Journal of Surgery
Marziali V, et al. J Surg 7: 1529
www.doi.org/10.29011/2575-9760.001529
www.gavinpublishers.com
Review Article

The Wide Range of Uses of Indocyanine Green in Thoracic Surgery: State of Art

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Citation: Marziali V, Frasca L, Longo F, Vega R, Crucitti P (2022) The Wide Range of Uses of Indocyanine Green in Thoracic Surgery: State of Art. J Surg 7: 1529. DOI: 10.29011/2575-9760.001529

Received Date: 06 July, 2022; **Accepted Date:** 11 July, 2022; **Published Date:** 14 July, 2022

Abstract

Background: Thoracic surgery is a constantly evolving field that require innovative solutions. Invisible near-infrared fluorescence imaging with indocyanine green is an intraoperative technology that could be help for surgeons. Indocyanine green is a nontoxic dye with low rate of adverse reaction. Indocyanine green binds with plasma proteins and lipoprotein that allow a deep tissue penetration, and also the amphiphilic proprieties allow indocyanine green to migrate within lymphatics.

Methods: We selected forty-nine previous studies from the literature searching terms “lung cancer”, “indocyanine green”, “thoracic surgery”, “fluorescent images”. The topics of the paper were: sentinel lymph node mapping, pulmonary nodes identification, intersegmental plane identification, and other application (pulmonary bullous lesions, bronchopleural fistula, bronchoplasty, pulmonary sequestration, chyle leak, hyperidrosis).

Results: In the different applications indocyanine green showed a high identification rate, overall accuracy, sensibility, and specificity.

Conclusions: This review describes the advantages and current applications in thoracic surgery of intraoperative near-infrared fluorescence imaging using indocyanine green.

Keywords: Intraoperative fluorescence imaging; Indocyanine green; Lung nodule; Near-infrared imaging system; Pulmonary segmentectomy; Sentinel lymph nodes; Thoracic surgery

Introduction

Thoracic surgery, nowadays, is constantly evolving with ever innovation in surgical methods and technologies, therefore surgeons must be versatile and updated. Over the years, thoracic surgery has turned towards even more minimally invasive surgery with the development of Video Assisted Thoracic Surgery (VATS) and Robot Assisted Thoracic Surgery (RATS) [1]. The range of kinds of surgery performed with the last methods are various and sometimes not so easy to carry out, therefore, intraoperative technologies could be helpful for the surgeon such as fluorescent dye combined with an imaging detection system [2]. The use of Intraoperative Fluorescence Imaging (IFI) consists of the utilization of a near-infrared (NIR) imaging system and a fluorescence-emitting contrast agent. Near-infrared light offers several significant advantages, as the relatively high photon penetration of living tissue. The range of wavelengths is 700 to 900 nm, invisible to the human eye, so imaging systems are required to show the tissue. Indocyanine Green (ICG) is one of the most used contrast agents in literature, because it is cheap, non-toxic (systemic doses as high as 5 mg/kg is safe) and easily available. ICG is a water-

soluble anionic, amphiphilic infrared fluorophore, the molecular weight is 774.9 kDA [3]. When given systemically, ICG rapidly forms nanoparticle binding with plasma proteins and lipoprotein and thanks to amphiphilic proprieties can migrate within lymphatics [3,4]. In thoracic surgery, ICG has a wide range of uses. In this review, we focus on summarizing the current applications and uses of ICG in the field of thoracic surgery.

Material and Methods

To evaluate the current application and uses of ICG in thoracic surgery, relevant studies were searched and selected from the databases Medline, PubMed, Google Scholar. Forty-nine previous studies were collected. A thorough search was conducted using search terms "lung cancer", "indocyanine green", "thoracic surgery", "fluorescent images". All the articles were systematically reviewed and divided into groups depending on the main topic of the paper: sentinel lymph node mapping, pulmonary nodes identification, intersegmental plane identification, and other application (pulmonary bullous lesions, bronchopleural fistula, bronchoplasty, pulmonary sequestration, chyle leak, hyperidrosis). Literature review and metanalyses were excluded, while case reports were included only for "other applications" group because of the lack of numerous studies on the subject. Articles in which another marker were utilized were excluded. All the study conducted on animal were excluded. In every study we searched and summarised some information as agent and dose used, location od injection, time of injection, detention system and time for detention. We collected, also, data about identification rate, overall accuracy, sensibility, and specificity, to highlight the efficiency of the technique. All these data are summarised in Tables 1-4.

