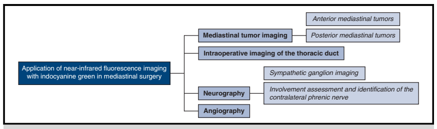
Application of near-infrared fluorescence imaging with indocyanine green in mediastinal surgery

Check for updates

Yilan Cao,[a] Xiaoyi Zhao, MD,[b] and Jian Zhou, MD[b]

ABSTRACT

Intraoperative near-infrared (NIR) fluorescence imaging has emerged in recent years and is now used in many surgical procedures. Intraoperative fluorescence imaging can guide surgeons in identifying and localizing specific structures and boundaries, which can facilitate the optimization of surgical procedures. The components of the mediastinum are complex and functionally important, making identifying and locating different structures intraoperatively challenging, and NIR fluorescence imaging has potential clinical value in mediastinal surgery. Here we review the applications of NIR fluorescence imaging technology in mediastinal surgery in recent years. (JTCVS Techniques 2023;22:343-9)



Near-infrared sympathetic ganglion imaging.

CENTRAL MESSAGE

We review the application of NIR fluorescence imaging technology in mediastinal surgery in recent years.

PERSPECTIVE

We summarize the applications of near-infrared (NIR) fluorescence imaging technology in mediastinal surgery in recent years. This is significant, because NIR fluorescence imaging during surgery can facilitate the optimization of surgical procedures, which has great clinical value.

The mediastinum is a large space between the left and right mediastinal pleura that contains many important vital organs and structures, including the heart, large blood vessels, trachea, esophagus, nerves, thymus, thoracic duct, lymphoid tissue, and connective adipose tissue. Because there are many tissues and organs in the mediastinum and the sources of these structures are complex, accurate identification of the boundaries between lesions and surrounding organs and tissues during surgery has always been the main focus and difficulty of mediastinal surgery.

With the development and popularization of thoracoscopic technology, mediastinal surgery has gradually become minimally invasive. Near-infrared (NIR) fluorescence imaging technology can be used to image specific biological tissues with fluorescent probes. The basic principle is to inject a fluorescent dye intravenously or percutaneously, excite the dye with a light-emitting diode or a laser device, capture the emitted light by the imaging system, and form a real-time image through advanced data processing technology. NIR fluorescence thoracoscopy has been widely used in lung surgery, such as pulmonary nodule imaging and pulmonary intersegmental plane identification; however, its application in mediastinal surgery is still in the exploratory stage. NIR fluorescence can break through traditional visual limitations and realize the real-time imaging of tumors, blood vessels, thoracic duct, nerves, and other structures during surgery. Its application in mediastinal surgery could help surgeons better identify complex

From the [a]School of Basic Medicine, Peking University Health Science Center, Beijing, China; and [b]Department of Thoracic Surgery, Center for Mini-Invasive Thoracic Surgery, People's Hospital, Peking University, Beijing, China.

Disclosures: The authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

Y. Cao and X. Zhao contributed equally to this work.

This work was supported by the National Natural Science Foundation of China (82003316, 62027901, 81227901, 81930053, 82001984 and 92059207); Ministry of Science and Technology of China (2017YFA0205200); Peking University People's Hospital Scientific Research Development Funds (RDL2021-10, RDGS2022-06); Peking University Baidu Fund (2020BD013) and National Key Research and Development Program (2020AAA0109600).

Received for publication March 12, 2023; revisions received June 30, 2023; accepted for publication July 11, 2023; available ahead of print Aug 6, 2023.

Address for reprints: Jian Zhou, MD, Department of Thoracic Surgery, Center for Mini-Invasive Thoracic Surgery, People's Hospital, Peking University, #11 Xizhimen South Ave, Beijing 100044, China (E-mail: zhoujian@bjmu.edu.cn).

2666-2507

https://doi.org/10.1016/j.xjtc.2023.07.023

Abbreviations and Acronyms
IDG = indocyanine green
NIR = near-infrared

structures in the mediastinum and distinguish lesions from normal tissue. Additionally, NIR fluorescence can be used to accurately identify nerves and blood vessels and reduce accidental injuries and complications, such as massive bleeding, conversion to thoracotomy, and postoperative nerve injury.

