



Intra-Nodal Indocyanine Green Injection to Delineate Thoracic Duct During Minimally Invasive Esophagectomy

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Abstract

Introduction Post-operative chylothorax is a dreaded complication after esophagectomy; hence real-time identification of the thoracic duct (TD) may aid in avoiding its injury or promptly tackling injury when it occurs. We utilized intra-nodal injection of Indocyanine green (ICG) dye to delineate TD anatomy while performing esophagectomy for esophageal carcinoma.

Method Two ml of 1 mg/ml solution of ICG was injected into the inguinal lymph nodes under ultrasound guidance. TD was checked with the laparoscopic Karl Storz IMAGE1 STM or Robotic da Vinci Xi system. The thoracic esophagus, periesophageal tissue, and lymph nodes were dissected. The TD was visualized throughout the dissection using OverlayTM technology & Firefly modeTM and checked at the end to rule out any dye leak. TD was clipped if any dye leakage or TD injury (TDI) was noted using Near Infra-Red Spectroscopy.

Results Twenty one patients with M:F 13:8 underwent minimally invasive esophagectomy (MIE) [thoracoscopic assisted ($n = 15$) and robotic-assisted ($n = 6$)]. TD was visualized in all the cases after a median (IQR) time of 35 (30, 35) min. The median (IQR) duration of the thoracic phase was 150 (120,165) min. TDI occurred in 1 case, identified intra-operatively, and TD was successfully clipped. There were no post-operative chylothorax or adverse reactions from the ICG injection.

Conclusion Intra-nodal ICG injection before MIE helps to identify the TD in real-time and is a valuable intra-operative aid to prevent or successfully manage a TD injury. It may help to prevent the dreaded complication of post-operative chylothorax after esophagectomy.

Keywords Thoracoscopic · Robotic-assisted · Esophagectomy · Chylothorax · Thoracic duct · ICG fluorescence

Introduction

Post-esophagectomy chylothorax leads to loss of energy-rich chyle, T-lymphocytes, fluid, and electrolytes with an incidence of 4–10%.¹ It can make the patient hemodynamically unstable, cause rapid malnutrition and weight loss, and lead to bacterial and fungal sepsis, making it one of the dreaded complications leading to increased morbidity and mortality.^{1,2} In the minimally invasive esophagectomy (MIE) era, although reasonable success has been achieved in reducing

wound-related and pulmonary complications, the incidence of chylothorax remains similar to open esophagectomy. As chylothorax is a morbid complication and is challenging to manage, all attempts should be made to prevent it during esophagectomy.

The intraoperative identification and preservation of the thoracic duct (TD) is the most effective prophylactic measure to prevent its injury.³ However, intraoperative identification of the TD course or leak site in case of its injury is often difficult. With variable results, many techniques have been put forward to identify the TD intra-operatively, like pre-operative oral or enteral administration of olive oil, cream, fat-rich diet, etc. Conventional lymphangiography and lymphoscintigraphy are also challenging intra-operatively. However, the intraoperative use of indocyanine green (ICG) dye with near-infrared spectroscopy (NIRS) mode has been utilized to evaluate gastric conduit perfusion, identification of the site of chyle leak post esophagectomy, and during

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lateral neck dissection with profound benefit.^{4–6} Further, its utilization in identifying TD during thoracoscopy to prevent postoperative chylothorax has been reported in a few case series with variable results.^{7–9}

In the present study, we report our experience with ICG-NIRS to identify the TD anatomy and check intraoperative TD injury during thoracoscopic and robotic-assisted esophagectomy for malignancy of the esophagus. To our knowledge, this is the first series describing ICG-NIRS to identify TD in both forms of minimally invasive McKeown esophagectomy.

Methods

The study was performed in the Department of Surgical Gastroenterology at All India Institute of Medical Sciences, Jodhpur, India. The data were analyzed retrospectively from the prospectively maintained database from January 2020 to December 2021 for patients who had undergone McKeown esophagectomy (robotic and thoracoscopic assisted) for carcinoma esophagus and GE junction (Siewert type I and II). All biopsy-proven patients who received either neoadjuvant chemoradiotherapy or chemotherapy were included. The standard ERAS protocol steps were followed with strict peri-operative adherence.