Study	N.	Histology	Indocyanine Green Dose	Location / Injection	Timing / Injection	Detention system	Time Detention	Identification Rate of SLN	Accuracy	Sensitivity	Specificity
Ito 2004 [5]	38	All histology lung cancer	5 mL (5 mg/mL) + hyaluronidase 400 IU	Transpleural	Intraoperative	a)NIR camera 1.25x	64 ± 16 min	a) 100%	a) 97.5%	a) 87.5%	-
						b)NIR camera 1.50x		b) 100%	b) 97.5%	b) 87.5%	
						c)NIR camera 1.75x		c) 51%	c) 89.5%	c) 66.6%	
Yamashita 2012 [6]	61	NSCLC	2 mL (5 mg/mL)	Transpleural	Intraoperative	NIR-system	10 min	80.30%	97.90%	50%	100%
Imai 2013 [7]	17	NSCLC	0.3 mL (5 mg/mL)	Subpleural	Intraoperative	NIR-system	5 min	17.60%	-	-	
Gilmore 2013 [2]	33	NSCLC	In albumin or plasma	Transpleural	Intraoperative	FLARE open surgery imaging or NIR-system	30 (3-125) min	a) 20%	-	-	-
			a) 3.8 µg - 0.6 mg					b)33.3%	b)100%	b)100%	b)100%
			b) 0.6 mg					c)50%	c)100%	c)100%	c)100%
			c) 0.8 mg					d)80%	d)100%	d)100%	d)100%
			d)1 mg					e)100%	e)100%	e)100%	e)100%
			e)2.5 mg								
Hachey 2017 [8]	10	NSCLC	0.5-1 mL (2.5 mg/mL) + albumin		Preoperative	ENB guided NIR-system	3h	80%	100%	100%	100%
Akopov 2017 [9]	35	NSCLC	2ml	Transpleural	Intraoperative	NIR-system	25 min	97%	100%	100%	100%
Kawakami 2020 [10]	22	NSCLC	0.5-1 ml (5 mg/ml)	Transpleural	Intraoperative	charge-coupled device camera		72.70%	93.80%	-	-

ICG: Indocyanine Green; ENB: Electromagnetic Navigational Bronchoscopy; NIR: Near-Infrared; NSCLC: Non-Small Cell Lung Cancer; SLN: Sentinel Lymph Node

Table 1: Indocyanine Green for the detention of sentinel lymph nodes.