Herein we review the existing feasible applications of NIR fluorescence thoracoscopic mediastinal surgery, divided into 4 aspects: imaging of mediastinal tumors, identification of the thoracic duct, neurography, and angiography.

MEDIASTINAL TUMOR IMAGING

Anterior Mediastinal Tumors

The most common anterior mediastinal masses include thymoma, teratoma, retrosternal goiter, and lymphoma, among others.[1] The treatment of most anterior mediastinal tumors typically requires complete surgical resection and adjuvant therapy. Traditionally, surgeons determine the extent of lesions through visual assessment and palpation, which is somewhat subjective. There are many important structures in the mediastinum, including the phrenic nerve and aorta, and damage to these structures has serious consequences. Therefore, a more objective technique—NIR fluorescence imaging—has been applied in mediastinal surgery.

Predina and colleagues[2] first demonstrated the potential clinical role of NIR fluorescence imaging in anterior mediastinal tumor resection in 2018. They administered 5 mg/kg indocyanine green (ICG) intravenously 24 hours before surgery in 25 patients. The NIR imaging systems used included the Artemis (Quest) and Iridium (VisionSense) systems. Twenty-one of 25 subjects had lesions that showed fluorescence, including thymoma (n = 13), thymic carcinoma (n = 4), and liposarcoma (n = 2) lesions and hematologic malignancies (n = 2), and those that were not visualized were benign masses or hematologic tumors. In 20 patients with solid tumors, after tumor resection, NIR detection indicated complete resection in 18 cases, and residual disease was found in 2 cases. Figure 1 shows a representative NIR imaging view of a thymic carcinoma lesion. The first column shows a preoperative computed tomography scan, the second column shows a standard white light view, and the last column shows a merged NIR view.[2]

The reason why ICG can persist in tumor tissues is controversial. ICG combines with plasma proteins in the blood to form a macromolecular structure, and although it cannot pass through the capillaries of normal tissues, it can pass through the capillaries of tumor tissues; thus, owing to its size, shape, charge, polarity, and other characteristics, the exuded macromolecular substance can be retained in tumor tissues.[3]

NIR is associated with a certain level of safety and feasibility for determining the boundaries of anterior mediastinal tumors and residual disease. This method is effective in the treatment of large solid tumors; however, there are certain limitations, such as the inability to identify benign lesions of the thymus. At present, there have been few clinical trials in this field, and more research is needed for further verification in the future.

Posterior Mediastinal Tumors

Posterior mediastinal tumors are usually neurogenic tumors.[1] To date, no clinical trials have reported the successful application of NIR fluorescence imaging in posterior mediastinal tumors.

INTRAOPERATIVE IMAGING OF THE THORACIC DUCT

ICG NIR fluorescence also has been used for thoracic duct imaging to help identify the thoracic duct in real time and prevent its damage in thoracic surgery. The thoracic duct is the largest lymphatic vessel in the body, extending from the second lumbar vertebra to the neck and transporting chyle and 75% of the body's lymph into the blood.[4] Locating and identifying the thoracic duct in thoracic surgery is a great challenge. Lymphatic fluid is colorless and transparent, and there are many variations of

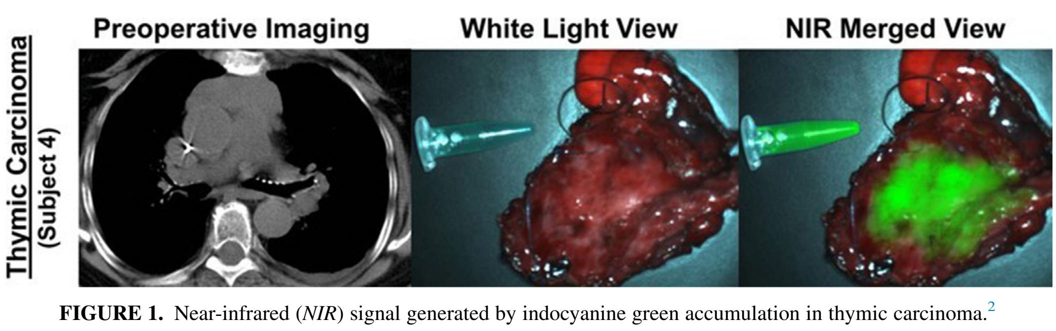


FIGURE 1. Near-infrared (*NIR*) signal generated by indocyanine green accumulation in thymic carcinoma.[2]