Cases where esophagectomy was performed for benign disease, patients with a pre-existing iodine allergy, cases where inguinal lymph node targeting was not feasible, and intra-operative conversion to open thoracotomy was performed, were excluded from the study. Informed written consent was obtained from all the patients pre-operatively, and the institutional ethical committee clearance was taken (AIIMS/IEC/2022/3915).

After general anesthesia, a 5-ml solution containing 25 mg ICG (Aurogreen™, Aurolabs Madurai) was diluted to 25 ml to make a 1 mg/ml solution. Now, 2–3 ml of this solution was injected percutaneously into bilateral inguinal lymph nodes (LNs) under ultrasound guidance in a supine position using a 22G needle (Fig. 1a–b). This injection was done at the junction of the hilum and cortex of the LN to

avoid the spilling of dye. In case of dye spill outside the LN, the procedure was repeated. Any adverse or allergic reaction to ICG insertion or any complication of the injection procedure was carefully monitored for and recorded.

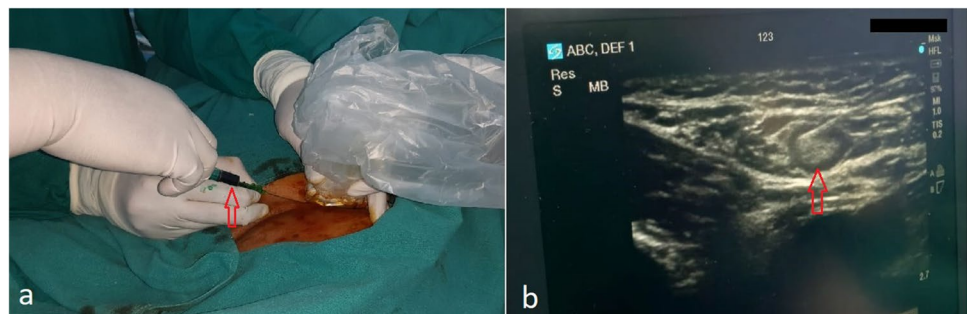
The patient was positioned prone, and standard ports were placed in the right hemithorax. The Karl Storz IMAGE1 S™ Rubina™ overlay technology (in thoracoscopy) or the Firefly® mode (in da Vinci Xi robotic system) was used to visualize the TD. Time from the injection of ICG to the visualization of TD was recorded. The thoracic esophagus, periesophageal tissue, and lymph nodes were dissected and completely mobilized, keeping the TD in view using overlay technology in thoracoscopy. The entire course of TD was checked at the end to rule out any dye leakage and confirm its continuity. Dissection in regions where the tumor was adherent to the TD was done under NIRS overlay guidance. Any patient with an unintentional TD injury as recognized by ICG-NIRS or active dye leakage from the TD at the end of the thoracic phase underwent its clipping under NIRS mode (Fig. 2a–f). Similarly, during robotic-assisted dissection of the esophagus, firefly mode was utilized to visualize TD and rule out any injury (Fig. 3a–d). The abdominal phase dissection was carried out via open, robotic, or laparoscopic technique as per the operating surgeon's discretion. A standard two-field lymphadenectomy was performed in all the cases.

The TD anatomy, intra-operative TD injury or chyle leak, post-operative chylothorax, and daily ICD output till removal were recorded. All patients were followed until post-operative day 30, and all significant complications (Clavien-Dindo grade \geq IIIa) were recorded.

Statistical Analysis

Data were analyzed using Statistical Package for the social sciences (SPSS) version 23 (IBM Corp., Armonk, NY). Continuous and categorical data have been presented as median with inter-quartile range (IQR) and proportions, respectively.