Study	N.	Size (cm)	Lesion ype	Depth at CT (cm)	ICG dose	Lung Marker System	Location Injection	Time for detention	Surgical Technique	Nodule identification	Negative surgical margins
Okusanya 2014 [11]	23	2.6 (0.2-11)	-	0.4 (0-1.3)	5 g/kg	-	Intravenous	24h	Open thoracotomy	91%	-
Kim 2016 [12]	9	2.3 (0.3-5)	-	0.4 (0-1.4)	1 mg/kg	-	Intravenous	24h	VATS	88.90%	-
Nagai 2017 [13]	37	0.9 (0.2-2.2)	Solid 32.4% Mixed 27.0% GGO 40.5%	1 (0-3.3)	25 mg + 2 mL water	-	Percutaneous (CT guided)	102 (84-179) min	VATS	95%	100%
Ujiie 2017 [14]	20	1.2 (0.5-2.4)	Solid: 20% Mixed 25% GGO: 55%	1.4 (0.2-4.8)	0.1-0.15mL (0.125mg/mL)	microcoil	Percutaneous (CT guided)		VATS	90%	100%
Hachey 2017 [8]	14	<1: 21.4% 1-1.5: 21.4% 1.5-2: 35.7% >2: 21.4%	Solid: 50% Mixed 42.9% GGO 7.1%	<1: 50% 1-1.5: 21.4% 1.5-2: 7.1% >2: 21.4%	0.5mL (2.5 mg/mL)	-	Transbronchial (NB guided)	65 (38-161) min	VATS	100%	100%
Anayama 2018 [15]	a) 16	a) 1 (0.4-1.7)	a) Solid 25 % GGO 75%	a) 1 ± 0.8	2.5 mg/mL + iopamidol 10 ml	-	a) Percutaneous (CT guided) (16) b) Transbronchial (NB guided) (23)	-	VATS	a)100%	-
	b) 23	b) 0.9 (0.4-1.6)	b) Solid 56.5% GGO 43.5%	b) 1 ± 0.8						b) 93.8%	
Zhong 2019 [16]	30	1.3 (0.6-1.9)	Solid 30% GGO 70%	1.7 (0.5-3.8)	2.5 mg/mL + albumin100-150 mL	Microcoil	Percutaneous (CT guided)		VATS	100%	100%
Chao 2019 [17]	11	0.6 (0.5-0.7)	Solid 27.3% GGO 72.7%	0.4 (0.3-0.9)	0.3-0.5 mL (0.125 mg/mL)	Microcoil	Percutaneous (CT guided)	19 (18-21) min	VATS	100%	100%
Li 2020 [18]	19	1.6 (0.8-3.8)	GGO 100%	0.7	ICG/lipiodol: 0.2-0.4 mL (1/9 or 2/8 ratio)	Hook wire	Percutaneous (CT guided)	42.6 min	VATS	68.40%	100%
Yang 2020 [10]	a) 35	a) 0.7 (0.3-2)	a) solid 60%; GGO 40%	a) 0.82 (0.1-3.8)	ICG/iopamidol	-	a) Percutaneous (CT guided)	-	VATS	a) 94.3%	-
	b) 15	b) 1.1 (0.7-1.8)	b) solid 63%	b) 1.3 (0.2-3.4)	0.3-0-5 ml (0.125mg/ml)		b) Transbronchial (ENB guided)			b) 100%	
			GGO 27 %								
Rho 2021 [19]	29	0.9 (0.3-1.4)	Solid 48.3% Mixed 10.3% GGO 41.4%	1.7 (0.3-5.9)	10% ICG solution at 0.5 mg/mL and 90% lipiodol		Percutaneous (CT guided)	15.8 (6-30) min	VATS	96.60%	100%
Wu 2021 [20]	36	0.76 (0.4-1.5)	Solid 41.7% Mixed 33.3% GGO 25%	-	0.3-1 ml (2.5 mg/ml)	-	Percutaneous (CT guided)	-	VATS	91.70%	-
Ding 2021 [21]	85	0.63±0.24	Solid 15.3% Mixed 34.1% GGO 50.6%	0.92±1.0	25 mg + Iopamidol 50ml	-	Percutaneous (CT guided)	-	VATS	100%	100%
Li 2021 [22]	512	0.91 (0.6-2.0)	Solid 5.9% Mixed 23.6% GGO 70.5%	0.9 (0.1-3.0)	0.4 ml (2.5 mg/ml)+ saline 0.8 ml		Percutaneous (CT guided)	-	VATS	98.40%	100%

CT: Computed Tomography; ENB: Electromagnetic Navigation Bronchoscopy; GGO: Ground-Glass Opacity; VATS: Video Assisted Thoracic Surgery

Table 2: Indocyanine Green for the detention of pulmonary nodules.

