Review Article

Applications of indocyanine green based near-infrared fluorescence imaging in thoracic surgery

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Abstract: Near-infrared (NIR) fluorescence guided surgery is an emerging technique. This technique uses the combination of dyes and NIR imaging devices to expand the visible spectrum. Thus it can provide more anatomic and functional information, and may facilitate a more complete resection of cancer, or better protection of important normal structures. Recently, significant progress has been made in the field of NIR fluorescence guided thoracic surgery. This may lead to better prognosis and health-economic outcomes. In this article, the current studies of indocyanine green (ICG) based NIR fluorescence guided thoracic surgeries are reviewed. The applications are classified into four categories, which are applications based on blood supply, lymphatic drainage, the enhanced permeability and retention (EPR) effect, and the other mechanisms.

Keywords: Near-infrared fluorescence; indocyanine green (ICG); blood supply; lymphatic drainage; enhanced permeability and retention effect (EPR effect)

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Introduction

The past two decades has witnessed a rapid technological advancement and maturation of minimally invasive thoracic surgery, most notably, thoracoscopic and robotic thoracic surgery. The development of mechanical staplers and energy platforms ensures much faster securing vascular or bronchus stumps than sewing or ligation. Robotic instruments provide more dexterity and degrees of freedoms than human hands. However, with respect to intraoperative "imaging modality", eye inspection and hand palpation have remained the choice for thoracic surgeons in most cases since the first thoracic surgeries decades ago. This problem is even worse in scenarios of minimally-invasive thoracic surgery, especially when surgeon sits at the robotic console and has no touch feedbacks of the surgical field.

Over the past several years, intraoperative imaging using invisible indocyanine green (ICG) induced near-infrared (NIR) fluorescent light has entered the surgical theatre to fill the gap between sophisticated preoperative imaging and immature intraoperative reality. Several reviews or perspectives (1-3) published in the Nature Reviews series in the past 2 or 3 years considered technical developments in NIR fluorescence imaging has highlighted the future of surgery.

Why NIR

NIR fluorescence imaging has several advantages. The first advantage is the low absorption rate in human tissues. The light absorption of hemoglobin and water may reduce the luminance and efficiency of the imaging. The spectrum of NIR is between the wavelength around 800 nm. It has minimal absorption compared to the other wavelengths. Secondly, this NIR band has low scattering in the tissues, resulting a deep penetration. Thirdly, the autofluorescence in the near infrared band is low. Autofluorescence is notably high in lights with wavelengths shorter than 600 nm. This is owing to many endogenous fluorophores, such as hemoglobin, myoglobin and cytochromes. Therefore, NIR wavelengths give less autofluorescence, deeper tissue penetration and easier separation from standard white-light reflectance. So it is suitable for intraoperative real-time imaging.

Dyes used in NIR fluorescence guided surgeries

NIRF dyes are classified into several categories, including cyanines, rhodamine analogs, 4,4-difluoro-4-bora-3a,4a-diaza-s-indacene (BODIPYs), squaraines, phthalocyanines, and porphyrin derivatives and other related dyes in light of their NIR organic fluorophore platforms.

ICG is a water-soluble anionic, amphiphilic fluorophore particular attractive due to its excitation (λ_{ex} =778 nm) and emission (λ_{em} =830 nm). ICG, which fluoresces at 800 nm, and is the only NIR contrast agent approved for a small number of indications in surgery by the FDA and European medicines agency (EMA). ICG was developed well before the era of infrared imaging in the Second World War, and was granted FDA approval in 1959. It was initially used primarily in hepatic function diagnostics and later in ophthalmology and cardiology. ICG is shown to have minimal toxicity. Clinical experience with ICG for intraoperative NIR fluorescence imaging is rather extensive and shows a favourable safety profile.

NIRF imaging systems

Over the past few years, various imaging systems have been developed by academic and industrial groups for intraoperative NIR fluorescence imaging. In addition to systems for open surgery, NIR fluorescence imaging is available for laparoscopic, thoracoscopic and robot-assisted surgery, most of which are the first production-grade development iteration. Specific challenges for these systems include the need for optimized light-sources to enable sufficient fluorescence excitation, and low-attenuation optics for NIR light, to detect low concentrations of NIR fluorophores.