Fig. 1 **a** Intra-nodal injection of ICG dye (arrow) under ultrasound guidance; **b** Inguinal lymph node (arrow) with a needle in situ



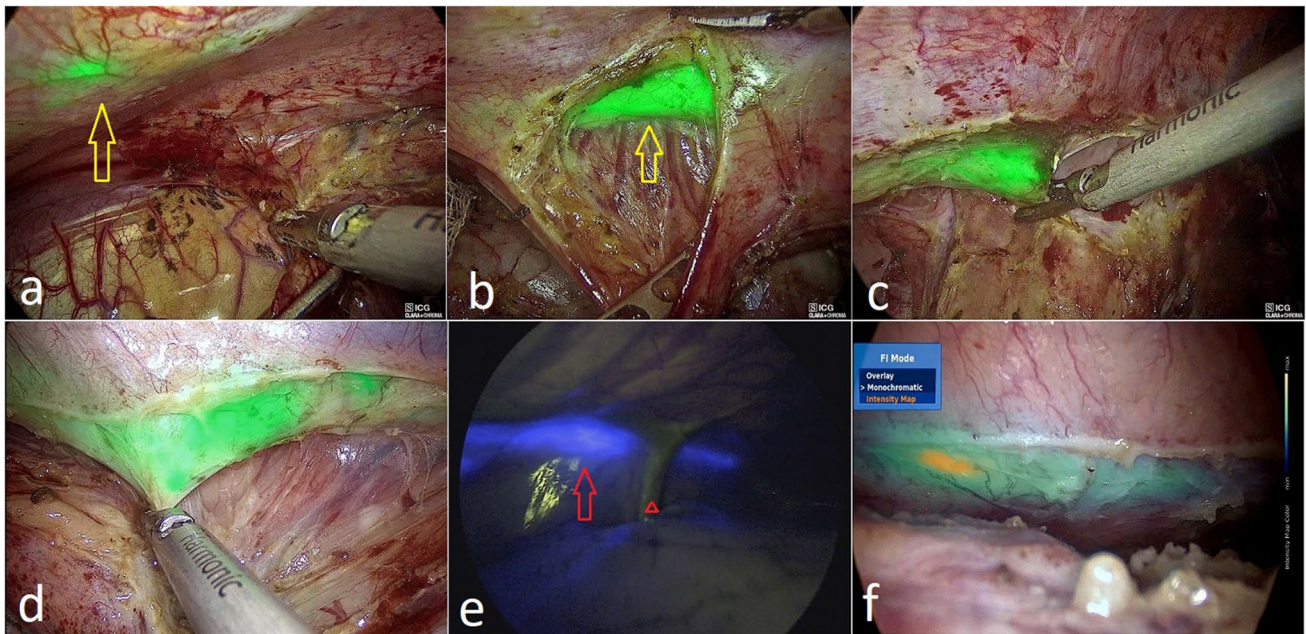
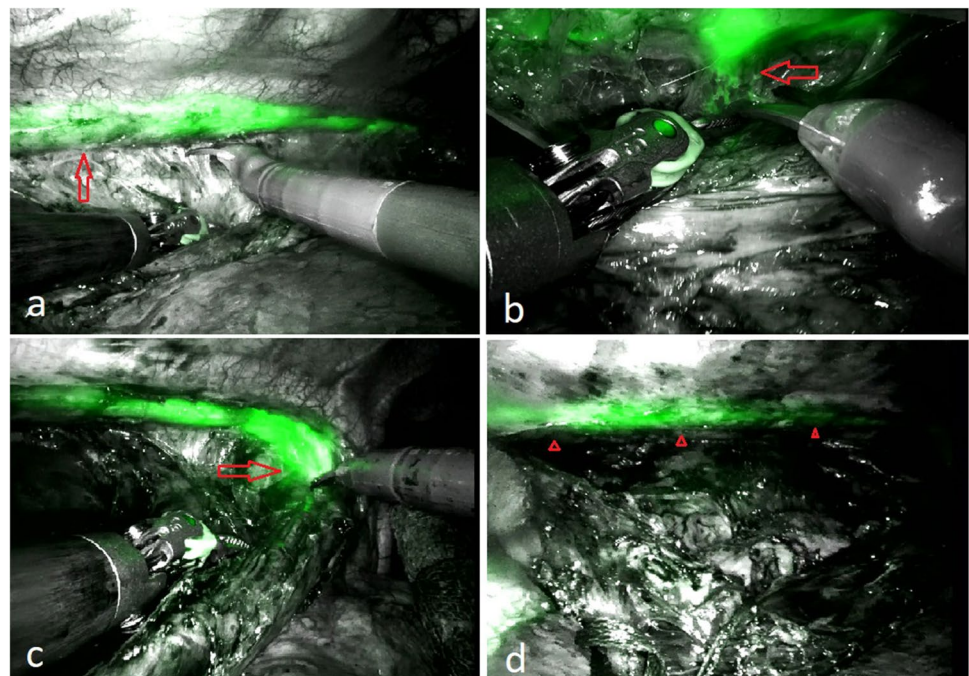


