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

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Disclosures

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Central Message

Review the applications of NIR fluorescence imaging technology in mediastinal surgery in recent years.

Central Picture Legend

Near-infrared sympathetic ganglion imaging

Perspective Statement

In this paper, 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 in the future.

Keywords

Near-infrared (NIR) fluorescence imaging; indocyanine green (ICG); mediastinal surgery; image-guided surgery

Glossary of Abbreviations

Near-infrared (NIR) fluorescence imaging
indocyanine green (ICG);
Abstract

Intraoperative near-infrared (NIR) fluorescence imaging has emerged in recent years and been 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; thus, it is challenging to identify and locate different structures intraoperatively, and NIR fluorescence imaging has potential clinical value in mediastinal surgery. This is a review of the applications of NIR fluorescence imaging technology in mediastinal surgery in recent years.

Introduction

The mediastinum is a large space between the left and right mediastinal pleura, which 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 boundary between lesions and the 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, the thoracic duct, nerves and other structures during surgery. Its application in mediastinal surgery could help surgeons better identify
complex structures in the mediastinum and distinguish lesions from normal tissue. Additionally, NIR fluorescence can also 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 four 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. 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, such as the phrenic nerve and aorta, and damage to these structures has serious consequences. Therefore, a more objective technique—NIR fluorescence imaging—was proposed and applied in mediastinal surgery.

Predina et al. first demonstrated the potential clinical role of NIR fluorescence imaging in anterior mediastinal tumor resection in 2018. They administered 5 mg/kg ICG intravenously 24 hours before surgery in 25 patients. The NIR imaging systems used included the Artemis (Quest, Middenmeer, the Netherlands) and Iridium (VisionSense Corp, Philadelphia, Pennsylvania) 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 view².

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 while it cannot pass through the capillaries of normal tissues, it can pass through the capillaries of tumor tissues; thus, due to its size, shape, charge, polarity and other characteristics, the exuded macromolecular substance can be retained in tumor tissues³.

NIR is associated with a certain level of safety and feasibility in 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 tumors¹. 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 near-infrared fluorescence has also 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 blood⁴. 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 the lymphatic system; thus, the thoracic duct is not easily identified intraoperatively. Several techniques for identifying the thoracic duct are already available, such as technetium 99 lymphography, which is considered to be a very
effective method for identifying the location of leakages causing postoperative chylothorax. However, it 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 identification of the thoracic duct, but the imaging contrast and reproducibility of this method are poor\(^6\). The emergence of ICG near-infrared fluorescence imaging technology may realize high sensitivity and specificity in identification and localization of the thoracic duct\(^7\).

In 2009, Kamiya \textit{et al.}\(^8\) 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 near-infrared fluorescence\(^8-13\) (see Table 1). In 2020, Vecchiato \textit{et al.}\(^11\) 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 KARL STORZ OPAL1\(^{®}\) technology. The thoracic duct was visible in all 19 patients, and the average time from injection to clear imaging was 52.7 min. Additionally, there were no cases of postoperative chylothorax or adverse reactions from the ICG injection. In 2022, Feng \textit{et al.}\(^12\) 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 leakages by near-infrared fluorescence during the operation. The thoracic duct was visible in high contrast in 38 cases (92.7%). In 2022, Barnes \textit{et al.}\(^14\) reported on 20 patients who underwent esophagectomy; after ICG was injected 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 or Stryker). Figure 2 shows representative images of intraoperative white light and near-infrared 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)\textsuperscript{14}.

The advantages of thoracic duct near-infrared 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 near-infrared 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 the precise repair of chylothorax under the guidance of fluorescence. However, the overall sample size of the above experiments is not large, and further work is required to optimize the procedure before it can be incorporated easily into routine practice.

**Neurography**

*Sympathetic ganglion imaging*

Thoracoscopic sympathectomy is currently used primarily for hyperhidrosis\textsuperscript{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 anatomical position of the sympathetic chain is not constant\textsuperscript{15-16}; thus, this method has certain limitations. In 2016, Weng et al.\textsuperscript{17} reported the first successful identification of sympathetic ganglia in 4 patients using NIR fluorescence imaging technology. An intraoperative image is shown in Supplemental Figure 1.

