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REVIEW

Use of Indocyanine Green Fluorescence Imaging in Thoracic and Esophageal Surgery

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ABSTRACT

BACKGROUND Fluorescence imaging using indocyanine green in thoracic and esophageal surgery is gaining popularity because of the potential to facilitate surgical planning, to stage disease, and to reduce postoperative complications. To optimize use of fluorescence imaging in thoracic and esophageal surgery, an expert panel sought to establish a set of recommendations at a consensus meeting.

METHODS The panel included 12 experts in thoracic and upper gastrointestinal surgery from Asia-Pacific countries. Before meeting, 7 focus areas were defined: intersegmental plane identification for sublobar resections; pulmonary nodule localization; lung tumor detection; bullous lesion detection; lymphatic mapping of lung tumors; evaluation of gastric conduit perfusion; and lymphatic mapping in esophageal surgical procedures. A literature search of the PubMed database was conducted using keywords *indocyanine green*, *fluorescence*, *thoracic*, *surgery*, and *esophagectomy*. At the meeting, panelists addressed each focus area by discussing the most relevant evidence and their clinical experiences. Consensus statements were derived from the proceedings, followed by further discussions, revisions, finalization, and unanimous agreement. Each statement was assigned a level of evidence and a grade of recommendation.

RESULTS A total of 9 consensus recommendations were established. Identification of the intersegmental plane for sublobar resections, localization of pulmonary nodules, lymphatic mapping in lung tumors, and assessment of gastric conduit perfusion were applications of fluorescence imaging that have the most robust current evidence.

CONCLUSIONS Based on best available evidence and expert opinions, these consensus recommendations may facilitate thoracic and esophageal surgery using fluorescence imaging.

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Fluorescence imaging using indocyanine green (ICG) has been explored for guiding various aspects of thoracic surgery since 2010.[1] ICG has a peak spectral absorption wavelength of 800 to 810 nm in plasma or blood and a peak spectral emission of

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835 nm.[2] ICG has no absolute contraindications other than previously demonstrated ICG hypersensitivity.[2] The maximum recommended daily dose is 2 mg per kilogram of patient body weight, although much lower doses are used effectively for a variety of purposes in thoracic and esophageal surgery.[2] ICG binds rapidly and extensively with plasma proteins, typically remaining in the vascular space when injected intravenously, with a half-life of 4 minutes.[2] In cases of interstitial or peritumoral injection of ICG, the dwelling time is much longer than the half-life in the vascular space.[3,4] After interstitial injection, ICG will drain into lymphatic channels and concentrate in lymph nodes before proceeding into the thoracic duct and vascular system, with eventual elimination through the bile.[5] When the protein-bound ICG is illuminated with near-infrared light in the range of 800 to 810 nm (excitation wavelength), the light will be absorbed and subsequently emitted at a wavelength of 835 nm (emission wavelength).[2] A fluorescence imaging system will employ an optic filter to remove the excitation wavelength of the illuminated tissues, allowing the camera sensor to reproduce a real-time image with the emission wavelength on the monitor.

ICG fluorescence has been used commonly around the world in different surgical specialties for sentinel node mapping, perfusion assessment for gastrointestinal anastomosis, and flap reconstructions.[6] The most frequent applications of ICG fluorescence imaging in thoracic surgery include identification of the intersegmental plane for sublobar resections, pulmonary nodule localization, tumor identification, sentinel lymph node mapping, and conduit perfusion assessment in esophagectomy. Additional uses, such as bullous lesion identification and lymphatic mapping during esophagectomy, are gaining increasing clinical attention.[7,8] The imaging technique has been demonstrated to facilitate surgical planning, disease staging, and reduction in postoperative complications. To optimize the adoption and clinical performance of ICG fluorescence imaging in thoracic and esophageal surgery, an expert panel discussed the current evidence and clinical experiences at a consensus meeting held in Hong Kong on July 27, 2019.

MATERIAL AND METHODS

PURPOSE OF THE CONSENSUS MEETING. The expert panel aimed to compile a set of consensus recommendations that could guide routine use of ICG fluorescence imaging in thoracic and esophageal surgery, with the goal of optimizing clinical outcomes and focusing the direction of future research in this area.