Study	N.	Tumor size (cm)	Indocyanine green dose	Location Injection	Time Injection	Time detention	Operative time (min)	Surgical technique	Segment identification	Negative surgical margins	Conversion	TP-PP (cm)	Chest Tube (days)
Misaki 2012 [23]	8	1.99 (0.8-5.0)	3.0 mg/kg	Peripheral Vein	Intraoperative after segmental artery	13 (8-18) seconds	150 (94-255)	Open	100%	100%	-	-	-
Tarumi 2014 [24]	13	1.4 (0.8-2.0)	3.0 mg/kg	Peripheral Vein	Intraoperative after segmental artery	-	191 (120-339)	VATS	84.60%	-	0%	-	2.8 (1.7-3.9)
Guigard 2017 [25]	22	-	5 ml (2.5 mg/ml)	Peripheral Vein	Intraoperative after segmental artery, vein, bronchus	Seconds to few minutes	137 (72-216)	VATS	100%	-	13.6% lobectomy 4.5% open	-	< 3
Pischik 2018 [26]	90	1.9 (0.7-5.1)	0.15 mg/kg	a) Central Vein b) Peripheral Vein	Intraoperative after segmental artery, vein, bronchus	a) immediatly b) 10-15 seconds	136 (60-280)	VATS	95.60%	-	0%	-	5.2±3.3
Mehta 2019 [27]	31	1.80±1.0	15-20 mg + saline 10 ml	Peripheral Vein	Intraoperative after segmental artery, vein, bronchus	-	133.7±27.4	VATS	74.20%	100%	3.2% open	2.41±1.6 (61.2%) -1.2±0.7 (12.9%)	-
Matsuura 2019 [28]	149	1.6 (0.6-6.4)	0.25 mg/kg	Peripheral Vein	Intraoperative after segmental artery, bronchus	-	167 (80-319)	VATS	98%	100%	0%	-	-
Sekine 2019 [29]	65	-	2.5 mg/ml + saline 20-30ml	Transbronchial with bronchoscope	Preoperative	20-30 minutes	212.4±53.0	VATS	89.20%	100%	3.7% lobectomy	0.2±0.29 -6.9%	-
Chen 2019 [30]	20	0.8-2	-	Peripheral Vein	Intraoperative after segmental artery	Few seconds	140.8	VATS	100%	100%	0%	-	4.6
Motono 2019 [31]	20	-	5 mg	Peripheral Vein	Intraoperative after segmental artery, vein, bronchus	-	137.5 (82-175)	VATS	90%	-	10% open	-	1 (1-8)
Jin 2019 [32]	21	1.06 ± 0.31	0.5 mg/kg	Peripheral Vein	Intraoperative after segmental artery	1 minute	126.2±15.3	VATS	100%	100%	0%		1.6±0.6
Funai 2020 [33]	10	-	5 ml (2.5 mg/ml) + 5ml blood	Bronchial stump	Intraoperative after segmental artery, vein, bronchus	-	193.8 (151-254)	VATS	80%	-	0%	-	3.5 (1-11)
Yotsukura 2020 [34]	209		0.25 mg/kg+ water 10ml	Peripheral Vein	Intraoperative after segmental artery, vein	15 (3-60) seconds	105 (94-118)	VATS	88%	100%	0%	-1.3 (0.75 to -0.18) mm	1 (1-26)
Sun 2021 [35]	100	1.16±0.39	5 mg/body	Peripheral Vein	Intraoperative after segmental artery, vein, bronchus	23.6±4.4 seconds	89.3±31.6	VATS	98%	100%	0%	-	4.3±1.8
Sekine 2021 [36]	28	1.24 (0.6-2.4)	25mg/10 ml+70 ml saline+20 blood	Transbronchial with bronchoscope	Preoperative	15-30 minutes	69.9 (33-116)	VATS	100%	100%	0%	0.8	-

PP: Predicted Intersegmental Plane; TP: True Intersegmental Plane; VATS: Video Assisted Thoracic Surgery

Table 3: Indocyanine Green for the intersegmental plane identification.

