Image-guided and bronchoscopic localization techniques used to facilitate minimally invasive pulmonary metastasectomies

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Abstract: Pulmonary metastasectomy is associated with increased disease-free and overall survival in well-selected patients. Prerequisites to pulmonary metastasectomy include adequate pulmonary reserve and the ability to completely resect the identified metastasis. The likelihood that a patient will benefit from metastasectomy is driven by control of the primary tumor and other sites of disease, tumor biology and is dictated by tumor histology, presence of nodal metastasis, and number of metastases. Traditionally, open thoracostomy and bimanual palpation of the lung were used to identify pulmonary metastasis for resection. Increasingly video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS) have been used in the performance of metastasectomy. These minimally invasive approaches reduce perioperative discomfort, length of stay, and may facilitate reintervention if new pulmonary metastasis develop. Given the reduced ability to palpate the lung using a minimally invasive approach, several techniques have been developed to facilitate intraoperative identification of pulmonary metastasis. These techniques fall into three broad categories: intraoperative imaging, image-guided labeling, and systemic targeting. This review provides an overview of the various risks, benefits, and effectiveness of these techniques. We also provide a brief review of the indications for minimally invasive metastasectomy. Finally, we perform a critical assessment of the associated literature with a focus on the current limitations and future directions of the field.

Keywords: Pulmonary metastasectomy; localization; video-assisted thoracoscopic surgery (VATS); robotic-assisted thoracoscopic surgery (RATS)

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Introduction

The lung is a common site of metastasis for several cancers including breast, colorectal, renal cell, soft tissue sarcoma, and osteosarcoma (1). Over the last several decades, pulmonary metastasectomy has been consistently associated with improved overall survival in well-selected patients (2-5). As with operations for primary lung cancer there has been a shift toward a minimally invasive approach

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to metastasectomy (6). This poses a challenge as small metastasis deep in the lung parenchyma can be difficult to appreciate without direct bimanual palpation through a thoracotomy.

Several techniques have been developed to facilitate localization of pulmonary metastases during minimal invasive resection using either a video-assisted thoracoscopic surgery (VATS) or a robotic-assisted thoracoscopic surgery (RATS) approach (7). To date, the ideal technique for localization of pulmonary metastasis remains undefined. Herein, we provide a brief review of the indications for minimally invasive pulmonary metastasectomy and in-depth comparison of the effectiveness and safety of each localization method. Our aim is to provide the reader with a focused clinical review of the available techniques and the limitations of the current literature.

Indication for minimally invasive metastasectomy

Indications for minimally invasive pulmonary metastasectomy are the same as for open metastasectomy. They have been expanded from the original criteria proposed by Alexander and Haight in 1947 to include five components (8,9). (I) Suitable patients must have sufficient pulmonary reserve and fitness to tolerate resection. (II) Primary disease must be controlled or controllable. (III) Extrathoracic metastasis must be resectable or previously resected. (IV) Pulmonary metastasectomy should achieve an R0 resection. (V) Operative treatment should represent the best treatment option among current therapeutic modalities. When these criteria are not met then pulmonary metastasectomy should not be performed and alternative treatments should be considered. More recently, other considerations for metastasectomy have been evaluated to help select patients most likely to benefit from pulmonary resection. Together these factors comprise a proposed tumor, node, metastasis (TNM) classification system for pulmonary metastasectomy and include primary tumor activity, nodal involvement, and number of metastasis (10). Additional risk factors for recurrence after pulmonary metastasectomy include age less than 70 and presence of extra-thoracic metastases. The type of primary tumor is also an important consideration (11). The timing of pulmonary metastasis relative to the original date of diagnosis can be considered as well. Synchronous pulmonary metastases are identified at the time of original primary cancer diagnosis. These are associated with a worse prognosis overall than metachronous pulmonary metastases which develop later as a site of progression or recurrence (12). In general, the number of pulmonary metastases should not be increasing in patients where pulmonary resection for disease control is planned. The ongoing appearance of new sites of disease within the lung suggests more diffuse and systemic disease than what is currently visualized on a chest computed tomography (CT) scan and local control of pulmonary disease in these patients is less likely to improve overall survival. Together, these works speak to the need to personalize treatment based on individual risk factors and the biology of tumor.