There are currently several available NIR imaging cameras for intraoperative use including the Artemis (Quest Medical Imaging Inc., Middenmeer, the Netherlands), PINPOINT (Novadaq Inc., Ontario, Canada), the Karl Storz PPD unit and the Firefly System (Intuitive Inc., Sunnyvale, CA, USA).

Ideally, new instruments will accommodate multiple wavelengths ranging from visible to infrared, given the wide variety of molecularly targeted probes being developed, the desirability of counterstaining healthy tissue with a contrasting color and the possibility of radiometric discrimination.

Notably, many of them carry NIR imaging capability around 800 nm, which is the excitation wavelength of ICG.

The currently used near infrared imaging systems include Novadaq SPY™ system, Artemis™, Hamamatsu's Photodynamic Eye (PDE™), Fluoptics' Fluobeam®, Functional intraoperative FMI systems: FLARE™ imaging system, etc. Most systems merged the infrared images displayed as a contrasting color superimposed with the visible-light images, while the Storz D-light P system displays the NIR fluorescence as a single image.

The application of NIR fluorescence imaging devices in thoracic surgeries

Applications based on blood supply

Identification of segmental border

The identification of intersegmental plane is essential in segmentectomy surgeries. The conventional method is the air inflation method. This technique involves ligation of the target segmental bronchi, and then inflation and deflation of the entire lung. However, during the video-assisted thoracoscopic surgery, the inflated segment may obstruct the surgical view. In 2009, Misaki *et al.* (4) reported a technique to identify the intersegmental line in animal models using infrared thoracoscopy. After ligating the target segmental artery, ICG was injected through peripheral vein. The intersegmental line was clearly detected. And the line was proved to correspond to the radiographic and pathologic analysis. Later on, this method was used in clinical trials by various centers (5-9). In these clinical trials, the intersegmental line showed in around 10 seconds, and the line was observed in around 84.6–100% patients (5-8). The reported duration time was 4–5 minutes (5-8), which is considered adequate to mark the intersegmental line.

Evaluation of gastric conduit perfusion

In esophagectomy surgeries, healing of the anastomotic site is a key factor after surgery. Anastomotic leaks are related to elevated morbidity and mortality. In Briel's study (10), conduit ischemia is considered to be a significant factor of leakage. So the evaluation of anastomotic site's perfusion is of great importance. The traditional method of blood supply evaluation is based on palpation and inspection of the gastric serosa. In 2011, Shimada and his colleagues (11) applied ICG for visualization of the gastric conduit perfusion. Their results showed the ICG fluorescence could help to observe the small vessels and the microcirculation of the gastric tube. In 2015, Yukaya's study (12) tried to quantitatively assess the perfusion of the conduit. They included 27 patients who underwent esophagectomy with gastric tube reconstruction. Based on the ICG inflow time and outflow time in two selected spots, they categorized the patterns of fluorescence luminance into three types, which are normal flow type, inflow delayed type and outflow delayed type. Although there were no significant differences among the three groups, the authors provided us a way of quantitative evaluation of the gastric tube, and showed the heterogeneity of blood supply in gastric tubes. Zehetner's study (13) performed intraoperative evaluation of gastric tube using fluorescent-dye in 150 consecutive patients. The leak rate is significantly lower in good perfusion groups (2% *vs.* 45%, P<0.0001). These published data showed the intraoperative NIR fluorescence imaging is a promising technology to illustrate the perfusion of the gastric conduit and may reduce the anastomotic leakage rate, and thus reduce the morbidity and mortality after esophagectomy surgeries.