Study	N.	Use	Indocyanine green dose	Location Injection	Time Injection	Time detention	Surgical technique	successful rate
Gotoh 2007 [37]	8	Spontaneous pneumothorax	3.0 mg/kg	Intravenous	Intraoperative	15.1 (10-20) seconds	VATS	100%
Li 2016 [38]	2	Spontaneous pneumothorax	1) 0.2 mg/kg 2) 0.6 mg/kg	Intravenous	Intraoperative	1) 10 seconds 2) 11 seconds	VATS	100%
Piort 2019 [39]	1	Bronchopleural fistula	2.5 mg + 10 mL water	Intravenous	Intraoperative		Thoracotomy	100%
Uramoto 2020 [40]	1	Bronchoplasty	5 mg	Intravenous	Intraoperative			
Kawamoto 2021 [41]	1	Bronchoplasty	5 mg	Intravenous	Intraoperative		Thoracotomy	100%
Yamanashi 2017 [42]	1	Pulmonary sequestration	5 mg	Intravenous	Intraoperative		VATS	100%
Motono 2019 [43]	1	Pulmonary sequestration	5 mg	Intravenous	Intraoperative		VATS	100%
Motohashi 2020 [44]	1	Pulmonary sequestration	0.1 mg/kg	Intravenous	Intraoperative		Thoracotomy??	100%
Hakiri 2021 [45]	1	Pulmonary sequestration	5 mg	Intravenous	Intraoperative		VATS	100%
Kaburagi 2013 [46]	1	Chylothorax	2 ml 5%	Mesentery of small bowel	Intraoperative		Mini-thoracotomy	100%
Shirotsuki 2018 [47]	10	Chylothorax	0.025 mg	Inter-toe	Preoperative	1h	VATS	100%
Yang 2018 [43]	4	Chylothorax	0.2 mg/kg	bilateral inguinal region	Preoperative	30 minutes	Right VATS	100%
Bibas 2019 [48]	1	Chylothorax	5% 2 ml	bilateral inguinal lymph nodes	Preoperative	5 minutes	VATS	100%
Pei 2020 [49]	142	Primary hyperhidrosis	5mg/kg	Intravenous	Preoperative	24 hours	VATS	96.7%

VATS: Video Assisted Thoracic Surgery

Table 4: other use of Indocyanine Green in thoracic surgery.

Results

Sentinel Lymph Node Mapping

In Table 1 is showed a review of the use of ICG for the detention of SLN. All study used ICG, someone added hyaluronidase, to increase the accumulatio of the dye [5] or dissolved ICG in human serum albumin [8], fresh-frozen plasma or saline solution [2]. The dose of the dye varied from 1.5 mg [7] to 25 mg [5]. The intraoperative injection was performed usually transpleural, in one study the injection was subpleural [7]. Hachey et al, used a preoperative transbronchial injection, in this case the time of detention was longer (3h) [8]. The time of migration and detention varied from 5 minutes [7] to 64 minutes [5]. The detention system was NIR thoracoscopic camera [2,5-8]. Gilmore et al used FLARE imaging system [2], while Kawakami et al used charge-coupled device (CCD) camera [10]. The accuracy to predict lymph node status ranged from 93.8% [10] to 100% [2,5,8,9]; sensitivity ranged from 50% [6] to 100% [2,5,8,9]; specificity was 100% in all study. Gilmore et al study was a prospective dose escalation trial. Their results showed that SLN detection was a dose-dependent phenomenon. Notably at 2.5 mg of ICG, 100% of SNL were detected [2].

Pulmonary Nodules Localization

In Table 2 is summarized a literally review of the use of ICG for the detention of pulmonary nodules. All study used preoperative injection of ICG, some added iopamidol [10,15,21], albumin [16] or lipiodol to reduces the diffusion of ICG to the adjacent tissue [14,15]. Tumors mean diameter at CT scan varied from 0.6 cm [17,21] to 2.6 cm [11], as well as the average depth from the pleural surface at CT scan that varied from 0.4 cm [12,17] to more than 2 cm [8]. Considering all the previous study analyzed, the prevalent type of lesion was GGO: of 882 nodules, 545 were GGO (61.8%), 148 were solid (16.8%) and 189 were mixed (21.4%), although the percentage of GGO and solid lesion varied among the study. In Hachey et al, solid nodules were 50%, mixed nodules were 42.9% and GGO were 7.1%; the nodule identification rate was 100% [8]. In Anayama et al solid nodules were 56.5% and GGO were 43.5%; the nodule identification rate was 93.8% [15]. About the injection of ICG we found different techniques. In some study [11,12], 24 h before the surgery an intravenous injection of the dye was performed, the ICG dose varied from 1 mg/kg [12] to 5 mg/kg [11]. Other studies preferred a preoperative transbronchial injection guided by navigation bronchoscopy [8,10,15]; the time for ICG migration and detention was 65 minutes [8]. Nevertheless, percutaneous CT guided injection into peritumoral area was most common. Yang et al compared percutaneous CT guided and electromagnetic navigation-guided bronchoscopic ICG injection: the success rate was 94.3% in the percutaneous marking and 100% bronchoscopic marking [10]. Some of those study, before the ICG injection, positioned a lung marker as microcoil [14,16,17] or hook wire [18]; while the remains used only ICG [13,15,19]. The time for ICG migration and detention varied from 15.8 minutes [19] to 102 minutes [13]. The nodule identification rate varied from 68.4% [18] to 100% [15,16,17]. In all study, after resection of the nodule the surgical margins resulted negative.