In 2018, He et al.\textsuperscript{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 indocyanine green (ICG). Pei et al.\textsuperscript{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\% (1369/1415). No moderate to severe adverse reactions were found, confirming the safety and feasibility of ICG near-infrared 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\textsuperscript{18}. The visibility rate of sympathetic ganglia is affected by various factors, such as the ICG dose, imaging time, intercostal fat thickness, and imaging system sensitivity\textsuperscript{19}.

As there is often variability in the position of thoracic sympathetic ganglia relative to the corresponding ribs and the conventional method can only be used 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 clear 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.

\textit{Involvement assessment and identification of the contralateral phrenic nerve}

The phrenic nerve originates 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 (VATS), identification of the contralateral phrenic nerve can be difficult due to the limited visual field. This led to the wider use of a bilateral VATS approach to allow each phrenic nerve to be identified directly and all tissue to be removed with certainty. However, in 2012, Wagner et al. 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 (PNB)—that runs parallel to the nerve with ICG near-infrared fluorescence imaging. Thus, this new technique has the potential to maximize thymic tissue resection with a unilateral approach while reducing the operative duration and incidence of nerve injury. An intraoperative image is shown in Supplemental Figure 2.

In addition, the phrenic nerve could be involved in large mediastinal tumors. Whether the phrenic nerve needs to be removed is mainly based on the surgeon's subjective judgment of visual and palpable sensory input. Predina et al. 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 near-infrared 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 could also 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 blood vessels may be damaged during surgery, increasing the perioperative risk. To date, ICG angiography under the first near-infrared wavelength window (NIR-I, 700-900 nm) has been applied in many surgical scenarios. This method was also applied under the NIR-
I window in most of the cases we have mentioned above. In recent research, it was found that the second near-infrared 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\textsuperscript{23}. In 2022, Mi et al.\textsuperscript{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, as shown in Figure 3.

Compared with NIR-I, which has been studied more, NIR-II is a new research field with great potential. Due 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\textsuperscript{22}. Of course, more research is required in the future.

**Summary**

In conclusion, we found that 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\textsuperscript{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 near-infrared fluorescence imaging has certain limitations. For example, the penetration depth cannot reach deeper tissue structures, and a consensus has not yet been reached regarding the optimal dose or imaging time. However, with the continuous deepening of related research, it is believed that near-infrared
fluorescence imaging technology can gradually be more widely used in mediastinal surgery, improving safety and reducing the duration of mediastinal surgery.

References

Table 1 Comparison of administration methods and imaging results of ICG in thoracic duct imaging in different tests\textsuperscript{9-13}

<table>
<thead>
<tr>
<th>Administration method</th>
<th>Injection site</th>
<th>Injection-to-imaging time</th>
<th>Imaging result</th>
<th>Author and year</th>
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<tr>
<td>0.5 mg/kg 14-16 h preoperatively</td>
<td>Bilateral subcutaneous inguinal</td>
<td>18-24 h</td>
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<td>Barbato G 2022</td>
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<tr>
<td>2.5-5 mg 15 min</td>
<td>Dorsal foot subcutaneous</td>
<td>15-90 min</td>
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<tr>
<td>0.5 mg/kg preoperatively</td>
<td>Percutaneous inguinal lymph node</td>
<td>35-80 min</td>
<td>100%</td>
<td>Vecchiato M 2020</td>
</tr>
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<td>20 mg 30 min preoperatively</td>
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<td>Average 30 min</td>
<td>92.7%</td>
<td>Yang F 2022</td>
</tr>
<tr>
<td>2-3 mg preoperatively</td>
<td>Percutaneous inguinal lymph node</td>
<td>Average 35 min</td>
<td>100%</td>
<td>Varshney VK 2022</td>
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</table>
Figure 1 Near-infrared signal generated by ICG accumulation in thymic carcinoma

Figure 2 Representative white light and near-infrared fluorescence views of the thoracic duct during minimally invasive thoracic dissection

Figure 3 Intraoperative NIR-II ICG angiography showing the left subclavian vein (red arrow) and left subclavian artery (blue arrow)

Suppl Figure 1 Near-infrared sympathetic ganglion imaging

Suppl Figure 2 Pleural view of the contralateral (left) pericardial phrenic neurovascular bundle (PNB) under fluorescence imaging with ICG in right unilateral robotic-assisted thymectomy
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