PANEL COMPOSITION. The panel included 12 experts from countries across the Asia-Pacific region, consisting of 7 specialists in pulmonary and upper gastrointestinal/esophageal surgery, 3 thoracic surgeons, and 2 specialists in upper gastrointestinal surgery. These surgeons chose to participate in this project on the basis of their expertise in minimally invasive thoracic and esophageal surgery and experience with fluorescence imaging. The panel meeting was organized and moderated by fluorescence pioneers Hyun Koo Kim and Simon Y.K. Law.

DEFINING THE CLINICAL QUESTIONS. The consensus meeting was aimed at addressing the feasibility and optimal use of ICG fluorescence imaging in 7 areas of focus:

I. Identification of the intersegmental plane during sublobar resections
II. Intraoperative localization of pulmonary nodules using image-guided ICG injection
III. Detection of lung tumors based on the enhanced permeability and retention effect
IV. Detection of bullous lesions
V. Sentinel lymph node mapping of lung tumors
VI. Evaluation of gastric conduit perfusion in esophagectomy
VII. Lymphatic mapping in esophageal surgical procedures

IDENTIFYING RELEVANT EVIDENCE. A literature search on the PubMed database was conducted with the keywords *indocyanine green*, *fluorescence*, *thoracic*, *surgery*, and *esophagectomy* to identify any human studies that addressed the use of ICG fluorescence imaging in the areas of focus, which might include randomized trials, cohort studies, and case series/reports as well as review articles; 2638 results were returned. Non-English language publications, publications investigating imaging agents other than ICG, and publications not relevant to the a priori defined clinical questions were excluded. The panelists sorted out the most relevant papers from the search results and selected 98 abstracts and papers for discussion at the consensus meeting. The 3 authors who perform lung surgery reviewed 69 papers relevant to their area of expertise, the 2 authors who perform esophageal surgery reviewed 46 papers, and the 7 authors who perform both thoracic and esophageal surgery reviewed 98 abstracts and papers in advance of the meeting. The authors unanimously agreed to add 1 paper[9] to this manuscript that was published after the consensus meeting because of its large sample size and relevance to the topic discussed, although the information did not change the recommendation class or level of evidence for the recommendation in the relevant area of focus.

CONSENSUS PROCESS. The discussion was chaired by Hyun Koo Kim and Simon Law. Using a modified Delphi

TABLE Finalized Consensus Recommendations

No.	Statement	Level of Evidence	Class of Recommendation
Section I: Identification of the intersegmental plane during sublobar resections			
1	Fluorescence imaging is helpful in delineating segmental boundaries for sublobar lung resections and lung segmentectomy procedures.	B–Non Randomized	II-a
1a	Negative staining through intravenous injection of ICG is less technically demanding and has a shorter dwelling time of fluorescence contrast agent, but additional injections of contrast agent may occasionally be required.	B–Non Randomized	II-a
1b	Positive staining through transbronchial instillation of ICG will allow a longer dwelling time of fluorescence contrast agent and can likely achieve similar results to negative staining in centers familiar with its use.	C–Limited Data	II-b
Section II: Intraoperative localization of pulmonary nodules using image-guided ICG injection			
2	Fluorescence imaging is helpful for intraoperative lung nodule localization for lesions located no deeper than 2 cm from the pleural surface by image-guided transthoracic or bronchoscopic injection of ICG. Compared with image-guided blue dye injection, ICG injection significantly reduces the risk of inability to localize a lesion because of the blue dye's being obscured by anthracosis.	B–Non Randomized	II-a
Section III: Detection of lung tumors based on the enhanced permeability and retention effect			
3	Fluorescence detection of lung tumors may be performed by intravenous injection of contrast agent and enhanced permeability and retention effect. However, this technique may also detect inflammatory lesions.	B–Non Randomized	II-b
Section IV: Detection of bullous lesions			
4	Fluorescence imaging may assist in guiding resection of bullous lesions.	C–Limited Data	III–No benefit
Section V: Sentinel lymph node mapping of lung tumors			
5	Sentinel lymph node mapping of lung tumors with fluorescence may assist in intraoperative identification of draining lymph nodes.	B–Non Randomized	II-b
Section VI: Evaluation of gastric conduit perfusion in esophagectomy			
6	Fluorescence imaging can assist in assessing perfusion of gastric conduit and choosing the site of anastomosis intraoperatively in esophagectomy.	B–Non Randomized	II-a
Section VII: Lymphatic mapping in esophageal surgical procedures			
7	Lymphatic mapping in esophageal surgical procedures with fluorescence imaging may assist in intraoperative identification of draining lymph nodes.	C–Limited Data	II-b