Detection of bullous lesions

VATS has become a standard of care for some patients with spontaneous pneumothorax. However, the recurrence rate of pneumothorax can be as high as 10% (14). Failure to detect all the bullous lesions maybe one of the reasons for recurrence. Gotoh *et al.* developed a method to observe pulmonary emphysematous lesions in a canine model (15). ICG was injected through peripheral vein. Because the perfusion of the bullous lesion is poorer than the normal tissue. The demarcation of bullous lesion is well detected. In 2007, the authors applied infrared thoracoscopy in eight patients (16). In three of eight cases, the bullous lesions were poorly detectable under white light, but well visualized under infrared light. Li *et al.* (17) in our center reported the application of laser induced NIR thoracoscope in bullectomy surgeries. In two patients with spontaneous pneumothorax, no well-identified bullous lesions were detected under white light. Using NIR thoracoscope, the authors detected obviously decreased fluorescent densities comparing to adjacent normal tissue. The suspected lesion was resected. The specimens were confirmed as bullous lesions by pathology. With the help of infrared thoracoscope, the treatment pattern of the two patients has shifted from pleurodesis to precise resection of bullous lesion. Matsumoto *et al.* (18) also reported the delineation of a large bullous lesion using infrared system. These studies imply the infrared thoracoscope can help in the precise resection of bullous lesions.

Applications based on lymphatic drainage

Imaging of thoracic duct and treatment of chylothorax

Chylothorax is a complication which can occur in both lung surgeries, esophagectomies and other cardiothoracic surgeries. Iatrogenic chylothorax should be suspected when the pleural effusion volume is excessive and the color of the effusion is milky-white. When conservative treatment fails, the surgical exploration of the chylous fistula and ligation of the thoracic duct is required. The imaging of the chylous fistula and the thoracic duct is the key to the success of the surgery. The traditional method is ingestion of milk or olive oil before surgery. But ingestion before surgery may increase the risk of gastric regurgitation and aspiration. Some centers prefer to inject the milk or oil through a nasogastric tube into the duodenum. Kamiya *et al.* reported intraoperative ICG lymphography in a patient diagnose as chylothorax after esophagectomy. ICG was injected subcutaneously in the bilateral inguinal region. The fluorescence dye goes along the thoracic duct. Then the leakage point was detected and sutured with the help of the infrared camera. The chyle ooze stopped and the patient recovered uneventful. Kaburagi and Chang reported the ICG fluorescence lymphography in chylothorax patient after esophagectomy and congenital heart surgery respectively. Both patients recovered well after surgery. These reports show the ICG induced fluorescence lymphography is a promising method to reveal the chylous leakage sites.

Applications based on the enhanced permeability and retention (EPR) effect

Detection of pulmonary nodules and solid tumor tissues

In the surgery of malignant tumors, the detection and complete resection of all the tumors is essential. The detection of pulmonary nodules is based on the preoperative CT scan and finger palpation. However, the resolution power of CT scan is limited. The palpation of finger may not discriminate small and soft nodules, and is more limited in thoracoscopic surgeries. This may lead to the neglecting of small nodules.

Okusanya *et al.* (19) enrolled 18 patients undergoing pulmonary surgeries. The patients were given systemic ICG 24 hours before surgery. All the patients underwent computed tomography with at least 0.1 cm thin CT scan. All the patients were performed thoracotomy, and surgeons located all the primary nodules using inspection and manual palpation. Then the NIR cameras were used to search for additional nodules. The NIR imaging identified five additional nodules, which were neither identified by CT scan nor by thoroughly palpation under thoracotomy. All the five additional nodules were confirmed as malignant. The result implies the high chance existence of small nodules. And the conventional procedures possess a high chance of missing the small nodules. This might be one of the reasons of recurrence after surgery.

Kim *et al.* (20) applied the similar ICG injection procedure and found 10 out of 11 nodules were fluorescent. Keating *et al.* injected ICG into four groups of mice models with thymomas. Two groups of the mice received chemotherapy. All the mice receive systematic injection of ICG before surgery. The authors detected NIR imaging in all the animal models. And the NIR imaging is superior to the standard techniques at detecting retained tumors.

The mechanism of the tumor imaging is hypothesized to be the EPR effect of ICG. The small molecules such as ICG or the ICG and protein complex may passively accumulate in solid tumors due to increased vasculature and dysfunctional lymphatics. Although the EPR effect of ICG is non-target, it is the only FDA approved drug of NIR imaging agent in most regions for now. The application of ICG in solid thoracic tumors is to be studied.