When a complete resection cannot be performed through a minimally invasive approach than an open thoracotomy should be considered. Traditional thoracotomy remains an excellent option for metastasectomy and in some cases may be the preferred treatment option (13). As reported by Cerfolio *et al.*, bimanual palpation of the lung through thoracotomy may result in discovery of occult nodules in up to 20% of patients (14). However, there is also ample evidence supporting the use of both a VATS and RATS approach to metastasectomy and a minimally invasive approach is preferred in expert consensus (15). In metanalysis, systematic review, and large registry series, a minimally invasive approach has been associated with equivalent disease-free and overall survival (6,16,17). Metastasectomy can be performed on multiple occasions upon the development of new nodules and an initial minimally invasive approach may facilitate additional ipsilateral procedures through reduction of adhesions (18).

Localization techniques

Several techniques have been developed to aid in the intraoperative identification of metastatic nodules during minimally invasive metastasectomy. There is no formal recommendation for when to use a localization technique. However, lesions less than 1 cm in size and more than 5 mm in depth from the pulmonary surface tend to be the most difficult to appreciate in a minimally invasive approach (19). Localization methods fall into three broad categories: (I) intraoperative imaging; (II) image-guided labeling; (III) and systemic targeting (*Figure 1*). The merits of each of these techniques are discussed in depth below and outlined in *Table 1*.

Intraoperative imaging

Intraoperative imaging for identification of pulmonary metastasis is primarily accomplished through ultrasonography

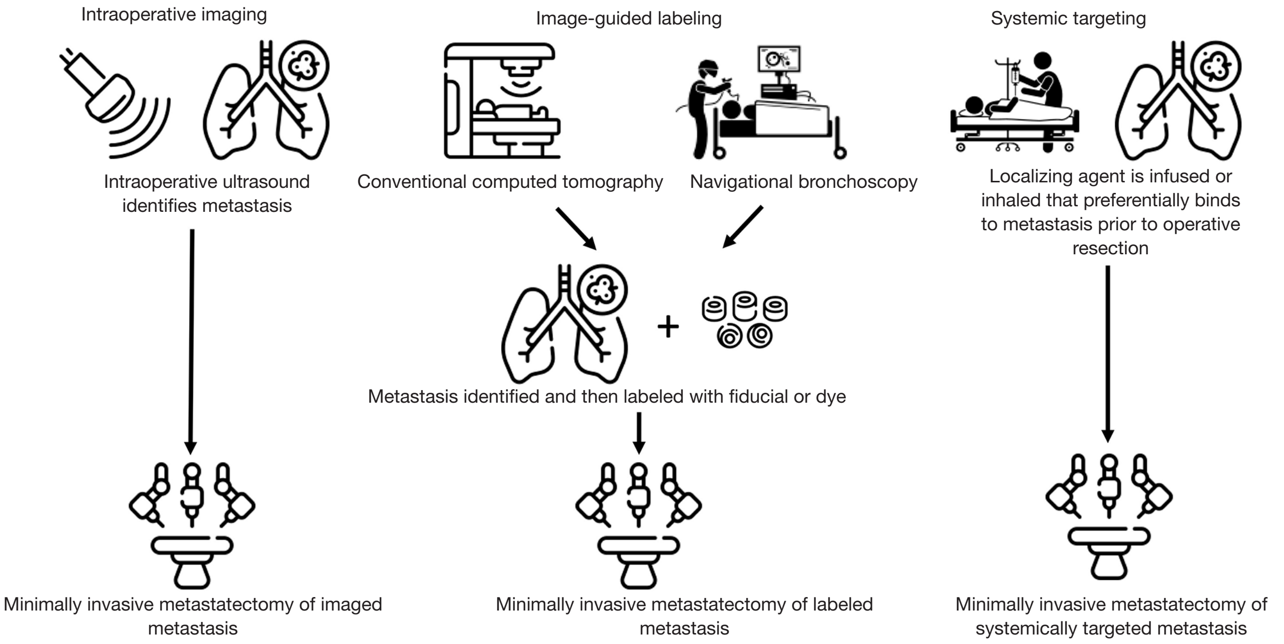

Figure 1 Methods of localization in minimally invasive metastatectomy.