Fig. 2 Thoraco-laparoscopic esophagectomy: **a** Initial image after entering the thoracic cavity showing ICG (arrow); **b** thoracic duct (TD) with dye visualized after dividing the pleura posteriorly; **c** and **d** ongoing dissection close to TD in the overlay mode; **e** Visualization

of the TD (blue color) in continuity (arrow) behind the intact azygous vein (arrowhead); **f** Intensity map mode to display the signal intensity of ICG dye using a color scale in an overlay image (yellow for maximum and blue for minimum intensity)

Fig. 3 Robotic-assisted Esophagectomy: **a** and **b** Dissection of the esophagus with thoracic duct (TD) in view; **c** ongoing dissection of esophageal cancer with tenting of TD adherent to it (arrow); **d** Visualization of the intact TD (green color) in continuity (arrowheads) at the end of esophageal mobilization



Results

Twenty-seven patients were screened for inclusion in the study. Six were excluded for various reasons: 3 underwent esophagectomy for benign disease, 2 had dense adhesions

in the thorax requiring a transhiatal esophagectomy, and one was found to have peritoneal metastasis intraoperatively. The remaining 21 patients underwent curative McKeown esophagectomy with a minimally invasive thoracic phase (15 thoracoscopic and six robotic) aided

Table 1 Demographic and Intra-operative details of the study group

S.No	Parameters	Combined (<i>n</i> =21)	Thoracoscopic (<i>n</i> =15)	Robotic (<i>n</i> =6)
1	Age in years; median (IQR)	54 (43.5, 62)	54 (42,62)	53 (48.5,62)
2	Gender Male: Female	13: 8	9: 6	4: 2
3	BMI in kg/m ² ; median (IQR)	20.6 (18.9, 22)	19.2 (18.6,22)	21 (19.6,22.4)
4	Type of tumor (n, %)			
	Squamous cell carcinoma	21 (100)	15 (100)	6 (100)
	Adenocarcinoma	0 (0)	0 (0)	0 (0)
5	Location of tumor			
	Mid-thoracic esophagus	11 (52.4)	8 (53.3)	3 (50)
	Lower thoracic esophagus	7 (33.3)	4 (26.7)	3 (50)
	Siewert type 1 & 2	3 (14.3)	3 (20)	0 (0)
6	Neoadjuvant therapy (n, %)			
	Chemoradiotherapy	9 (42.9)	5 (33.3)	4 (66.7)
	Chemotherapy	12 (57.1)	10 (66.7)	2 (33.3)
7	Time taken for ICG insertion in minutes; median (IQR)	15 (10,17.5)	15 (10,15)	15 (13.8,16.3)
8	Interval between dye insertion and visualization in minutes; median (IQR)	35 (30,35)	35 (30,35)	32.5 (28.8,36.3)
9	TD clipped intra-operatively (n, %)	3 (14.3)	2 (13.3)	1 (16.7)
10	Duration of thoracic phase minutes; Median (IQR)	150 (120,165)	120 (120,150)	150 (142.5,180)
11	Intraoperative blood loss ml; median (IQR)]	200 (200,200)	200 (200,200)	200 (200,200)

IQR inter-quartile range, BMI body mass index, ICG indocyanine green, TD thoracic duct

by ICG-NIRS. The demographic characteristics have been presented in Table 1.

