time imaging technology to lymph node sorting to enhance the detection rate of lymph nodes and the accuracy of TNM staging (tumor node metastasis classification). We present this article in accordance with the AME Case Series and STROBE reporting checklists (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-1939/rc).

Methods

Study design

This single-center, retrospective study collected the data of patients who underwent esophageal cancer resection and lymph node dissection in the Beijing Chuiyangliu Hospital's Department of Thoracic Surgery from August 2022 to June 2023. The *ex vivo* specimens of 12 of the patients were subjected to ICG injection and underwent secondary lymph node sorting. These patients were designated as the ICG group. Additionally, 54 patients underwent conventional postoperative lymph node sorting and were designated as the control group.

Inclusion criteria

To be eligible for inclusion in this study, the patients had to meet the following inclusion criteria: (I) be aged between 18 and 85 years; (II) have esophageal primary lesions diagnosed as esophageal squamous cell carcinoma via endoscopic biopsy and histopathology; and/or (III) understand and be willing to participate in this clinical study and have signed the informed consent form (or have the consent form signed by a family member).

Exclusion criteria

Patients were excluded from the study if they met any of the following exclusion criteria: (I) had a severe mental

illness; (II) had a tumor involved in an adjacent organ, requiring combined organ resection; and/or (III) had another condition that made them unsuitable for the study as determined by the researchers.

Ethical considerations

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of the Beijing Chuiyangliu Hospital (No. 2023-012). This is a retrospective study, patient data is anonymized, and a consent form for "specimens to be used to participate in clinical studies" is signed before surgery.

Patient management and data collection

Immediately following esophageal surgery, the *ex vivo* esophageal specimens were subjected to lymph node sorting by dedicated pathology technician, which was done on the back table. After the initial lymph node sorting, ICG (25 mg/vial, Dandong Yichuang Pharmaceutical Co., Ltd., Dandong, China) was diluted to 2.5 mg/L with sterile injection water, and 2 mL of ICG was injected submucosally at the proximal and distal ends of the tumor using a 5-mL syringeon the back table. After 5 minutes, fluorescent devices were used to irradiate *ex vivo* specimens, capturing visible light, fluorescence, and overlay images of the tumor and surrounding tissues. Green-fluorescent nodes were identified as lymph nodes. Under fluorescence imaging, secondary lymph node sorting was performed on the specimens, with nodes being marked, counted. All the specimens and sorted lymph nodes were sent to pathology for diagnosis. The number of lymph nodes detected by conventional methods and those identified after fluorescence imaging were recorded. In the control group, the *ex vivo* specimens were immediately subjected to lymph node sorting by dedicated pathology technician using conventional methods. The number of lymph nodes in each group was carefully recorded.

Statistical analysis

The statistical analysis was performed using IBM SPSS 22.0 statistical software. The normally distributed continuous variables are expressed as the mean ± standard deviation, and were analyzed using the *F*-test, while the non-normally distributed continuous variables were compared using a rank-sum test (i.e., the Mann-Whitney *U* test or Wilcoxon signed-rank test). The count data are expressed as the percentage, and were analyzed using the chi-square test (χ^2 test). A P value less than 0.05 was considered statistically significant.

Results

Patient characteristics

The basic characteristics between the two patient groups were compared (*Table 1*). There was no statistically significant difference between the two groups in terms of gender, age, history of alcoholism, and preoperative adjuvant therapy.

Before injecting ICG into the excised specimens, there was no statistically significant difference in the number of lymph nodes detected between the two groups (P>0.05). This study included 12 patients treated with ICG. *Table 2* sets out the basic information of these 12 patients.

The average age of the patients was 65.9 years, and 83% were male, and 66.7% had a long history of alcohol abuse. Of the patients, 41.6% (n=5) had esophageal lesions located in the middle segment, and 58.4% (n=7) had esophageal lesions located in the lower segment. The tumor infiltration depth mainly involved the esophageal serosal layer (58.3%, n=7). Preoperative pathological staging was N0, N1, N2, and N3 in 41.7%, 16.7%, 33.3%, and 8.3% of the patients, respectively.

Main endpoint

Figure 1 shows images of lymph nodes in *ex vivo* specimens. After the submucosal injection of ICG around the tumor, green-stained lymph nodes were visible in the adjacent areas.