Table 1 Comparison of localization methods

Method	Mechanism	Advantage	Disadvantage
Intraoperative imaging	US probe through thoracoscopic port used to identify pulmonary nodules	Real-time imaging of lung	User dependent
		Potential discovery of occult nodules	Limited in emphysema and incomplete lung collapse
		Low complication risk	
		Single invasive procedure	
Image-guided labeling	Preoperative image-guided percutaneous or transbronchial labeling of pulmonary nodules	Established technology with significant body of supporting literature	Requires multiple invasive procedures
	Multiple agents used including wires, fiducials, dyes, radiotracer, and ICG	Various methods may be more suited to RATS or VATS approach	Can be resource demanding
		Can be performed with or without specialized cameras/fluoroscopy	Potential for complications (hemothorax/pneumothorax)
			Only enables resection of pre-operatively identified nodules
Systemic targeting	Peripheral infusion or inhalation of ICG prior to resection localizes to pulmonary nodules	Single invasive procedure	May require hospital visit for infusion 24 hours prior to procedure
	Intraoperative imaging using an NIR thoracoscope provides real-time identification of NIR fluorescence	Potential for discovery of occult metastasis	Requires NIR camera
		Low complication risk	Emerging technology

US, ultrasound; ICG, indocyanine green; RATS, robotic-assisted thoracoscopic imaging; VATS, video-assisted thoracoscopic imaging; NIR, near infrared.

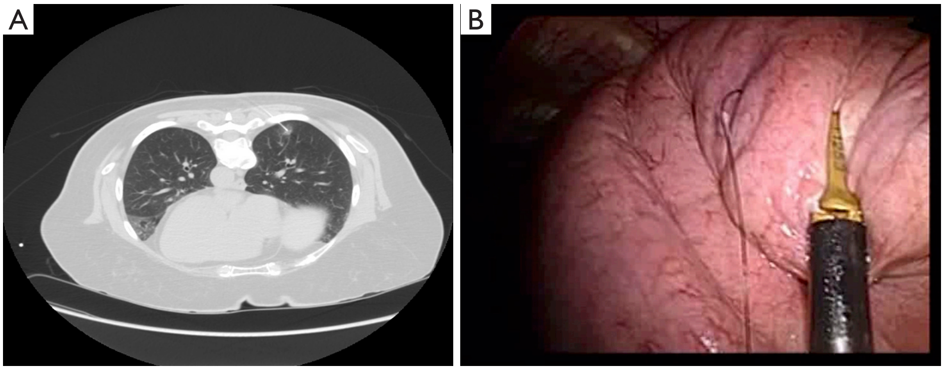

Figure 2 Hook-wire localization of colorectal metastasis. Hook-wire is directed into lesion using computed tomography (A). The hook-wire is then identified during robotic-assisted thoracoscopic surgical resection (B).

(US). Real-time intraoperative CT is an option but is extremely cumbersome and limited by associated radiation exposure to the patient and operating room staff. Thoracoscopic US of the collapsed lung was popularized in 1990s and has been refined since that time (20-22). It provides visualization of metastatic as well as primary disease, but is more limited when used for ground glass opacities and subsolid nodules (23). During thoracoscopy a 10 mm ultrasound probe is introduced through a VATS port or the assistant port in an RATS approach. The probe is run over the surface of the lung to identify nodules that lie deep within the parenchyma. In comparison to palpation, Matsumoto *et al.* reported a 12% increase in the number of lesions found using US (24). In a similar comparison, Taurchini reported a 6% increase in occult nodules found with intraoperative US (25). Compared to radio-guided techniques, intraoperative US resulted in a similar number of discovered nodules but with an associated decrease in complications (26).