The median (IQR) time taken for the ultrasound-guided insertion of the ICG dye was 15 (10, 17.5) minutes. None of these patients had an allergic or adverse reaction to the dye insertion. Intra-operatively, the TD was visualized in its entire thoracic course in all cases after a median (IQR) time of 35 (30, 35) minutes post dye injection via either IMAGE1 S™ Rubina™ (Karl Storz, Tuttlingen, Germany) or da Vinci Xi (Intuitive Surgical, Sunnyvale, US) systems. The dissection of the esophagus was carried out while simultaneously visualizing TD in the Overlay mode™ in the thoracoscopic phase and the Firefly mode™ in the robotic technique. The median (IQR) duration of the thoracic phase was 150 (120,165) minutes. The TD was visualized in all the patients until the end of the thoracic phase.

Three of our patients (14.3%) required intra-operative clipping of the TD, one in whom an unintentional injury occurred and was missed on standard view but identified by the pool of fluorescent fluid when we checked using ICG-NIRS towards the end of the thoracoscopic phase. The TD was skeletonized in the region of injury and clipped proximal to it. The remaining two patients had mid-thoracic tumors adherent to the TD (one in the robotic arm and the other in the thoracoscopic arm), and hence its ligation was done to achieve oncological radicality. A part of the adherent TD was taken with the specimen, and the final resection margins were negative in both these cases. None of the

patients developed post-operative chylothorax, including in these three cases.

Post-operative and pathological outcomes (Table 2)

The median times for ICD removal, initiation of oral diet, and length of hospital stay were 3, 5, and 6 days respectively. Though Clavien-Dindo major complications (grade ≥ 3a) occurred in 7 patients (33.3%), four of them had a mild anastomotic leak and were discharged & managed at home on feeding jejunostomy. One patient expired on the second post-operative day owing to refractory adult respiratory distress syndrome. All patients had an R0 resection with an overall median LN yield of 26 nodes.

Discussion

MIE, either thoracoscopic or robotic-assisted, has become the standard of care for esophageal cancer. However, it is associated with significant morbidity (~50%) and mortality even in high-volume centers.¹⁰ Chylothorax is the most dreaded complication to manage in post-esophagectomy patients, with an incidence varying from 4–10%.¹ The reasons for mortality in such patients are nutritional loss, respiratory distress syndrome, sepsis, and multiple organ failure.²

Table 2 Post-operative and pathological outcomes of the study group

S.No	Parameters	Combined (n = 21)	Thora-coscopic (n = 15)	Robotic (n = 6)
1	Length of ICU stay days; median (IQR)	1 (0,1)	1 (0,1)	0.5 (0,1)
2	Length of hospital stay; median (IQR)	6 (6,7.5)	6 (6,7)	6 (6,6.3)
3	Initiation of oral diet; median (IQR)	5 (4,6)	5 (4,6)	5 (4,6)
4	ICD tube removed on day; median (IQR)	3 (3,4)	3 (3,3)	3.5 (3,4)
5	Clavien-Dindo \geq 3a complications (n, %)	7 (33.3)	6 (40)	1 (16.7)
6	Complications (n, %)			
	Pulmonary	7 (33.3)	5 (33.3)	2 (33.3)
	RLN Neuropraxia	5 (23.8)	5 (33.3)	0 (0)
	Anastomotic leak	4 (19.1)	3 (20)	1 (16.7)
	30-day mortality	1 (4.8)	1 (6.7)	0 (0)
7	R0 resections (n, %)	21 (100)	15 (100)	6 (100)
8	Pathological stage of tumor; AJCC 8 (n, %)			
	0	6 (28.6)	2 (13.3)	4 (66.7)
	I	6 (28.6)	4 (26.7)	2 (33.3)
	II	3 (14.3)	3 (20)	0 (0)
	III	6 (28.6)	6 (40)	0 (0)
9	Overall LN yield; median (IQR)	26 (19,28)	26 (17,30)	26 (22,28)
	Thoracic	20 (14,22)	19 (13,24)	20 (15,21.5)
	Abdominal	6 (4,7)	6 (4,7)	6 (4.8,7)