The statistical analysis showed that there was no significant difference in the number of lymph nodes detected between the two groups (34.06±15.66 *vs.* 29.75±9.19, P=0.21). However, after the application of ICG for the secondary sorting of the excised specimens in the ICG group, the average number of lymph nodes increased to 29.75±9.19, and there was a statistically significant difference between the secondary sorting result and the initial sorting result of 28.33±9.93 (P=0.02). This suggests that the use of ICG increased the number of lymph nodes detected (how were the control arm patients receiving secondary sorting).

Table 1 Comparison of basic characteristics between the two patient groups

Characteristic	ICG group (N=12)	Control group (N=54)	P value
Gender (male/female)	10/2	43/11	0.69
Age (years)	65.91±11.04	65.85±8.07	0.06
Alcoholism history (yes/no)	8/4	29/25	0.41
Neoadjuvant therapy before surgery (yes/no)	7/5	31/23	0.95
Tumor invasion depth			
Entire layer of the esophagus	0	6 (11.1)	
Entire layer of the esophagus	0	6 (11.1)	
Serosal layer	7 (58.4)	16 (29.6)	
Muscular layer	2 (16.6)	14 (25.9)	
Submucosal layer	3 (25.0)	18 (33.3)	
Number of lymph nodes	28.33±9.93	34.06±15.66	0.23

Values are presented as n, average ± standard deviation or n (%). ICG, indocyanine green.

Table 2 Characteristics of the 12 patients treated with ICG

Patient No.	Gender	Age (years)	Tumor location (distance from incisors) (cm)	Tumor infiltration depth	Pathological type	History of alcohol abuse	N stage
1	Male	50	26–29	Serosal layer	Squamous cell carcinoma	30 years	N2
2	Male	51	27–29	Submucosal layer	Squamous cell carcinoma	30 years	N1
3	Male	79	30–35	Serosal layer	Squamous cell carcinoma	30 years	N3
4	Male	71	25–38	Submucosal layer	Squamous cell carcinoma	30 years	N0
5	Male	58	20–40	Submucosal layer	Squamous cell carcinoma	30 years	N0
6	Male	56	27–38	Serosal layer	Squamous cell carcinoma	20 years	N2
7	Male	84	28–30	Serosal layer	Squamous cell carcinoma	None	N2
8	Female	71	27–29	Serosal layer	Squamous cell carcinoma	None	N0
9	Male	74	31–39	Serosal layer	Squamous cell carcinoma	None	N0
10	Female	73	31–41	Serosal layer	Squamous cell carcinoma	None	N2
11	Male	64	32–40	Muscular layer	Squamous cell carcinoma	30 years	N1
12	Male	60	39–40	Muscular layer	Squamous cell carcinoma	30 years	N0

ICG, indocyanine green.

Among the 12 ICG patients, a total of 329 lymph nodes were detected from the excised specimens, and each of the 12 patients met the National Comprehensive to ensure tumor staging accuracy, National Comprehensive Cancer Network (NCCN) guidelines recommend that at least 15 lymph nodes be extracted and evaluated. Among the 12 patients, five had lymph node metastasis, of whom three were diagnosed as N1 and two were diagnosed as N2. After the ICG injection, additional lymph nodes were detected in six patients with a detection rate of 50%. A total of 17 lymph nodes were detected. No metastatic lymph nodes were found among the detected lymph nodes, and there was no change in lymph node staging compared to before the injection of the fluorescent agent (*Table 3*).