ICG, indocyanine green.

method,[10] the panelists addressed each area of focus by sharing the available evidence and discussing their clinical practice during a 6-hour meeting. The first draft of consensus statements on the use of ICG fluorescence in thoracic and esophageal surgery was derived from the initial proceedings and during further discussion the same day. The first round of voting was done in person through written questionnaires. Final agreement and revisions were made by 2 rounds of further discussion using email correspondence. A total of 3 rounds of voting were conducted, and each finalized statement was reviewed. Each statement was assigned a level of evidence and a grade of recommendation based on established recommendations for developing clinical guidelines (Supplemental Tables 1 and 2).[11,12] All final statements were unanimously agreed on by all participants.

RESULTS

A total of 9 consensus recommendations (Table) were derived from the meeting proceedings.

SECTION I: IDENTIFICATION OF THE INTERSEGMENTAL PLANE DURING SUBLOBAR RESECTIONS. Sublobar resections, primarily anatomic segmentectomy, can be an effective and safe alternative to lobectomy for the treatment of early-stage non-small cell lung cancer (NSCLC), especially in patients with poor cardiopulmonary function or small peripheral nodules.[13,14] To demarcate the intersegmental plane for segmentectomy, the conventional method is the inflation-deflation technique, which involves ligation of the target segmental bronchi.[6,15] The major limitation of this method is that the inflated segment

may obstruct the surgical view during video-assisted thoracoscopy, especially in patients with emphysema.[6,15]

Fluorescence imaging using ICG can facilitate clear real-time intraoperative identification of the intersegmental plane (Supplemental Figure).[16] Misaki and coworkers[1] were among the first to use the technique by systemic intravenous administration of ICG after ligating the artery of the target segment. Liu and associates[9] compared the inflation-deflation technique with the fluorescence-guided technique in uniport video-assisted thoracic surgical procedures and found the fluorescence-guided technique to be superior in regard to operative time (79 ± 29 minutes vs 96 ± 38 minutes; $P < .01$), ability to visualize the intersegmental plane (91.4% vs 64.2%; $P < .01$), drainage duration (4.6 ± 2.9 days vs 5.9 ± 3.3 days; $P = .02$), rate of prolonged air leak >5 days (7.6% vs 14.1%; $P = .01$), and hospital stay after the operation (5.6 ± 2.1 days vs 7.1 ± 3.2; $P = .01$). Sekine and coworkers[17,18] developed an alternative method that involves transbronchial administration of ICG to the target segment for intersegmental delineation. These 2 techniques of fluorescence imaging are referred to as negative staining and positive staining, respectively (Supplemental Table 3).

Negative Staining. Following the practice of Misaki and coworkers,[1] a number of studies have shown the success of ICG fluorescence imaging with negative staining.[19-26] Mehta and colleagues[22] also reported that the imaging technique is associated with an increase (mean, 2.41 cm) in the oncologic margin, over and above the best judgment of the surgeon, in >60% of robotic segmentectomies.

In practice, preoperative 3-dimensional computed tomography (3D-CT) reconstruction of the pulmonary anatomy may be performed to identify the dominant arteries of the target segment, which are then ligated. After that, a dose in the range of 0.25 to 0.6 mg/kg ICG, depending on device and user preference, can be injected into a peripheral vein. After 10 to 20 seconds, the demarcation line can be identified; normal lung tissues, instead of the target segment, will be highlighted for a few minutes on near-infrared fluorescence thoracoscopy, allowing the target segment to be resected under fluorescence guidance.

Positive Staining. The use of fluorescence imaging with positive staining has been far less commonly reported than negative staining in the literature. As demonstrated by Sekine and coworkers,[18] positive staining with transbronchial ICG instillation is applicable to all types of sublobar resections, including complex segmentectomies and deep wedge resections, enabling successful identification of the segmental border in >90% of cases, with no same-lobe recurrences observed.

