Review Article

Clinical use of near-infrared fluorescence imaging with indocyanine green in thoracic surgery: a literature review

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Abstract: Invisible near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) has advantage in detecting for certain anatomy. The method is currently used in some types of surgery, such as sentinel lymph node (SLN) mapping, intraoperative solid tumor identification, and organ perfusion assessment. However, the literature of clinical application in thoracic surgery is lacking. This paper presents the advantages, current applications and potential developments of NIR fluorescence imaging with ICG in thoracic surgery.

Keywords: Indocyanine green (ICG); fluorescence; thoracic surgery

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Introduction

Indocyanine green (ICG), a water-soluble and tricarbocyanine dye, is used for determining cardiac output, hepatic function, liver blood flow and ophthalmic angiography (1). The safety of ICG use is high, and few adverse events occur at a dosage lower than 0.5 mg/kg. ICG can rapidly bind to plasma protein through intravenous injection, and the peak spectral absorption in the blood is 800–810 nm. This characteristic facilitates its use as a fluorescent contrast agents, which is approved by the Food and Drug Administration.

Invisible near-infrared (NIR) fluorescent light (700–900 nm) can provide images that are invisible to human eye because of the low autofluorescence background and deep penetration features of this light (2). Invisible NIR light fluorescence imaging is applied in surgery for real-time visualization of certain anatomical structures. The NIR fluorescence imaging system combined with fluorescent contrast agents can facilitate the identification of specific structures in more detail.

NIR fluorescence imaging with ICG is currently used in some types of surgery, such as sentinel lymph node (SLN) mapping (3-5), intraoperative solid tumor identification (6-8), and organ perfusion assessment in gastrointestinal anastomosis or flap reconstruction surgery (9-11). In thoracic surgery, this imaging tool can be applied in SLN mapping, pulmonary nodules identification, pulmonary intersegmental plane identification, pulmonary bullous lesion detection, thoracic duct imaging, and conduit vascular evaluation during esophagectomy.

In this study, we used "indocyanine green," "fluorescence," and "thoracic surgery" as keywords for our searches in PubMed without any date or language limitations. This review updates the advantages, current applications, and potential developments of NIR fluorescence imaging with ICG in thoracic surgery.

Clinical use of NIR fluorescence imaging with ICG in thoracic surgery

SLN mapping

SLN is the first lymph node involved in the lymphatic drainage of a tumor. Lymph node metastasis is determined by examing SLN in oncologic surgery, such as melanoma and breast cancer surgery. Although lobectomy with extensive lymph node dissection is the standard treatment for lung cancer, some authors have indicated that segmentectomy with limited lymphadenectomy is sufficient for early-stage lung cancer treatment, particularly in patients with limited pulmonary function.

Some methods have been employed for detecting SLN during lung cancer surgery. The most simple method is dye injection; however, the identification rate is poor in this method because of the difficulty in distinguishing SLN from anthracosis (12). A high SLN identification rate is obtained through radioisotope tracer injection; however, this method is complex and may cause radiation exposure (13,14). Therefore, clinicians require other methods for SLN identification.

In 2004, Ito *et al.* used NIR fluorescence imaging with intra-operative peri-tumoral ICG injection for SLN mapping in lung cancer and reported a sensitivity of 87.5% and negative predictive rate of 100% (3). SLN could be easily detected under NIR fluorescence imaging despite the existence of anthracosis (4). In addition, Yamashita *et al.* and Nomori *et al.* have reported identification rates of more than 80% for SLN mapping with ICG fluorescence imaging systems (4,5).

Overall, SLN mapping by using NIR fluorescence imaging with ICG provides results similar to those of SLN mapping by using radiotracers (15). In addition, NIR fluorescence imaging with ICG does not cause radiation exposure and is clinically easy to perform.

Pulmonary nodule identification

The identification of small pulmonary nodules during thoracic surgery is challenging. Traditionally, surgeons detect these lesions through visual inspection or finger palpation; however, these methods may be difficult to perform during video-assisted thoracoscopic surgery (VATS) or robotic surgery. Several techniques, such as intraoperative ultrasound, methylene blue staining, hook wires, spiral wires, microcoils, and radionuclides have been proposed for pulmonary nodule localization (16). The use of intraoperative ultrasound is limited because of its high operator dependence and the presence of air in the lungs. The patients are required to receive radiation in pre-operative computed tomography (CT)-guided localization with methylene blue, hook wires, spiral wires, microcoils, or radionuclides. In addition, these patients are at risk of procedure-related complications, such as bleeding or pneumothorax. Furthermore, the target lesion stain may become vague as time elapses after initial methylene blue tattooing. Therefore, additional modalities for pulmonary nodule identification have been proposed.

In their animal study, Anayama *et al.* reported that electromagnetic navigation bronchoscopy-guided transbronchial ICG injection followed by intraoperative NIR fluorescence detection is a feasible method for locating multiple pulmonary nodules (17). Clinically, ICG fluorescence imaging systems can effectively detect pulmonary nodules, including primary lung nodules (6,7) and metastatic lung lesions (8). Okusanya *et al.* further demonstrated that intraoperative NIR fluorescence imaging with intravenous ICG injection (5 mg/kg) 24 h prior to surgery can help in detecting nodules as small as 0.2 cm and as deep as 1.3 cm from the pleural surface (6).

In summary, ICG fluorescence imaging systems can detect small pulmonary nodules in real time without the risk of bleeding or pneumothorax.