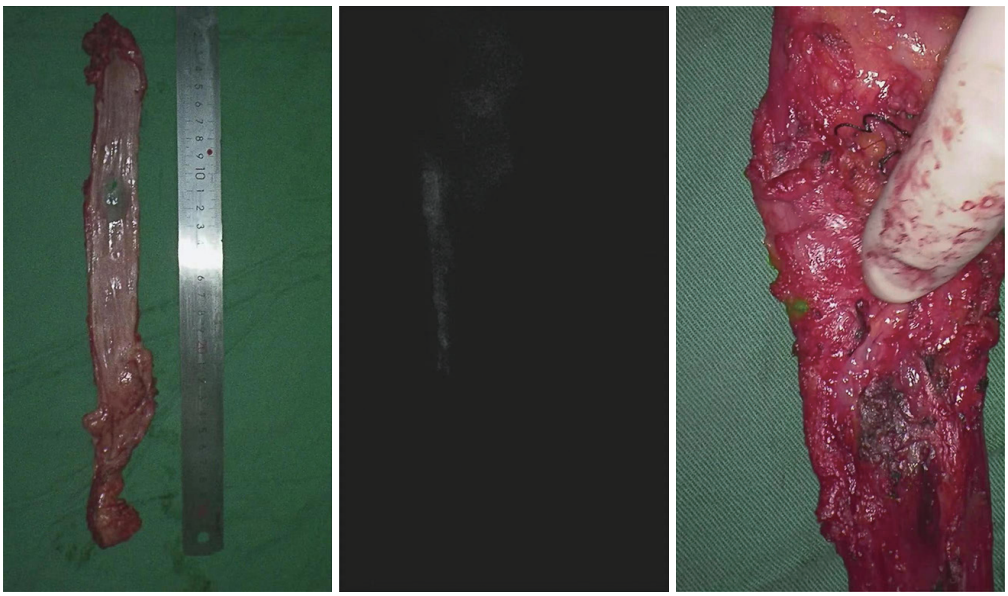

Figure 1 Lymph nodes in *ex vivo* specimens. Visible light (left), overlay (middle), and fluorescence (right).

Discussion

Esophageal cancer is a common malignancy of the digestive tract with high incidence and mortality rates (1). Lymph node metastasis is a common pathological characteristic of esophageal cancer, and the number of metastatic lymph nodes, non-lymph node metastasis, and the total lymph node count have been found to be correlated with postoperative survival in esophageal cancer patients (8).

The number of lymph node metastasis is considered closely related to patient prognosis and is an important indicator of poor outcomes. Studies have reported a negative correlation between the number of metastatic lymph nodes and survival in esophageal cancer patients. Generally, the higher the number of metastatic lymph nodes, the higher the pathological N stage, and the worse the prognosis (8,9).

Current research suggests that combining the number of non-metastatic lymph nodes with the number of metastatic lymph nodes provides better prognostic guidance for esophageal cancer patients. Research reports that esophageal cancer patients with pathological N1–2 staging and more than three non-metastatic lymph nodes have better survival rates (10).

The ratio of positive lymph nodes to the total number detected (i.e., the lymph node ratio) is also an independent prognostic factor for patients undergoing radical surgery. A lymph node ratio of 10% is considered the optimal threshold for categorization based on overall survival rates. Patients with a lymph node ratio >10% show a significantly higher rate of distant metastasis recurrence (11).

Brunner *et al.* (12) showed that the number of non-metastatic lymph nodes is an independent prognostic factor for patients undergoing primary esophagectomy. However, the benefit of the number of negative lymph nodes varies between esophageal cancer patients undergoing surgery with or without neoadjuvant chemoradiotherapy. Brunner *et al.* (12) analyzed 136 esophageal cancer patients with Group 1 undergoing primary surgery and Group 2 receiving preoperative chemoradiotherapy. The results showed that in Group 1, patients with a higher number of negative lymph nodes (>40) had better overall survival, while no significant difference was observed in Group 2 using the same threshold. Therefore, the number of non-metastatic lymph nodes is considered an independent prognostic factor in patients undergoing primary esophagectomy.

In the present study, a 50% re-detection rate of lymph nodes was observed. The re-detected lymph nodes were not metastatic; however, the increase in the number of non-metastatic lymph nodes could provide guidance in terms of clinical prognosis in esophageal cancer patients. Additionally, five patients in this study did not receive chemotherapy or immunotherapy before surgery, and eight lymph nodes were re-detected after ICG injection. No metastatic lymph nodes were re-detected; however, based