To perform positive staining, a virtual segmentectomy should be performed preoperatively using a 3D-CT volume analyzer to determine the locations and number of bronchi for ICG instillation. In each target bronchus, 10 mL of 10-fold diluted ICG is injected through a bronchial catheter with a balloon, which is inflated to prevent fluid leakage and to maintain positive pressure. After that, 200 to 400 mL of air is injected to allow peripheral distribution of ICG within the targeted segment of lung. The intersegmental plane will be visualized for several hours on near-infrared fluorescence thoracoscopy.

Negative vs Positive Staining. Both negative and positive staining are clinically feasible in facilitating the identification of the intersegmental plane for sublobar resections. In practice, both approaches benefit from the preoperative use of a 3D-CT image analyzer for precise understanding of the pulmonary anatomy, although this system is necessary for positive staining.

Compared with positive staining, negative staining is much easier to perform, but the duration of fluorescence visibility is shorter, which may necessitate reinjection of ICG. As the dose for this procedure is 0.25 to 0.6 mg/kg ICG and the maximum daily recommended dose is 2 mg per kilogram of body weight, reinjection is usually well tolerated.

One of the advantages of positive staining is the ability to determine the resection area at the beginning of the operation. Another advantage is a long dwelling time of the fluorescence contrast agent, which is useful in more complex segmentectomies. Notably, the major limitation of positive staining is the demand for familiarity with accurate bronchoscopic application of ICG.

Recommendations

1. Fluorescence imaging is helpful in delineating segmental boundaries for sublobar lung resections and lung segmentectomy procedures. (Level of evidence: B-Non Randomized; Recommendation class: II-a)

1a. Negative staining through intravenous injection of ICG is less technically demanding and has a shorter dwelling time of fluorescence contrast agent, but additional injections of contrast agent may occasionally be required. (Level of evidence: B-Non Randomized; Recommendation class: II-a)

1b. Positive staining through transbronchial instillation of ICG will allow a longer dwelling time of fluorescence contrast agent and can likely achieve similar results to negative staining in centers

familiar with its use (Level of evidence: C-Limited Data; Recommendation class: II-b)

SECTION II: INTRAOPERATIVE LOCALIZATION OF PULMONARY NODULES USING IMAGE-GUIDED ICG INJECTION. Demand for accurate localization of pulmonary nodules is rising. The traditional method of localization involves the preoperative use of microcoils, hook wires, or methylene blue under the guidance of computed tomography (CT).[6,15] The drawback of microcoils and wires is the risk of procedure-related pneumothorax or hemopneumothorax, whereas the target lesion stained with methylene blue may be obscured by anthracosis.[6,15] Novel modalities for pulmonary nodule identification are required to solve these problems.

Several surgeons have reported the use of CT-guided percutaneous ICG injection (quantity, 0.3-0.5 mL; concentration, 0.125 mg/mL) followed by intraoperative near-infrared fluorescence thoracoscopy for safe and accurate localization of pulmonary nodules (median size, ≤1 cm; median distance from the pleural surface, ≤1 cm), including primary tumors, metastases, and benign nodules.[27-29] The advantages of the technique include straightforward implementation, no risk of localization wire migration, durable visualization of the target nodule, less influence on pathologic diagnosis, and reduced risk of pneumothorax or hemopneumothorax vs wire localization. The limitations include the inability to detect nodules in blind areas (eg, mediastinal pleura, interlobular fissures, and scapular cover) and risk of ICG diffusion through the lung parenchyma, which may be prevented by mixing ICG with lipiodol.[16]

ICG can also be administered under the guidance of electromagnetic navigation bronchoscopy (ENB) for intraoperative localization of small pulmonary nodules near the pleural surface.[16,30,31] To allow better visualization on fluoroscopy during ICG injection and on subsequent cone beam CT scans, lipiodol or iopamidol can be added.[16,31] Anayama and coworkers[31] suggested that the ENB-guided approach could enable localization of multiple lesions with a lower risk of causing pneumothorax compared with a transthoracic approach (Supplemental Table 4). Notably, this technique requires skillful manipulation of bronchoscopy.

The expert panel recognized the benefit of fluorescence imaging for localization of pulmonary nodules that are up to 2 cm from the pleural surface.