ICD intercostal drainage, RLN recurrent nerve palsy, LN lymph node, IQR interquartile range

There are varying opinions among surgeons regarding the management of the TD during esophagectomy. The proponents of routine TD ligation argue that besides preventing this disastrous complication, it allows for complete resection of lymph nodes along with the TD, thereby providing a higher yield of lymph nodes and possibly improving recurrence-free survival.¹¹ However, the opponents argue that routine TD resection increases the operating time, blood loss and causes hemodynamic disturbances in the immediate post-operative period. Further, it has been stated that in the era of neoadjuvant chemoradiotherapy, TD resection does not increase lymph node yield and has no significant impact on survival.¹² Besides, the TD has variable anatomy in almost 50% of cases, and it may not be possible to ligate all the branches routinely. A systematic review by Yiyan et al. showed no evidence of reduction of post-operative chylothorax even with prophylactic TD ligation.¹³ Hence, intra-operative identification and preservation of TD are practiced as a standard of care in many centers worldwide. Occasionally, oncological radicality may demand TD ligation, especially in cases where the tumor in the mid-thoracic esophagus is densely adherent to the TD, as in two of our cases.

Various techniques have been described for intra-operative identification of the TD, like ingestion of a high-fat diet like cream, olive oil, or milk feeds, 6–8 h prior to surgery via the oral or enteral route.^{3,14} However, these

techniques are cumbersome, need preparation many hours before the planned surgery, and none of them are standardized or reliable for identifying the TD. In contrast, intranodal ICG injection is a simple technique that is well-tolerated and needs administration just after induction of anesthesia. With this technique of ICG-NIRS, we delineated TD in both thoracoscopy and robotic approach in all the patients. Besides delineation of TD, it also helped identify chyle leakage in case of accidental injury to TD during dissection in one of our cases post neoadjuvant chemoradiotherapy therapy and enabled us to clip the duct under visualization, thus averting the risk of post-operative chylothorax. Many patients may have radiotherapy-induced fibrosis, and not merely tumoral infiltration into the TD and ICG-NIRS may help in a meticulous dissection of the esophagus away from the duct in such cases.

In the literature, only a few case series and anecdotal case reports have discussed the NIRS technique for visualization of TD, illustrated in Table 3.^{4,7–9} Vecchiato M et al. described the technique where there is a need to switch between white light and the NIRS phase to delineate the TD.⁷ On the other hand, in the overlay mode used in the current study, the surgeon can dissect around the esophagus, keeping the TD in view all the time. Further, the authors did not demonstrate a check imaging to detect active chyle leak at the end of the thoracic phase. In one of our patients, we missed an inadvertent injury to the TD

Table 3 Comparison of the present study with the published literature

S.No	Study	Num-ber of patients	Procedure	ICG insertion site	Dose (mg)	TD visualized (%)	Time for visualization	Ligation of TD	TDI	Post-operative chylothorax
1	Vecchiato et al. 2020 ⁷	20	TTE status NACRT	Inguinal LN	0.5 mg/kg	19 (95)	35–80 min	2	0	0
2	Barnes et al. 2021 ⁸	20	TTE (Thoracoscopic and Open)	Enteral route or small bowel mesentery	3–6.2	16 (80)	10–185 min	4	4	1
3	Barbato et al. 2022 ⁹	18	Robotic Ivor-Lewis esophagectomy	Subcutaneously in the inguinal region	0.5 mg/kg	18 (100)	18–24 h	18*	1	0
4	Present study	21	Robotic and Thoracoscopic-McKeown esophagectomy status NACRT / NACT	Inguinal LN	2.5–7.5	21 (100)	30–80 min	3	1	0

ICG indocyanine green. TD thoracic duct, TDI thoracic duct injury, TTE transthoracic esophagectomy, NACRT neoadjuvant chemo-radiotherapy, NACT neoadjuvant chemotherapy, LN lymph node. *Routine prophylactic ligation done

on a standard mode, which was identified using ICG-NIRS enabling us to clip the TD safely. Hence, it is advisable to visualize TD to rule out any injury or leak at the end of the thoracic phase.