Pulmonary Intersegmental Plane Identification

In Table 3 is showed a review of the use of ICG for the intersegmental plane identification. The ICG was injected, most commonly, in peripheric vein during the surgery after segment pulmonary artery ligation [23,24,30,32,34] or after segmental pulmonary artery, vein and bronchus [25-27,31,33,35]; in Matsuura et al the injection followed the segmental pulmonary artery and bronchus ligation [28]. The minimum time for migration and detention was seconds [23,26,30], the maximum was few minutes [25,32]. Pischik et al, compared peripherally and central vein injection and found a faster detention after central injection [26]. The peripherally administration dose in some study was calculated basing on the patient weight (range 0.15 mg/kg [27] to 3 mg/mg [23,24]); other studies used a standard dose (range 5 mg [31] to 15-20 mg [27]). This method of administration allowed a rate of surgical plan identification that varied from 74.2 % [27] to 100% [23,25,30,32]. Transbronchial ICG injection was performed in patients under general anesthesia with double lumen or laryngeal mask and the injection was guided by the bronchoscope. The time for detention was 15-30 minutes [36] and the rate of plane identification varied from 89.2% [29] to 100% [36]. In Funai et al the intraoperative ICG injection (5 ml of ICG 2.5mg/ml + 5 ml of bool) was performed directly into the bronchial stump after segmental artery, vein, and bronchus ligation; the identification of the rate was 80% [33]. In all study, the surgical resection was performed with negative margins. In some study was evaluated the difference between true intersegmental plane and predicted intersegmental plane. Metha et al predicted the plane with the inflation method, they found in

61.2% of patients a difference of 2.41±1.6 cm and in 12.9% of patients a difference of -1.2±0.7 cm [30]. Sekine et al used a high-resolution CT three-dimensional (3D) pulmonary angiography and virtual bronchoscopy for vessels and bronchial anatomy, founding a difference of 0.2±0.29 cm in 6.9% of patients [27]. The conversion rate to lobectomy ranged from 3.7% [29] to 13.6% [25]; while conversion to open surgery ranger from 3.2% [27] to 10% [31] although in most of the study no conversion occurred. In Anajama et al different diluitons of ICG was insufflated into the subsegmental bronchi. The volume of the targeted pulmonary segments was calculated with preoperative computed tomography. To obtain a uniform fluorescence visualization of the segments they determined, using the ROC curve, the optimal cut-off volume proportion at 0.089 ml of diluted ICG per unit volume (ml) of the segment [50].

Other applications of ICG

In Table 4 is showed a review of "other application" of ICG in thoracic surgery. Pulmonary bullous lesion detection Li et al. included in their study two male with spontaneous pneumothorax and poorly identified bullae with normal light. They used two different doses of ICG injection (0.2 and 0.6 mg/kg) to detect bullous lesions during VATS bullectomy. The dosage of ICG 0.6 mg/kg allowed an excellent detection of the bullae border [38]. Bronchopleural Fistula Piort et al used ICG to prevent bronchopleural fistula after pneumonectomy: pedicled intercostal muscle flap was collected at the start of the thoracotomy, ICG 2.5 mg with 10 mL of water was administered intravenously and an ischemic portion 3 cm long of flap was detected and removed [39].

Bronchoplasty

Uramoto et al used ICG during right upper sleeve lobectomy after neoadjuvant chemoradiotherapy: they found clear green mark of the bronchial stumps, so the blood supply of the bronchial anastomosis judged to be enough [40]. Kawamoto et al used ICG after right meddle sleeve lobectomy to observe the maintenance of the blood supply at the bronchial anastomosis to prevent the bronchoplasty ischemia and the risk of bronchial leakage [41].

Pulmonary Sequestration

Motohashi et al performed left basilar segmentectomy for intralobar pulmonary sequestration; they used ICG to confirm the perfusion area and abnormal blood flow governed by aberrant arteries [44]. Motono et al treated the pulmonary sequestration right video-assisted thoracoscopic wedge resection using ICG to detect the boundary between the sequestration and the normal lung [43].