An additional benefit of intraoperative US is characterization of the visualized nodule which can help differentiate malignancy from benign disease (27). Unlike preoperative localization techniques, intraoperative US provides a survey of the lung parenchyma and can facilitate the discovery of occult nodules not identified on pre-operative imaging. This technique is particularly useful in the pediatric population as it does not expose the patient to an additional radiation dose (28). In adults with extensive emphysema, failure of the lung to fully collapse can limit the utility of this technique as the residual air obscures the ultrasonographic view. Furthermore, thoracoscopic US is user dependent and success depends on the skills and fastidiousness of the surgeon or bedside assistant.

Image-guided labeling

Labeling of pre-operatively imaged nodules is the most common method of localizing for metastasectomy. Fiducials or injectable solution can be placed or instilled in the target nodule percutaneously with CT-guidance or with navigational bronchoscopy (29). Methods compatible with percutaneous CT-guidance include hook wires (30-34), microcoils (34-39), fiducials (40,41), and liquid injectables including dyes [methylene blue, indigo carmine, indocyanine green (ICG)] (42-57), contrast agents (lipiodol) (58-60), and radiotracers [technetium-99m (^{99m}Tc)] (61-70) (*Figure 2*). All these techniques can be performed with navigational bronchoscopy with the exception of hook wires. A transbronchial approach may avoid complications such as pneumothorax, hemothorax, dislodgement/migration, and chest pain. Nevertheless, iatrogenic bronchial injury is still possible. The choice of which modality to use depends on the location of the nodule, preference of the surgeon, and the institutional experience. The various methods of image-guided labeling are compared below and outlined in *Table 2*.

Hook wires

Metallic wires can be used for direct site visualization. Under CT guidance, a needle is introduced into or near the pulmonary nodule of interest. A hook wire is then advanced and anchored (*Figure 2*). Hook wire localization is relatively straightforward and does not require specialized equipment such as infrared camera or fluoroscopy. Success rates range from 91–100%; however, the risk of complications is higher compared to other methods. Pneumothorax is reported in 18–68% of patients (30-34). Most patients are asymptomatic but will occasionally require aspiration or chest tube

Table 2 Image-guided labeling techniques for minimally invasive metastasectomy

Methods	Mechanism	Delivery	Compatibility	Durability	Advantages	Disadvantages	Level of evidence
Hook wire	Visualization of wire with camera	Percutaneous	VATS or RATS	Hours	No specialized equipment	Dislodgement Higher complication rate Requires same day procedure	Case series, prospective trials, and randomized controlled trials
Microcoil	Fluoroscopy	Percutaneous or navigational bronchoscopy	VATS or RATS but fluoroscopy limited with docked robot	Days	Low complication Reduced parenchymal resection Can be combined with ICG Can be staged	Requires fluoroscopy if not combined with ICG	Case series, prospective trials, and randomized controlled trials
Gold fiducial	Fluoroscopy	Percutaneous or navigational bronchoscopy	VATS or RATS but fluoroscopy limited with docked robot	Days	Low complication rate Can be staged	Requires fluoroscopy	Case series
Methylene blue	Visualization of dye with camera	Percutaneous or navigational bronchoscopy	VATS or RATS	Minutes to hours	No specialized equipment Inexpensive	Rapid diffusion Challenging to localize deeper nodules	Case series, retrospective cohort studies
Indigo carmine/ lipiodol	Fluoroscopy and visualization of dye with camera	Percutaneous or navigational bronchoscopy	VATS or RATS but fluoroscopy limited with docked robot	Hours	Visual and fluoroscopic confirmation Reduced dispersion	Requires fluoroscopy	Case series
Radiotracer (^{99m}Tc, ^{99m}Tc-MAA)	Detection of radioactivity with gamma probe	Percutaneous or navigational bronchoscopy	VATS or RATS	36 hours	Hand-held gamma probe can be used with docked robot Can be combined with dyes and other visualization techniques	User dependence Special precautions with use of radiotracer	Case series, prospective trials, retrospective cohort studies
ICG	Visualization using near infra-red camera	Percutaneous or navigational bronchoscopy	VATS or RATS	24 hours alone, several days in combination with microcoils	Can be combined with microcoils Robotic camera with built in near-infrared camera	Specialized camera Can disperse and spread	Case series, prospective studies