Pulmonary intersegmental plane identification

Several studies have revealed that segmentectomy is as effective as lobectomy in the treatment of early-stage lung cancer. However, accurate identification of the intersegmental plane of the lung can be challenging for surgeons. Methods, such as inflation-deflation and jet ventilation, have been applied for identifying the intersegmental plane (18,19); although these methods are clinically easy to use, the inflated lung may obstruct exposure, particularly in emphysema.

In their animal study, Misaki *et al.* demonstrated that the intersegmental plane can be identified without inflating the lung by using NIR fluorescence imaging with ICG (20). Several experts (21-23) have reported that the intersegmental plane can be identified under NIR fluorescence imaging with various ICG applications. Pardolesi *et al.* reported that the intersegmental plane can persist for 1 min under NIR fluorescence with intravenous ICG injection after dividing the target pulmonary artery (PA), pulmonary vein, bronchus, and bronchial vessels (23).

The duration of intersegmental plane can be lengthened (3.5 min) by dividing only the segmental PA (21). Furthermore, Sekine *et al*. reported that the intersegmental plane can persist for several hours by using transbronchial ICG injection (22). Recently, Iizuka *et al*. reported that heavy smoking and a small attenuation area on CT are factors that impede visibility in NIR fluorescence imaging with ICG (24).

To summarize, surgeons can easily detect the intersegmental plane under an NIR fluorescence imaging system with ICG without impeding the surgical field.

Pulmonary bullous lesion detection

Bullectomy through VATS is a widely accepted procedure for spontaneous pneumothorax treatment. However, the recurrence rate may increase because of inadequate margins during bullectomy or undetected bullous lesions. Presently, surgeons can only detect these lesions through visual inspection. However, some bullous lesions are difficult to detect.

Gotoh *et al.* first used NIR fluorescence imaging with ICG to detect an emphysematous area in their animal study (25,26). In their clinical study, Gotoh *et al.* demonstrated that obscure bullous lesions that are difficult to detect under normal white light could be effectively detected under NIR fluorescence imaging with ICG in 3 of 8 cases (27). Moreover, Li *et al*. concluded that ICG fluorescence imaging system is a safe, accurate, and real-time method to detect bullous lesions of lung tissue in clinical use (28).

In brief, NIR fluorescence imaging with ICG can help surgeons to identify the boundary between bullous lesions and healthy lung tissue for some obscure bullous lesions.

Thoracic duct imaging

The treatment of chylothorax resulting from thoracic duct injury is challenging because of the difficulty in its identification and repair. Lymphangiography and lymphoscintigraphy can be used to detect chyle leakage during preoperative planning. However, these examinations have limited benefits in the intraoperative detection of chylous leak.

In their 2011 animal study, Ashitate *et al.* reported that NIR fluorescence imaging with ICG can provide real-time imaging of thoracic duct anatomy (29). Kaburagi *et al.* detected the precise location of chyle leakage and performed successful thoracic duct ligation under NIR fluorescence imaging with ICG injection (2 mL, 0.5%) into the mesentery of the small bowel (30). Furthermore, Chang *et al.* reported similar results by using bilateral inguinal region ICG injection (2 mL, 0.5%) (31).

In brief, NIR fluorescence imaging with ICG has potential benefits in the treatment of chylothorax despite the limited evidence.

Conduit vascular evaluation during esophagectomy

Anastomotic leakage is a leading cause of morbidity and mortality after esophagectomy with reconstruction. Factors, such as congestive heart failure, hypertension, renal insufficiency, and cervical anastomosis, are associated with anastomotic leakage (32). These factors are supposed to impair conduit circulation. Therefore, surgeons require a reliable tool to monitor the perfusion of reconstructive conduit.

Traditionally, surgeons evaluate conduit circulation through visual inspection of gross conduit color, and by monitoring the bleeding condition of cutting edge or palpation of conduit pulsation. These methods are easy to perform in clinical practice; however, they are subjective and difficult to quantify. Several modalities have been applied in the evaluation of conduit perfusion, including esophagogastroduodenoscopy (EGD), conventional angiography, single-photon emission computed tomography, CT angiography, handheld Doppler, laser Doppler flowmetry and spectrophotometry, transmucosal oxygen saturation, hydrogen clearance, visible light spectroscopy, and fluorescence angiography or Wood lamp (9). However, these methods are not extensively adopted in clinical practice because of their disadvantages. For example, performing an EGD immediately after esophageal reconstruction may increase the risk of anastomotic injury, and it does not enable direct visualization of the vasculature.

ICG fluorescence imaging system had been used in the vascular assessment of gastrointestinal tract anastomosis and free flap surgery (10,11). Several studies have revealed that vascular networks of esophageal anastomoses can be easily detected under NIR fluorescence imaging with intravascular ICG bolus injection (2.5 mg) (33,34). Compared with other methods, this method can effectively facilitate real-time intraoperative vascular assessment (9). Despite being a promising tool, the leakage rate of esophageal anastomosis cannot be reduced using this technique (11). Further studies are warranted to expand its use.

In brief, NIR fluorescence imaging is an easy-to-use tool for revealing real-time conduit circulation after esophageal reconstruction surgery.

Conclusions

NIR fluorescence imaging with ICG presents the advantages of real-time identification of specific structures. Although it is expansive and the image duration is sometimes short, it can enable surgeons to perform operations more precisely. In conclusion, NIR fluorescence imaging with ICG is a promising tool in thoracic surgery. However, because of the current limited evidence, large-scale randomized controlled studies are required to confirm the application of NIR fluorescence imaging with ICG in thoracic surgery.

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Footnote

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

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