TABLE 1. Comparison of administration methods and imaging results of indocyanine green in thoracic duct imaging in different tests

Administration method	Injection site	Time from injection to imaging	Imaging result	First author and year of publication
0.5 mg/kg 14-16 h preoperatively	Bilateral subcutaneous inguinal	18-24 h	100%	Barbato 2022[9]
2.5-5 mg 15 min preoperatively	Dorsal foot subcutaneous	15-90 min	83.3%	Chakedis 2018[10]
0.5 mg/kg preoperatively	Percutaneous inguinal lymph node	35-80 min	100%	Vecchiato 2020[11]
20 mg 30 min preoperatively	Subcutaneous and intradermal injections in the right groin	Average 30 min	92.7%	Yang 2022[12]
2-3 mg preoperatively	Percutaneous inguinal lymph node	Average 35 min	100%	Varshney 2022[13]

the lymphatic system, and thus the thoracic duct is not always easy to identify intraoperatively. Several techniques for identifying the thoracic duct are currently available, including technetium 99 lymphography, which is considered a very effective method for identifying the location of leaks causing postoperative chylothorax. However, this technique cannot provide intraoperative real-time imaging and is relatively inaccurate, with low resolution.[5] Another example is the intake of fat in the gastrointestinal tract before surgery, which is conducive to identifying the thoracic duct, but the imaging contrast and reproducibility of this method are poor.[6] The emergence of ICG NIR fluorescence imaging technology may provide high sensitivity and specificity in identifying and localizing the thoracic duct.[7]

In 2009, Kamiya and colleagues[8] reported the first case in which NIR was used for chyle fistula detection in an open procedure. Intraoperative thoracic duct imaging was performed, and the fistula was localized by a subcutaneous injection of 1.5 mL of ICG in the bilateral groin. Subsequently, there have been many successful clinical trials of identification and ligation of the thoracic duct under the guidance of ICG NIR fluorescence[9-13] (Table 1). In 2020, Vecchiato and colleagues[11] reported on 19 patients who underwent minimally invasive esophagectomy with a percutaneous injection of 0.5 mg/kg ICG into the inguinal lymph nodes before thoracoscopic examination with OPAL1 technology (Karl Storz). The thoracic duct was visible in all 19 patients, and the average time from injection to clear imaging was 52.7 minutes. Additionally, there were no cases of postoperative chylothorax or adverse reactions from the ICG injection. In 2022, Feng and colleagues[12] reported on 41 patients who underwent minimally invasive thoracoscopic-laparoscopic esophagectomy for esophageal cancer with the injection of ICG into the right inguinal area before surgery and examination of the thoracic duct and monitoring for chylous leak by NIR fluorescence during the operation. The thoracic duct was visible at high contrast in 38 cases (92.7%). In 2022, Barnes and colleagues[14] reported on 20 patients who underwent esophagectomy; after ICG injection into the mesentery of the small intestine, the thoracic duct could be identified in 70% of patients using a commercially available fluorescence-enabled laparoscope compatible with ICG (PINPOINT; Stryker). Figure 2 shows representative images of intraoperative white light and NIR fluorescence views of the thoracic duct, which demonstrate that the thoracic duct is difficult to identify under white light but can be clearly observed under fluorescence (green).[14]

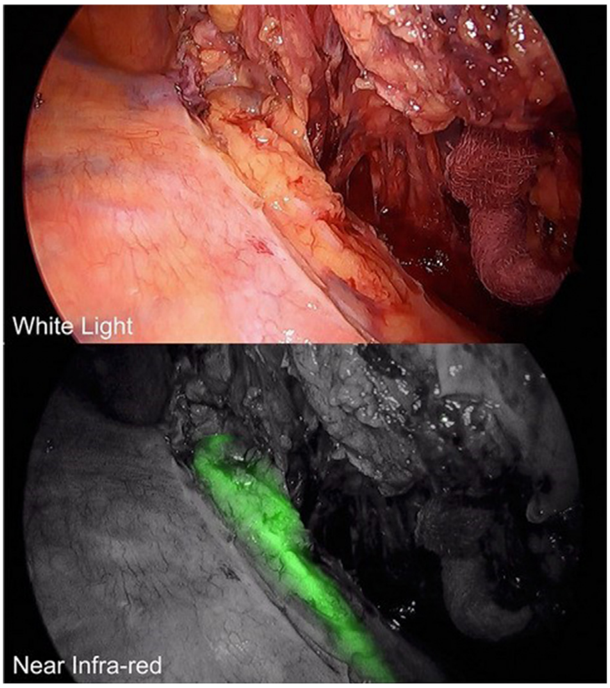


FIGURE 2. Representative *white light* and near-infrared fluorescence views of the thoracic duct during minimally invasive thoracic dissection.[14]