Other applications

The imaging of sympathetic ganglions

The sympathectomy surgery is an effective method of treating palmar hyperhidrosis. But the curative effect is unstable and recurrent cases are reported. One possible reason is that the current localization and identification method of the sympathetic level is based on ribs. But the exact spatial relationship between the ganglions and the ribs may vary due to anatomical variations (21). Weng *et al.* (22) of our center reported a promising method to identify sympathetic ganglions intraoperatively. Four patients were systematically administrated with ICG through peripheral veins. The sympathetic ganglions were visible during NIR thoracoscopic surgeries. Though the mechanism is not clear by now, this technique may lead to the precise localization and resection of sympathetic ganglions, and may improve the quality of sympathectomy surgeries.

Localization of small pulmonary nodules

As low-dose CT scan is widely applied in routine health screenings. More and more small early lung cancers are revealed. The mortality of lung cancer is decrease. But the precisely localization and resection of the small nodules is a clinical challenge faced by more and more thoracic surgeons. The traditional method of localization includes micro-coil, hook wire, and colored dye, etc. These methods are effective and generally safe, with minor chance of pneumothorax and hemopneumothorax. But this potential complication prevents the completely localization of multiple nodules. Anayama *et al.* (23) reported a localization method using NIR camera and electromagnetic navigation bronchoscope (ENB). The bronchoscope is guided by reconstructed way of real-time electromagnetic tracking system. And the ICG mixed with iopamidol was injected into the pulmonary nodules. And the ICG fluorescence spot is visualize under NIR thoracoscope. The NIR fluorescence is detectable under 24 mm depth of inflated lung tissue. This technique doesn't need the percutaneous penetration, thus avoids the chance of pneumothorax and hemopneumothorax. So this is a feasible method to localize multiple pulmonary nodules.

Conclusions

Surgery is the fundamental procedure for diagnosis and intervention of many thoracic diseases. As a benefit from the science and technology development, thoracic surgery has embraced a rapid technological advancement and maturation. The sewings and ligations are becoming faster and more efficient due to the development of mechanical staplers and energy platforms. The instruments have gained more dexterity and become more less-invasive. But the intraoperative imaging modality, which involves detection of small lesions and identification of surgical margins, changed little over centuries. Thoracic surgeons today rely on the same white light inspection and human hand palpation as Evarts A. Graham did in the first pneumectomy in 1933. But the disease spectrum has dramatically changed over the decades. Meanwhile thoracic surgeons are pursuing less invasive intervention and lower mortality and morbidity rate. Therefore, there is a pressing need for more precise intraoperative imaging technologies.

NIR fluorescence imaging is a promising technology which can aid in intraoperative imaging. The NIR light is non-invasive and non-radioactive. Moreover, it has relatively deeper tissue penetration, lower autofluorescence, and lower scattering. These advantages enable NIR fluorescence imaging to be suitable for intraoperative imaging.

ICG is a widely used fluorescent contrast agents in hepatic function assessment and ocular angiography. It is an FDA-approved commercial non-ionizing agent with low toxicity. Due to the insufficiency of the NIR imaging device's performance, the applications of ICG based intraoperative NIR imaging in thoracic surgeries are relatively rare compared to the other fields, such as breast cancer and hepatic surgeries. However, as the development of the intraoperative imaging devices, especially the NIR fluorescence thoracoscopy devices, more and more studies on the application of ICG based NIR imaging are reported. With the aid of ICG distribution based on blood supply, lymphatic drainage, EPR effect, etc., surgeons can easily locate the nodules, structures, or demarcations during surgeries. Thus they can perform surgeries more precisely and may achieve better surgical outcomes.

Though ICG based NIR fluorescence imaging has become a highlight over the past few years. The applications of the NIR imaging in thoracic surgeries are still in its early stage. The optimal dosage in different applications is not clear. The quantitative analysis of fluorescence is far from satisfying. The repeatability of some applications is poor. The mechanisms of some observed phenomena remains unknown. So more studies will be needed in future. On the other hand, ICG is a non-targeting fluorescence agent. Thus the imaging is not satisfying under specific scenarios, and the required dosage is high. Intraoperative molecular imaging using cancer or organ specific agents are to be developed and studied on in the future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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