Recommendations

2. Fluorescence imaging is helpful for intraoperative lung nodule localization for lesions located no deeper than 2 cm from the pleural surface by image-guided transthoracic or bronchoscopic injection of ICG. Compared with image-guided blue dye injection, ICG injection significantly reduces the risk of inability to localize a lesion because of the blue dye's being obscured by anthracosis. (Level of evidence: B-Non Randomized; Recommendation class: II-a)

SECTION III: DETECTION OF LUNG TUMORS BASED ON THE ENHANCED PERMEABILITY AND RETENTION EFFECT. ICG has been used successfully for lung tumor imaging in some cases. This is hypothesized to be due to the enhanced permeability and retention effect of ICG, which may accumulate in tumor tissues much more than in normal tissues as a result of increased vasculature and dysfunctional lymphatics of tumor tissues compared with normal tissues.[32,33] ICG can achieve high avidity in tumor cells because of its amphiphilic properties.[34] In addition, tumor cells may preferentially take up ICG because of the high endocytic activity associated with the disruption of their tight junctions.[35] ICG has also been used for tumor imaging in organs such as the liver, colon, and thymus.[36-38]

Okusanya and coworkers[39] first reported the use of ICG fluorescence imaging for the detection of lung tumors. Patients (N = 18) underwent a fine-cut 1-mm CT scan, followed by systemic administration of ICG (5 mg/kg) 24 hours before an open thoracotomy.[39] Intraoperative near-infrared imaging visualized 5 malignant nodules that were not detected on CT or by palpation.[39] The technique could detect nodules as small as 0.2 cm and as deep as 1.3 cm from the pleural surface.[39]

Several surgeons in other centers also reported the feasibility of ICG fluorescence imaging in detecting lung tumors.[40-42] Notably, Kim and associates[40] found 2 false-positive nodules on ICG fluorescence that were areas of obstructive pneumonitis with no malignant transformation, suggesting the inability of ICG to differentiate tumors from inflammation and the need for tumor-specific fluorescence agents in the future (Supplemental Table 5).

The expert panel acknowledged the safety and feasibility of ICG fluorescence imaging for the detection of lung tumors. However, they noted that the nature of lesions detected on fluorescence imaging should be confirmed with CT and clinical judgment.

Recommendations

3. Fluorescence detection of lung tumors may be performed by intravenous injection of contrast agent and the enhanced permeability and retention effect. However, this technique may also detect inflammatory lesions. (Level of evidence: B-Non Randomized; Recommendation class: II-b)

SECTION IV: DETECTION OF BULLOUS LESIONS. Video-assisted thoracoscopic bullectomy is the mainstay treatment of spontaneous pneumothorax.[6,15] However, there is a significant rate of recurrence in some patients in whom it may be difficult to detect all bullous lesions on visual inspection.[6,15] Several surgeons reported success with infrared (or near-infrared) fluorescence thoracoscopy after intravenous injection of ICG in detecting bullous lesions in a small number of patients (Supplemental Table 5).[43-45] However, the expert panel noted that the heterogeneity of lesions might make it difficult to differentiate all bullous lesions from normal tissues on fluorescence imaging. Well-designed, controlled studies are warranted to confirm the usefulness of this technique in routine practice.

Recommendation

4. Fluorescence imaging may be useful to assist with guiding resection of bullous lesions. (Level of evidence: C-Limited Data; Recommendation class: III-No benefit)

SECTION V: SENTINEL LYMPH NODE MAPPING OF LUNG TUMORS. A sentinel lymph node (SLN) is the first lymph node involved in the lymphatic drainage of a tumor, and the pathologic status of the SLN can predict lymphatic metastatic spread, which affects disease staging, prognosis, and subsequent treatment.[6,7] In selected patients, SLN biopsy may be an alternative to extensive lymphadenectomy, which may be associated with risks such as prolonged air leak, hemothorax, chylothorax, recurrent laryngeal nerve injury, and bronchial fistula, among others.[46] Conventional agents for SLN mapping in lung cancer surgical procedures include methylene blue and technetium Tc 99; however, methylene blue yields a low detection rate because of the presence of anthracotic lymph nodes in the lung and mediastinum, whereas ^{99}Tc is associated with radiation exposure and a complex administration method.[6] To improve intraoperative thoracic SLN mapping, ICG fluorescence imaging may be considered.