The advantages of thoracic duct NIR fluorescence imaging are obvious. First, it can realize real-time intraoperative imaging. Second, it has high specificity, sensitivity and resolution. Third, it is easy to operate, safe, and repeatable. Thus, ICG NIR fluorescence imaging can be applied for identification and protection of the thoracic duct; at the same time, the presence of fluorescent chylous fluid can be detected and corresponding thoracic duct fistulas can be ligated in a timely manner during the operation to prevent additional surgery for thoracic duct ligation. Furthermore, this method allows precise repair of the chylothorax under the guidance of fluorescence. However, the overall sample sizes of the foregoing experiments were not large, and further work is needed to optimize the procedure before it can be readily incorporated into routine practice.

NEUROGRAPHY

Sympathetic Ganglion Imaging

Thoracoscopic sympathectomy is currently used primarily for hyperhidrosis,[8] and accurate identification of thoracic sympathetic ganglia during surgery is crucial. At present, surgeons mainly estimate the position of ganglia roughly by counting ribs, but some studies have reported that the anatomic position of the sympathetic chain is not constant[15,16]; thus, this method has certain limitations. In 2016, Weng and colleagues[17] reported the first successful identification of sympathetic ganglia in 4 patients using NIR fluorescence imaging technology. An intraoperative image is shown in Figure E1.

In 2018, He and colleagues[18] reported on 15 patients with pulmonary nodules who received an intravenous injection of 5 mg/kg ICG 24 hours before undergoing surgery using a novel self-developed NIR and white-light dual-channel thoracoscope system. The sympathetic ganglia and neural chains of the patients were successfully measured and recorded during surgery, providing evidence of the feasibility and validity of intraoperative imaging of thoracic sympathetic nerves using ICG. Pei and colleagues[19] expanded the scope of the study and reported in 2020 on 142 patients who underwent sympathectomy after infusion with 5 mg/kg ICG 24 hours before surgery. Intraoperative imaging procedures were performed using the FloNavi endoscopic fluorescence imaging system, and the visibility rate among all sympathetic ganglia was 96.7% (1369 of 1415). No moderate to severe adverse reactions were found, confirming the safety and feasibility of ICG NIR fluorescence imaging in sympathectomy. Thoracic sympathetic nerves show distinct fluorescence signals, possibly associated with a connective tissue membrane on the surface of sympathetic ganglia, which contains blood vessels, nerves, and fat cells, similar to some types of cancer tissue, resulting in enhanced permeability and retention of ICG.[18] The visibility rate of sympathetic ganglia is affected by various factors, such as ICG dose, imaging time, intercostal fat thickness, and imaging system sensitivity.[19]

As there is often variability in the position of thoracic sympathetic ganglia relative to the corresponding ribs and the conventional method can be used only to visualize the sympathetic chain and not specific sympathetic ganglia, conventional surgical treatment is likely to be compromised by the variation in the location of sympathetic ganglia. This new technique with a nonradioactive and nontoxic fluorescent contrast agent, which can provide a more accurate and clearer view of the position of thoracic sympathetic ganglia, has enormous potential and may be able to replace the rib localization method as the standard method for identifying thoracic sympathetic nerves in the future.