VATS, video-assisted thoracoscopic surgery; RATS, robotic-assisted thoracoscopic surgery; ICG, indocyanine green; ^{99m}Tc, technetium-99m; MAA, macroaggregated albumin.

placement (32,33). Other complications include hematoma, parenchymal hemorrhage, and hemothorax. Hook wire dislodgement or migration can impact wedge resection, but success can still be achieved using the puncture site as guidance (33). Ichinose *et al.* reports a case of systemic air embolism, but without sequelae and with spontaneous resolution (32).

Microcoils and fiducial markers

The use of microcoils to guide VATS excision of small nodules was piloted by Mayo *et al.* in 2009 (35). Like hook wires, the fiber-coated microcoils are deployed into the lung parenchyma in or near the nodule through a Chiba needle. When deployed it assumes a tightly coiled ball configuration to anchor it in place. VATS success rates range from 93–100% (34-39). Complications are similar to those of the hook wire technique but occur with lower frequency (34,36). Additionally, resection procedure time was found to be shorter and excised lung volume smaller for microcoils compared to hook wire (34).

Like hook wires and microcoils, percutaneous placement of gold fiducial markers can achieve successful localization for pulmonary metastasectomies. Typically, a 3-mm gold fiducial marker is delivered preoperatively under CT guidance, then identified intraoperatively using fluoroscopy. Reported success rates for this technique are at 98% (40,41). Due to the inert properties of gold and small size of the fiducial, advantages over other metallic markers include patient comfort and flexibility of time between placement and resection. Complications, however, were still reported including pneumothorax, hemoptysis, hematoma, and fiducial migration and embolization (40,41). Finally, all fiducials require use of intraoperative fluoroscopy which can be cumbersome with a docked robotic platform and increase radiation exposure.

Injectable dyes

CT-guided methylene blue dye localization for pulmonary nodules dates back several decades (42-44). The patient is positioned, then 0.3–0.5 mL methylene blue dye is delivered through a Chiba needle into the nodule under local anesthesia with CT guidance. Its distinctive blue color facilitates direct visualization by thoracoscopic vision during VATS.

Methylene blue is advantageous in its simplicity, requiring no special equipment during resection. The localization procedure is short and accurate with success rates as high as 98% (45-47). Kleedehn *et al.* reported that methylene blue is more efficacious and with less complications when compared to hook wire localization (45). The drawbacks of methylene blue are its rapid diffusion characteristics, risk for spillage, and risk for pneumothorax or hemothorax as with other percutaneous methods. Rapid dye diffusion restricts flexibility and requires same-day operation following dye localization.

Indigo carmine is another blue synthetic dye used for localization, and when coupled with lipiodol, an iodinated oil-based contrast agent, it provides both visual and imaging-based detection. Lipiodol's radiopacity allows identification by fluoroscopy. The indigo carmine-lipiodol mixture is reported to have a localization success rate of 96–100% (48,49). Complications are related to the risks associated with percutaneous injection.

Lipiodol

Although used in combination with many other agents, lipiodol by itself can be a reliable marker for pulmonary metastatic lesions. Lipiodol is a lipid-soluble contrast medium used for several contrast imaging modalities. Its use has extended to marking pulmonary nodules through fluoroscopy. Localization success rates of 97–99.9% have been reported (58-60). Its advantages are that it does not induce an inflammatory response, identifies nodule depth, and exhibits minimal diffusion. Complications are limited to those attributed to needle insertion as outlined previously, except for extremely rare cases of lipiodol embolization (58).

Radiotracer

The use of ^{99m}Tc radiotracer injection was reported by Chella *et al.* for thoracoscopic resection, with Daniel *et al.* developing a macroaggregated albumin (MAA) coupled solution that has become the standard (66,71). Preoperatively, ^{99m}Tc-labeled radiotracers are injected under CT guidance within the lesion under local anesthesia, typically MAA or colloid (62), same day or the day before. Some centers report injecting 0.1–0.3 mL of nonionic contrast medium (61-64). Intraoperatively, a handheld gamma probe is used to identify areas of increased radioactivity. The maximal radioactivity of the resected nodule can then be compared to residual radioactivity within the parenchyma to ensure compete resection of the injected region.