Based on studies of patients with early-stage NSCLC (Supplemental Table 6),[47-51] the technique yielded an SLN detection rate of ≥80%, comparable to that of ^{99}Tc, with a low rate of false negatives (ie, metastases found in non-SLNs instead of SLNs) of up to 2.9%. SLNs can be visualized with fluorescence despite the presence of anthracosis.[47] To carry out fluorescence imaging, ICG (quantity, 1-2 mL; concentration, 5 mg/mL) can be injected around the tumor or staple line after resection. To avoid leakage of dye, the injection site should be ligated immediately after the injection. Alternatively, ICG (0.5 mL; 2.5 mg/mL) mixed with 20 mL of autologous blood or 25% human serum albumin (HSA) can be injected peritumorally under the guidance of CT or ENB and is expected to identify SLNs on fluorescence 10 to 30 minutes after injection. A sufficient dissection of structures should be performed to identify likely candidate nodes.

To avoid missing true SLNs, Nomori and colleagues[50] reported in the largest lung SLN study available (N = 135) that all 3 of their false-negative cases involved non-SLNs with metastases at stations 12 or 13. In addition, 57% of SLNs were located in station 12 or 13.[49] These findings led Nomori and colleagues to suggest that stations 12 and 13 should be examined by frozen section in addition to any SLNs identified by fluorescence imaging. This group also stressed the importance of intraoperative frozen section during segmentectomy, allowing segmentectomy to be converted to lobectomy if the stage is not N0. Furthermore, it was recognized that an SLN protocol is useful and encouraged to allow improved focus of pathologic examination on the nodes most likely to harbor metastasis.

The expert panel recognized the potential of ICG fluorescence imaging for intraoperative SLN mapping, which could improve disease staging in patients with early-stage NSCLC.

Recommendation

5. Sentinel lymph node mapping of lung tumors with fluorescence may assist in intraoperative identification of draining lymph nodes. (Level of evidence: B-Non Randomized; Recommendation class: II-b)

SECTION VI: EVALUATION OF GASTRIC CONDUIT PERFUSION IN ESOPHAGECTOMY. Esophagectomy is associated with high morbidity and risk of death, which is largely related to the reconstruction and anastomosis of the gastric conduit.[52] ICG angiography is an emerging imaging modality that can facilitate real-time intraoperative assessment of gastric conduit perfusion in esophagectomy, with the goal of reducing the risk of anastomotic leak.

In a systematic review, Slooter and colleagues[53] identified 20 studies that demonstrated the feasibility and safety of ICG angiography for the evaluation of gastric conduit perfusion before anastomotic reconstruction (Supplemental Table 7). In these studies, ICG at doses ranging from 1.25 mg to 25 mg was injected intravenously during esophagectomy; within 1 minute after injection, perfusion was visualized on near-infrared fluorescence.[53] The pooled incidence of anastomotic leakage and graft necrosis in surgeries guided by ICG angiography was 11%.[53] Eight of the studies showed that the technique was

associated with a change in surgical procedure in 25% of the pooled cases. Slooter and colleagues[53] also conducted a meta-analysis of 5 controlled studies, which demonstrated that ICG angiography is associated with a reduction in anastomotic leakage and graft necrosis (odds ratio, 0.30; 95% CI, 0.14-0.63) compared with non-ICG assessment methods. The expert panel noted that it is reasonable to use ICG angiography for intraoperative assessment of gastric conduit perfusion and anastomotic sites in esophagectomy. Whereas this technique has been shown to reduce the risk of anastomotic leak related to perfusion deficit, fluorescence imaging does not eliminate anastomotic leak because there are multiple factors in addition to blood supply (eg, cardiovascular and renal comorbidities of patients) as well as variations in anastomotic technique that may contribute to leaks.[54] They also stated that device improvements allowing objective measurements of perfusion are warranted to help standardize the use of ICG angiography in esophagectomy.