Involvement Assessment and Identification of the Contralateral Phrenic Nerve

The phrenic nerves originate from the cervical plexus, and injury to one phrenic nerve may lead to paralysis of the ipsilateral diaphragm, often leading to symptoms of dyspnea. Minimally invasive thymectomy is performed to treat myasthenia gravis and small thymomas by removing the thymus gland between both phrenic nerves and variable amounts of anterior mediastinal fat. In unilateral video-assisted thoracoscopic surgery, identification of the contralateral phrenic nerve can be difficult owing to the limited visual field. This has led to wider use of a bilateral video-assisted thoracoscopic surgery approach to allow direct identification of each phrenic nerve and removal of all tissue with certainty.[20] However, in 2012, Wagner and colleagues[21] reported unilateral robotic thymectomy using the da Vinci Si HD Surgical System, in which the contralateral phrenic nerve was identified by visualizing the pericardiophrenic vasculature—the pericardiophrenic neurovascular bundle—that runs parallel to the nerve with ICG NIR fluorescence imaging. This new technique has the potential to maximize thymic tissue resection with a unilateral approach while reducing the duration of the operation and incidence of nerve injury. An intraoperative image is shown in Figure E2.

The phrenic nerve also can be involved in large mediastinal tumors. The decision of whether the phrenic nerve needs to be removed is based mainly on the surgeon's subjective judgment of visual and palpable sensory input. Predina and colleagues[2] assessed involvement of the phrenic nerve during mediastinal tumor resection and found that it was difficult to confirm involvement of the phrenic nerve with ordinary white light and manual palpation compared with NIR fluorescence imaging, which could quickly indicate whether the nerve was involved by the contrast of the tumor-specific signal. Thus, this new technique has the potential to help surgeons reduce the incidence of intraoperative nerve damage and the duration of surgery.

To date, there have been few studies on ICG in the field of neurography, and further studies are needed to confirm and optimize the use of ICG in this field. In future studies, ICG imaging of other nerves also could be explored.

ANGIOGRAPHY

Solid mediastinal tumors often have a rich blood supply and are often indistinguishable from adjacent vessels, which is a challenge in mediastinal surgery. If the complex vessels are not clearly identified during surgery, adjacent

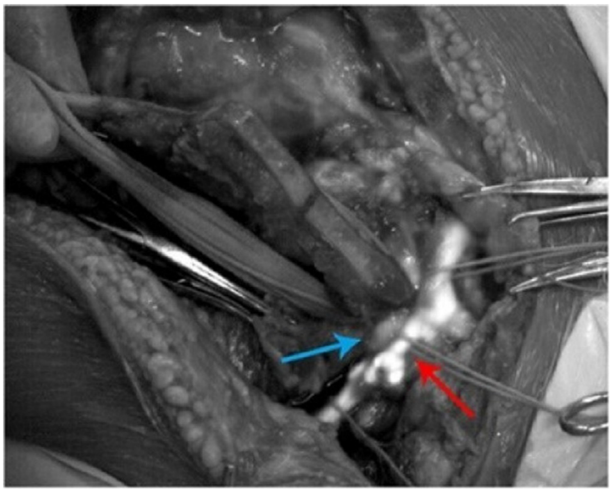


FIGURE 3. Intraoperative near-infrared II indocyanine *green* angiography showing the *left* subclavian vein (*red arrow*) and *left* subclavian artery (*blue arrow*).[22]

blood vessels may be damaged during surgery, increasing the perioperative risk.[22] ICG angiography under the first NIR wavelength window (NIR-I; 700-900 nm) has been applied in numerous surgical scenarios. This method also was applied under the NIR-I window in most of the aforementioned cases. A recent study found that the second NIR wavelength window (NIR-II; 1000-1700 nm) can reduce the light scattering of tissue and increase the penetration depth, potentially resulting in better image quality than NIR-I.[23] In 2022, Mi and colleagues[22] reported the first successful clinical application of NIR-II ICG angiography in a patient with a mediastinal tumor. In this patient, the mediastinal tumor was adjacent to the subclavian artery and vein. Intraoperative real-time imaging of the upper pole of the tumor using 5 mg/mL ICG with the NIR-II imaging system showed a clear vascular border (Figure 3).

Compared with NIR-I, which has been studied more, NIR-II is a new research field with great potential. Owing to the low tissue scattering and high penetration depth of NIR-II, it could be used not only in the identification of tumors and adjacent complex vascular structures, but also in the detection of blood vessel patency.[22] Of course, more research is needed.