Table 3 Lymph node sorting and staging

Patient No.	Surgical method	Preoperative neoadjuvant therapy	Regularly sorted normal lymph nodes	Regularly sorted metastatic lymph nodes	Total regularly sorted lymph nodes	Post-fluorescence normal lymph nodes	Post-fluorescence metastatic lymph nodes	Total post-fluorescence lymph nodes	Regular lymph node stage	Corrected lymph node stage
1	Minimally invasive McKeown	Chemotherapy + immunotherapy	29	0	29	0	0	0	N0	N0
2	Minimally invasive McKeown	Chemotherapy + radiotherapy	17	0	17	0	0	0	N0	N0
3	Minimally invasive McKeown	None	28	1	29	2	0	2	N1	N1
4	Minimally invasive McKeown	None	31	0	31	3	0	3	N0	N0
5	Minimally invasive McKeown	None	20	1	21	2	0	2	N1	N1
6	Left thoracoabdominal + cervical anastomosis	Chemotherapy	22	4	26	0	0	0	N2	N2
7	Minimally invasive McKeown	Chemotherapy + immunotherapy	39	0	39	0	0	0	N0	N0
8	Minimally invasive McKeown	Chemotherapy	50	0	50	0	0	0	N0	N0
9	Minimally invasive McKeown	Chemotherapy + immunotherapy	13	2	15	6	0	6	N1	N1
10	Minimally invasive McKeown	None	36	0	36	0	0	0	N0	N0
11	Minimally invasive McKeown	Chemotherapy + immunotherapy	24	3	27	3	0	3	N2	N2
12	Minimally invasive McKeown	None	20	0	20	1	0	1	N0	N0

on previous research by Brunner *et al.* (12), the number of non-metastatic lymph nodes actually increased, suggesting a higher overall survival rate for these patients.

The lymphatic drainage system of the esophagus is complex with abundant lymphatic vessels in the esophageal wall. The submucosal lymphatics primarily run longitudinally along the esophagus and are devoid of lymphatic valves, allowing the bidirectional flow of lymph fluid, both upwards to the neck, and downwards to the abdominal region. Moreover, there are numerous drainage pathways between the submucosal and extramural lymphatic systems. The submucosal lymphatic plexus can connect directly with regional lymph nodes or with the intermuscular lymphatic plexus, and thus with the extramural lymphatic vessels (13). Thus, injecting a fluorescent tracer into the submucosa can highlight lymph nodes in the esophageal lymphatic drainage area.

Lymph node sorting is a critical step in radical esophagectomy. Currently, lymph node sorting relies on the visual and tactile senses of the sorter, and thus has limitations (e.g., it can be influenced by the anatomical knowledge and skill level of the sorter, which can lead to potential missed detections). The NCCN guidelines for esophageal and esophagogastric junction cancers recommend a minimum retrieval and assessment of 15 lymph nodes for adequate staging (14).

To enhance the efficiency and accuracy of lymph node sorting, and the number of lymph nodes obtained meets the guidelines recommended criteria, ICG fluorescence real-time imaging technology has been introduced into radical esophagectomy for esophageal cancer. The use of ICG in *ex vivo* lymph node dissection has several advantages. First, ICG, a near-infrared fluorescent agent, has excellent fluorescent properties with excitation and emission wavelengths of 805 and 830 nm, respectively. After the submucosal injection in the esophagus, ICG binds rapidly to lipoproteins or plasma proteins in the body, reaching the lymphatic vessels and nodes. Fluorescent devices can clearly display the lymph-stained areas (15). Second, the staining process with ICG is simple, quick, and easy to perform, making it convenient for practical applications. Third, ICG is non-radioactive, non-toxic, and does not affect the pathological staining or immunohistochemistry of *ex vivo* specimens, making it a safe and reliable dye choice.

Previous uses of ICG real-time imaging technology to detect sentinel lymph nodes in solid tumors have shown high accuracy. Kawakami *et al.* reported a 72.7% identification rate of sentinel lymph nodes in lung cancer surgery using ICG, with an immediate postoperative accuracy rate of 100% and a follow-up accuracy rate of 93.8% (16). It also has clear advantages in locating sentinel lymph nodes in breast, gastric, colorectal, head and neck, skin, and thyroid cancers (17). Reports indicate that in intraoperative ICG near-infrared imaging-guided esophageal cancer surgery, most of the dissected lymph nodes (97.83%) were visible with fluorescence staining, and 3.32% of metastatic lymph nodes were fluorescent (18).

Currently, there are no reports on the application of fluorescence imaging technology in *ex vivo* esophageal lymph node sorting. Our study's *ex vivo* lymph node fluorescence staining results showed that after ICG injection, lymph nodes were re-detected in six patients, with a total of 17 lymph nodes detected, which significantly reduced the rate of missed detections. No metastatic lymph nodes were observed in the fluorescently stained nodes, which may be related to the small number of patients in this study.