Identifying Chyle Leak

Yang et al treated 4 patients who were diagnosed with chylothorax after major pulmonary resection and mediastinal lymphadenectomy. ICG was administered subcutaneously into bilateral inguinal region [51]. Bibas et al directly injected ICG into inguinal lymph node bilaterally and after only 5 minutes the thoracic duct was visible, and they could ligate the duct [48]. Kaburagi et al detected the location of chyle leakage with ICG injection (2 mL, 0.5%) into the mesentery of the small bowel [46]. Finally, Shirotsuki et preferred the inter-toe administration of 0.025 mg of ICG one hour before surgery [47].

Hyperidrosis

Pei et al, used ICG during thoracic sympathectomy, the visibility rate of all sympathetic ganglions was 96.7% [49].

Discussion

We have presented a systematic review of the different use of Indocyanine Green (ICG) in thoracic surgery. ICG is a versatile dye, thanks to the ability to migrate within lymphatic channel and the ability of binding protein [3,4], therefore it could have wide range of application: mapping of sentinel lymph node, identification of lung nodule, intersegmental plan identification, pulmonary bullous lesion detection, bronchopleural fistula, bronchoplasty, pulmonary sequestration, identification of chyle leak and hyperidrosis. To increase the accumulation ratio and to reduce the diffusion of ICG into adjacent tissue, some studies added hyalironidase [5], human serum albumin [8,16], iopamidol [15,21,33]. Finally, ICG has a low rate of adverse reaction. In Pei et al, the rate of mild adverse reaction was 0.70% that consisted in a mild stinging of the skin after subcutaneous extravasation; no severe adverse reaction occurred. As premedication they used 40 mg of methylprednisolone. Comparing patients with and without ICG administration, no significant difference was detected [49]. Anyway, Garski et al reported adverse reaction after intravenous administration of ICG: generalized urticarial with erythema and generalized itching; nausea, dyspnea, wheezing, and peripheral vasodilation; severe tachycardia and hypotension that leading to the death because of failure of resuscitation; severe anaphylaxis [52]. Sentinel lymph node (SLN) is defined as the first lymph node involved in the lymphatic drainage of the anatomical location of a cancer [53]. Moroga et al. found a difference in the higher rate of relapse and cancer-related death in patients without SLN mapping [54]. The SLN map in the lung cancer has been performed, by Little et al, using isoflurane blue [55], and Liptay et al, using radioisotope [56]. The rate of identification was 47% and 80%, respectively. Previous study demonstrated that SLN could be easily detected using ICG despite the existence of anthracosis [57]. ICG showed a high sensitivity, specificity and accuracy in the detection of sentinel lymph nodes. One study demonstrated that the identification rate increased with the administration of higher dose of ICG [2]. Transpleural injection near to tumor area was widely used technique and allowed a fast detection of the

lymph nodes, although transbronchial injection was still used with a longer detention time [8]. To distinguish sentinel lymph node to the other, Ito et al propose as cut-off the ICG concentration 1.5 time grater then the other lymph nodes [7].

The intraoperatively pulmonary nodules localization in some patients is still a challenge, particularly small nodules, or Ground Glass Opacity (GGO) nodules. However, during minimally invasive procedures as video-assisted thoracoscopic surgery (VATS) or robot-assisted thoracoscopic surgery (RATS), it is tough to identify them through visual inspection or finger palpation, so several techniques have been developed [1,58]. Intraoperative ultrasound, methylene blue staining, hook wires, spiral wires, microcoils, and radionuclides have been proposed for pulmonary nodule localization [58,59]. Park et al found that lipiodol had the highest success rate while microcoil the lowest complication rates [59]. Ding et al compared ICG and hook-wire marking: the successful targeting rate between for both groups is 100%, however, the success rate of hook-wire was 95.6%, due to hook-wire dislodgement, while 100% with ICG; overall complication rate of the hook-wire was 37.0% and was significantly higher than the ICG group (35.4%) [21]. Other technique used ICG for pulmonary nodule identification through intravenous injection, CT-guided or transbronchial administration with electro navigation bronchoscopy. The tumor depth from the pleural surface was a significant limitation in the intravenous administration [11,12]. Percutaneous CT guided injection or transbronchial NB guided injection allowed the identification of nodule less than 1 cm [10,15,17] and mode that 1 cm deep from pleural surface [19,14].