CONCLUSIONS

NIR fluorescence imaging has broad research prospects and clinical value in mediastinal tumor boundary imaging, intraoperative imaging of the thoracic duct, neurography, and angiography in mediastinal surgery. Fluorescence imaging has the advantages of high temporal and spatial resolution[23] and can be used for real-time imaging during surgery without considering the hazards of radiation. Additionally, few adverse reactions have been reported. However, ICG contains a small amount of sodium iodide and is injected intravenously and cleared by the liver; thus, it should be used with caution in those with sodium iodide allergy and liver insufficiency.

Of course, ICG NIR fluorescence imaging has certain limitations. For example, its penetration cannot reach deeper tissue structures, and consensus on the optimal dose and imaging time has not yet been reached. However, with the continuous deepening of related research, NIR fluorescence imaging technology should become more widely used in mediastinal surgery, improving safety and reducing operative duration.

References

1. Duwe BV, Sterman DH, Musani AI. Tumors of the mediastinum. *Chest*. 2005;128:2893-909.
2. Predina JD, Keating J, Newton A, Corbett C, Xia L, Shin M, et al. A clinical trial of intraoperative near-infrared imaging to assess tumor extent and identify residual disease during anterior mediastinal tumor resection. *Cancer*. 2019;125:807-17.
3. Matsumura Y, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer Res*. 1986;46:6387-92.
4. Kubik S. Anatomie des Lymphsystems [Anatomy of the lymphatic system]. *Radiol Clin Biol*. 1973;42:243-57.
5. Prevot N, Tiffet O, Avet J Jr, Quak E, Decousus M, Dubois F. Lymphoscintigraphy and SPECT/CT using 99mTc filtered sulfur colloid in chylothorax. *Eur J Nucl Med Mol Imaging*. 2011;38:1746.
6. Du ZS, Li XY, Luo HS, Wu SX, Zheng CP, Li ZY, et al. Preoperative administration of olive oil reduces chylothorax after minimally invasive esophagectomy. *Ann Thorac Surg*. 2019;107:1540-3.
7. Nusrath S, Thammineedi SR, Saksena AR, Patnaik SC, Reddy P, Usofi Z, et al. Thoracic duct lymphography by near-infrared indocyanine green fluorescence imaging in thoracic surgery. A review. *Indian J Surg Oncol*. 2022;13:415-20.
8. Kamiya K, Unno N, Konno H. Intraoperative indocyanine green fluorescence lymphography, a novel imaging technique to detect a chyle fistula after an esophagectomy: report of a case. *Surg Today*. 2009;39:421-4.
9. Barbato G, Cammelli F, Braccini G, Staderini F, Cianchi F, Coratti F. Fluorescent lymphography for thoracic duct identification: initial experience of a simplified and feasible ICG administration. *Int J Med Robot*. 2022;18:e2380.
10. Chakedis J, Shirley LA, Terando AM, Skoracki R, Phay JE. Identification of the thoracic duct using indocyanine green during cervical lymphadenectomy. *Ann Surg Oncol*. 2018;25:3711-7.
11. Vecchiato M, Martino A, Sponza M, Uzzau A, Ziccarelli A, Marchesi F, et al. Thoracic duct identification with indocyanine green fluorescence during minimally invasive esophagectomy with patient in prone position. *Dis Esophagus*. 2020;33:doaa030.
12. Yang F, Gao J, Cheng S, Li H, He K, Zhou J, et al. Near-infrared fluorescence imaging of thoracic duct in minimally invasive esophagectomy. *Dis Esophagus*. 2022;36:doac049.
13. Varshney VK, Nayar R, Soni SC, Selvakumar B, Garg PK, Varshney P, et al. Intra-nodal indocyanine green injection to delineate thoracic duct during minimally invasive esophagectomy. *J Gastrointest Surg*. 2022;26:1559-65.
14. Barnes TG, MacGregor T, Sgromo B, Maynard ND, Gillies RS. Near infra-red fluorescence identification of the thoracic duct to prevent chyle leaks during oesophagectomy. *Surg Endosc*. 2022;36:5319-25.
15. Cerfolio RJ, De Campos JR, Bryant AS, Connery CP, Miller DL, DeCamp MM, et al. The Society of Thoracic Surgeons expert consensus for the surgical treatment of hyperhidrosis. *Ann Thorac Surg*. 2011;91:1642-8.
16. Street E, Ashrafi M, Greaves N, Gouldsborough I, Baguneid M. Anatomic variation of Rami communicantes in the upper thoracic sympathetic chain: a human cadaveric study. *Ann Vasc Surg*. 2016;34:243-9.
17. Weng W, Liu Y, Zhou J, Li H, Yang F, Jiang G, et al. Thoracoscopic indocyanine green near-infrared fluorescence for thoracic sympathetic ganglions. *Ann Thorac Surg*. 2016;101:2394.
18. He K, Zhou J, Yang F, Chi C, Li H, Mao Y, et al. Near-infrared intraoperative imaging of thoracic sympathetic nerves: from preclinical study to clinical trial. *Theranostics*. 2018;8:304-13.