Recommendation

6. Fluorescence imaging can assist in assessing perfusion of gastric conduit and choosing the site of anastomosis intraoperatively in esophagectomy. (Level of evidence: B-Non Randomized; Recommendation class: II-a)

SECTION VII: LYMPHATIC MAPPING IN ESOPHAGEAL SURGICAL PROCEDURES. In esophageal cancer, even an aggressive 3-field lymphadenectomy may miss key lymph nodes and occult nodal metastases,[55] suggesting a need for improving the identification of tumor-associated lymph nodes and possible lesions, thereby informing a personalized lymphadenectomy with better outcomes. Furthermore, extensive lymphadenectomy carries additional risks, which may include bleeding, recurrent laryngeal nerve injury, and devascularization that may impair healing.[56] It was hoped that SLN mapping using radioisotope tracers would improve intraoperative nodal staging in esophageal cancer; however, neither the SLN concept nor a standard mapping technique in esophageal cancer has been validated.[57]

Multiple groups have investigated the feasibility of near-infrared imaging using ICG for lymphatic mapping in esophageal cancer surgery. In 2016, Hachey and coworkers[58] reported the first experience with the technique for intraoperative assessment of regional lymph nodes during minimally invasive esophagectomy (N = 9). After peritumoral, submucosal injection of ICG 2.5 mg alone (n = 5) or premixed in HSA (n = 4), fluorescence imaging identified regional lymph nodes in 6 patients (2 with ICG alone; 4 with ICG + HSA).[57] In 2018, Park and coworkers[59] demonstrated the feasibility of ICG fluorescence lymphatic mapping for the assessment of bilateral recurrent laryngeal nerve nodes in early-stage esophageal squamous cell carcinoma (N = 29). ICG (0.5 mL; 0.5 mg/mL) was injected submucosally 1 day before operation; during upper mediastinal dissection, ICG-stained basins were identified on fluorescence in 25 patients (86.2%), of whom 6 (24.0%) had nodal metastasis.[59] The negative predictive values in the detection of nodal metastasis for the right and left recurrent laryngeal nerve chains were 100% and 98.2%, respectively (Supplemental Table 7).[59]

Based on the encouraging preliminary evidence, the expert panel noted that ICG fluorescence imaging is safe and might assist in identifying drainage lymph nodes intraoperatively in esophageal surgical procedures. However, in line with other experts' opinions,[8] the panelists emphasized that more high-level evidence is warranted to confirm the benefits of the technique in improving disease staging, informing the extent of lymphadenectomy, and identifying or ruling out occult nodal metastases.

Recommendation

7. Lymphatic mapping in esophageal surgery with fluorescence imaging may assist in intraoperative identification of draining lymph nodes. (Level of evidence: C-Limited Data; Recommendation class: II-b)

COMMENT

The consensus recommendations reflect the safety and feasibility of ICG fluorescence imaging in various aspects of thoracic and esophageal surgery. Identification of the intersegmental plane for sublobar resections, intraoperative localization of superficial pulmonary nodules, sentinel lymph node mapping in lung tumors, and assessment of gastric conduit perfusion appear to be the most promising applications of the technique. Notably, there is a need for concurrent use of other imaging modalities, such as a 3D-CT image analyzer for the assessment of pulmonary anatomy before positive staining in segmentectomy and CT or ENB for guiding ICG injection in pulmonary nodule localization.

The role of ICG fluorescence imaging is uncertain in some areas. For detection of bullous lesions, the effectiveness of the technique cannot be supported by current evidence or clinical experience. In addition, as with other applications of fluorescence imaging, the technique may not be able to localize deep nodules because of the depth of penetration limitations of fluorescence light. Owing to the nonspecific enhanced permeability and retention effect, fluorescence imaging cannot differentiate lung tumors from benign or inflammatory nodules. Moreover, the clinical

significance of ICG fluorescence for SLN mapping in staging for NSCLC is not fully understood, especially in the setting of segmentectomy. Further investigation into mapping sentinel nodes in stations 12 and 13 would be beneficial for this use of ICG fluorescence. Whereas the clinical benefit for SLN mapping in esophageal cancer is clear, the clinical efficacy of this application requires further validation. In general, higher level evidence, such as results from randomized controlled trials or multicenter prospective studies with controls, is expected to further standardize the routine use of ICG fluorescence imaging in thoracic and esophageal surgery.

Looking beyond ICG fluorescence imaging, future advances that will further optimize surgical procedures and safety are anticipated. These might include tumor-specific contrast agents for refining localization of lung nodules, an entity that combines preoperative and intraoperative imaging tools, and various technologies that leverage artificial intelligence.

In conclusion, the expert panel established a set of consensus recommendations aimed at facilitating thoracic and esophageal surgery using ICG fluorescence imaging based on the best available evidence and shared experiences.

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