Segmentectomy is still the focus of discussion for stage IA NSCLC. Some studied considered segmentectomy outcomes compare favorably with standard lobectomy for stage I NSCLC [60] with also a better pulmonary function preservation [61]. However, segmentectomy requires identification and isolation of specific segmental vascular and bronchial anatomy, and delineation of intersegmental parenchymal planes. Sun et al compared intersegmental plane identification using ICG injection with inflation-deflation method: the ICG group demonstrated a shorter time for detention, while the incidence of postoperative air leaks was higher in the inflation-deflation group [10]. Liu et al demonstrated that segmentectomy using ICG in patients with chronic lung diseases (emphysema od pulmonary bullae) allowed good intersegmental plane identification, shorter operation time and less complications [62]. Peripheral intravenous injection was widely used and allowed a fast identification of the segmental plane, though central injection showed a faster migration and detention time [26]. Intravenous injection was performed after ligation of segmental structures: only segmental artery ligation [23,24,30,32,34], segmental artery and vein [34] or segmental artery, vein and bronchus [25-27,31,33,35]. Transbronchial administration needs a longer time for demarcating the intersegmental plane [29], however with this method ICG stays in the alveolar space up to several hours [63], compared to duration of intersegmental plane demarcation with IV injection of 3.5 min [64]. The advantage of this approach was that a systemic dose of ICG was not necessary and did not require previous ligation of any vasculature. Geraci et al, performed 245 RATS sublobar resection; in 90 patients performed transbronchial and intravenous ICG injection: 25 mg ICG in 10 ml of sterile water, 0.5 ml of the solution transbronchial through the bronchoscope and the remaining 9.5 ml was later given intravenously after ligation of the segmental pulmonary artery or arteries. In these patients, transbronchial injection identified the target nodule in 80 patients (86%), while after intravenous ICG identification of intersegmental plane was achieved in all patients 100% [65]. The identification of the intersegmental plane with the use of ICG enables to obtain negative margins in all the specimens. The ICG dose used in the studies was not standardized. Only Anjama et al calculated the optimal cut-off of ICG for the identification of intersegmental plane as 0.089ml of ICG per unit volume (ml) of the segment [50].

Several other applications of ICG in thoracic surgery can be found in literature, so it might be a valid help in for surgeon in different occasions. Gotoh et al demonstrated that since tissue density and blood flow are reduced in bullae, quantitative analysis revealed a decrease of indocyanine green intensity [37]. The treatment of chylothorax can be technically challenging because of the difficulty in identifying the source of this leak. ICG can migrate within lymphatic channels. The administration was commonly performed subcutaneously into inguinal region [41,48,51]. Shirotsuki et al demonstrated that with NIR imaging could be performed direct sutures of the leakage sites and ICG could be also used to marked postoperative decrease in chylous leakage of the chest drain [47]. The surgical treatment for pulmonary sequestration is resection of the non-functional area of the lung parenchyma and the ligation or cutting of the aberrant artery. The intravenous injection of ICG could help the identification of aberrant vessels [42-45]. ICG has been used during bronchoplasty: the success of the bronchoplasty is both tension and the blood flow, so ICG could help to evaluate the blood supply of the bronchial anastomosis [40,41]. ICG might also have a role to prevent bronchopleural fistula after pneumonectomy [39]. Finally, the last application of ICG we found was during thoracic sympathectomy because increase the visibility rate of all sympathetic ganglions [49].

In our study we collected and summarised the major applications of ICG in thoracic surgery, anyway a lot of other apllications could be developed in the future. In this review we reported the tecnique adopted in the differet paper so we no give

a precise indication for the procedure because of the lack of standardization.

Conclusions

NIR fluorescence imaging with ICG have a wide range of practical applications within thoracic surgery. However, because of the current limited evidence and the absence of a standardized procedure. Therefore, larger experiences and prospective trials will be necessary to delineate the indications and specific applications.

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