19. Pei G, Liu Y, Liu Q, Min X, Yang Y, Wang S, et al. The safety and feasibility of intraoperative near-infrared fluorescence imaging with indocyanine green in thoracoscopic sympathectomy for primary palmar hyperhidrosis. *Thorac Cancer*. 2020;11:943-9.
20. Lee CY, Kim DJ, Lee JG, Park IK, Bae MK, Chung KY. Bilateral video-assisted thoracoscopic thymectomy has a surgical extent similar to that of transsternal extended thymectomy with more favorable early surgical outcomes for myasthenia gravis patients. *Surg Endosc*. 2011;25:849-54.
21. Wagner OJ, Louie BE, Vallières E, Aye RW, Farivar AS. Near-infrared fluorescence imaging can help identify the contralateral phrenic nerve during robotic thymectomy. *Ann Thorac Surg*. 2012;94:622-5.
22. Mi J, Liu G, Lu L, Yang F, Zhao H, Li Y, et al. Case report: the second near-infrared window indocyanine green angiography in giant mediastinal tumor resection. *Front Surg*. 2022;9:852372.
23. Hu Z, Fang C, Li B, Zhang Z, Cao C, Cai M, et al. First-in-human liver-tumour surgery guided by multispectral fluorescence imaging in the visible and near-infrared-I/II windows. *Nat Biomed Eng*. 2020;4:259-71.

Key Words: image-guided surgery, indocyanine green, mediastinal surgery, near-infrared fluorescence imaging

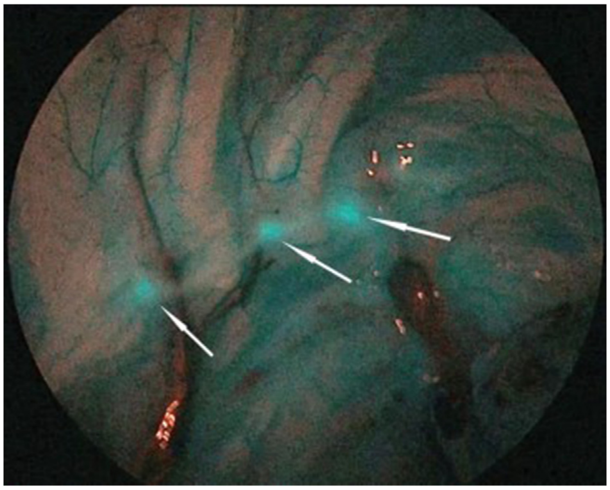


FIGURE E1. Near-infrared sympathetic ganglion imaging, and the *white arrow* is the identification of sympathetic ganglias.[17]

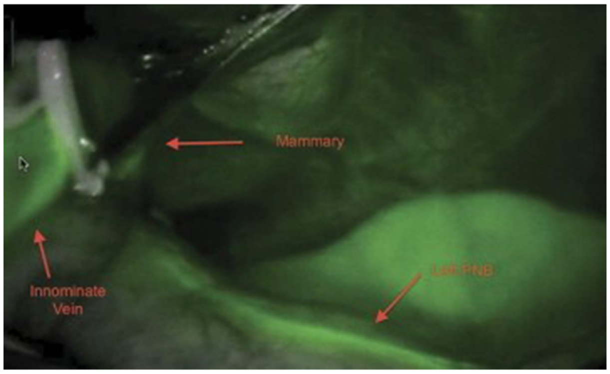


FIGURE E2. Pleural view of the contralateral (*left*) pericardial phrenic neurovascular bundle (*PNB*) under fluorescence imaging with indocyanine *green* in *right* unilateral robotic-assisted thymectomy.[21]