Further, Barnes TG et al. injected the ICG into the feeding jejunostomy limb or the small bowel mesentery root to delineate the TD.⁸ The enteral ingestion prior to surgery did not light up the TD, while the injection into the root of mesentery necessitated a laparotomy. On the other hand, instilling ICG under ultrasound guidance in the inguinal LN is easy to perform, not time-demanding, and inexpensive. It delineates the TD within a median time of about 35 min, and this time was utilized in securing central venous and arterial lines by the anesthetic team and for prone positioning of the patient for the thoracic phase dissection by the surgical team. Further, they could visualize the TD in only 80% of their study cohort, whereas we could appreciate the TD in all cases, reinforcing the superiority of the present technique.

Barbato G et al. reported their subcutaneous injection technique of ICG one day prior to surgery in 18 patients with a median time of 20 h for delineation of TD.⁹ On the other hand, our technique took only 15 min and was done in the operation theatre after the patient was under general anaesthesia, decreasing patient pain and anxiety. They prophylactically ligated the TD in all cases under ICG-NIRS guidance while performing robotic Ivor-Lewis esophagectomy. In contrast, we refrained from prophylactic TD ligation given its morbidity and adverse post-operative outcomes in terms of complications and survival.¹⁵ Moreover, we have described our technique in both thoracoscopic and robotic McKeown esophagectomy for mid and lower thoracic tumors and gastroesophageal junction cancers. This is the first case series where robotic McKeown esophagectomy with NIRS (Firefly mode) has been described to identify and preserve the TD intra-operatively.

During our study, we did not encounter any iatrogenic injury at the injection site or any adverse/allergic reactions to ICG. As mentioned in the literature, the risk of severe adverse reactions to ICG is very low (0.05%).¹⁶ Furthermore, the present study had the highest rates of dye visualization post-injection, which could be ascribed to the meticulous dye injection technique at the junction of the lymph-nodal hilum and cortex. Further, ICG fluorescence may be utilized to carry out LN dissection around the TD while visualizing it and avoiding its injury.

This “Intra-nodal ICG injection technique” for identification of TD allows a safe dissection while performing esophagectomy, gives constant anatomic feedback to the surgeon, and can easily be reproduced. Further, this technique can also be utilized to manage post-operative chylothorax.^{4,6} Yang and colleagues utilized ICG fluorescence in 4 patients who underwent re-operative surgery for a chyle leak, and

in all patients, the location of the leak was identified and clipped.¹⁷ To further reinstate the benefit of ICG, even a routine ligation of the TD can be performed under vision with this technique.

The limitations of our study include the small sample size and lack of a matched control group. However, when we analyzed our previous data on MIE without ICG usage, we found that 8.6% of patients had a post-operative chylothorax vis-a-vis none during the present study. Further, it is difficult to use this technique in cases where inguinal LN targeting is not feasible or when the TD is not visualized even after dye injection, but we did not encounter any such cases in our study. Sometimes, it may not be possible to visualize the TD if it is embedded in fat or fascial layers with thickness > 5 mm and may require some blind dissection prior to its identification. On the flip side, a single operating team, standardized procedure, and strict adherence to peri-operative protocols further strengthen the credibility of our findings.

In conclusion, the technique proved to be effective for identifying the TD in all patients, with precise anatomic details of the tributaries and aberrant ducts. Further, during the MIE thoracic phase, the most promising advantage was the constant visualization of normal tissue and clear delineation of TD without switching images from standard light to NIRS mode, making the dissection safe and ‘comfortable’ for the surgeon. Routine TD identification with ICG fluorescence may be a step forward in preventing chylothorax and improving peri-operative outcomes in MIE.

Declarations

Conflict of Interest The authors declare no competing interests.

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