During the process of ICG fluorescence imaging-assisted *ex vivo* lymph node sorting, we made a number of observations. First, after the submucosal injection of ICG in *ex vivo* specimens, the imaging gradually appeared within about 5 minutes. It first appeared in the tumor area, indicating rich lymphatic drainage around the tumor, and it then spread in order from the mucosa to the submucosa, fibrous membrane, and serosal layer, finally appearing in the lymphatic tissue of the adipose tissue at the distal end of the tumor. Second, it is advisable to inject ICG into *ex vivo* specimens as soon as possible. Currently, there are no clear standards for the timing, concentration, dosage, and observation of the ICG injection in *ex vivo* specimens. We used a concentration of 2.5 mg/mL and a dose of 2 mL; however, further experiments and the control of the aforementioned variables are needed to establish reasonable operational standards. Third, the injection site should be chosen submucosally at the proximal and distal ends of the tumor to ensure the sufficient imaging of the lymph nodes around the tumor. Care should be taken during injection to avoid the smearing of ICG and obstructing the fluorescence imaging field. Fourth, a specialized lymph node sorting team should be established to standardize operations and improve the lymph node detection rate.

One of the primary limitations of this study was its small sample size; only 12 patients were treated with ICG. This limited number restricts the generalizability of the findings, and this study cohort might not accurately represent the broader population of esophageal cancer patients.

Additionally, the retrospective nature of the study might have introduced selection bias, as it relied on previously collected data that might not have accounted for all relevant variables influencing the outcomes. Thus, while promising, the use of ICG fluorescence real-time imaging technology in lymph node sorting requires further validation in a larger, more diverse cohort to ascertain its efficacy and applicability in different clinical settings. Further, the study did not directly compare this technique with other lymph node detection methods, which limits our ability to assess its relative advantages or disadvantages comprehensively. Given these limitations, the study's findings need to be interpreted cautiously and larger, prospective studies need to be conducted to confirm the utility and effectiveness of ICG fluorescence real-time imaging in lymph node sorting during radical esophagectomy.

Conclusions

ICG fluorescence real-time imaging technology has potential in lymph node sorting during radical esophagectomy for esophageal cancer in the *ex vivo* model. This technology is safe and effective. As a limited supplement to conventional visual and tactile sorting, it can assist physicians to more accurately identify the location and number of lymph nodes, thereby improving the detection rate of lymph nodes. This technology still has many imperfections; however, it is believed that with continuous exploration and improvement, this technology will become a powerful technique for precise staging in esophageal cancer treatment. It is not meant to replace accurate intraoperative staging but may facilitate lymph node identification in resected specimens.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the AME Case Series and STROBE reporting checklists. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-1939/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-1939/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-1939/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-2024-1939/coif). The authors have no conflicts of interest to declare.

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 ethical principles of the Ministry of Health's Regulations on the Ethical Review of Biomedical Research Involving Humans, National Medical Products Administration (NMPA's) Good Clinical Practice for Drug Clinical Trials, NMPA's Guidelines for the Ethical Review of Drug Clinical Trials, the Quality Management Norms for Clinical Trials of Medical Devices, World Medicines Administration (WMA's) Declaration of Helsinki (as revised in 2013), Council for International Organizations of Medical Sciences (CIOMS's) International Ethical Guidelines for Biomedical Research Involving Human Subjects, and International Technical Harmonization Council for Registration of Medicines for Human Use-Guidelines for Good Clinical Practice Practices (ICH-GCP). The study was approved by the Ethics Committee of the Beijing Chuiyangliu Hospital (No. 2023-012). This is a retrospective study, patient data is anonymized, and a consent form for "specimens to be used to participate in clinical studies" is signed before surgery.

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Cite this article as: Wang X, Liu W, Hu X, Zhao Y, Zhao Y, Xue X, Liu X, Wang L, Bauer T, Cui J, Li Y. Case series on the use of the indocyanine green fluorescence real-time imaging technique for lymph node sorting in patients undergoing radical esophagectomy. J Thorac Dis 2024;16(12):8611-8619. doi: 10.21037/jtd-2024-1939