^{99m}Tc radiotracer has a success rate of 95–100% in localizing and resecting lesions (61-72). The marker remains localized at the site of injection up to 24–36 h after injection (53), allowing for flexibility in scheduling operations. Intraoperatively, the handheld gamma probe provides continuous reassessment of location to confirm accurate resection. This technique can be combined with injection of methylene blue to provide an additional visual guidance (72). The procedure is well-tolerated and has minimal risk of complications and morbidity; however, pneumothorax has been reported during radiolabeling (64). Spillage of radiotracer into pleural space is possible, especially if the injection site is near the pleural surface of a major fissure.

Percutaneous ICG

ICG has emerged as a fluorophore for the localization of pulmonary nodules. This near-infrared (NIR) contrast agent is characterized by its ability to emit fluorescence when exposed to specific wavelengths of light, allowing for dynamic imaging of the pulmonary vasculature and nodule localization. A thoracoscopic fluorescence camera allows for immediate detection of ICG during VATS or RATS metastasectomy. The advantages of NIR imaging are its high tissue penetration and low autofluorescence (50).

Reported localization success rates range from 88.6–100% (51-56); a systematic review and meta-analysis by Gkikas *et al.* [2022] pinned the median reported success rate of CT-guided localization at 94.3% (57). One study used percutaneous ICG as a complementary technique to CT-guided microcoil localization (51). Overall, procedural complications were minimal, with a pneumothorax incidence of 3.4% (52). Minimal diffusion of dye was observed across studies and coupling ICG with albumin further prevented dispersion from the site of injection (53).

Bronchoscopic localization

Endobronchial localization of pulmonary metastases can be achieved using conventional flexible bronchoscopy. However, it is limited by poor access to more peripheral nodules, favoring the advent of newer techniques such as electromagnetic navigation bronchoscopy (ENB), virtual-assisted lung mapping (VAL-MAP) (73), and robotic-assisted bronchoscopy (RAB). After guiding the probe to the target lesion, a number of previously described localization methods can be used, including dyes, lipiodol, and microcoils.

ENB uses the combination of three components: a planning software that converts preoperative CT scans into a virtual three-dimensional (3D) model of the airways, a steerable probe with a position sensor, and an electromagnetic board connected to a computer. This system allows visualization of probe position within the electromagnetic field, which can be used to guide bronchoscopic localization (74). ENB has been used with several marker solutions. Indigo carmine has been studied with a localization success rate of 95.8% (75). Abbas *et al.* reported a localization success rate of 98.1% with a mixture of iopamidol (a fluorophore), methylene blue, and ICG (76). ICG/iopamidol has also been used comparing ENB with CT-guided percutaneous localization with success rates of 100% and 94.3%, respectively. Its advantages over percutaneous techniques are the lower rates of complications such as pneumothorax and parenchymal hemorrhage, ability to reach lesions not easily accessible percutaneously, and improved patient comfort (77).

Sato *et al.* expanded on virtual bronchoscopic localization, wherein a 3D virtual reconstruction from thin-slice CT images is used with fluoroscopic dye injection to achieve multiple simultaneous lung markings, the basis of VAL-MAP (73). A prospective, multicenter study with 500 patients who underwent VAL-MAP with indigo carmine marking reported a localization success rate of 91% (78). Detectable marking rates was found to be higher (95.7%) in a study using ICG/indigo carmine dual staining compared to either alone (79).

RAB has emerged as a novel tool for localization of difficult-to-access nodules. Two FDA-approved commercially available systems are currently in use: the electromagnetic Monarch system and shape-sensing Ion system (80). Their use has mainly been piloted for biopsy of pulmonary nodules but has recently expanded to preoperative localization for thoracoscopic surgery. Chan *et al.* reported a localization success rate of 80% using robotic-RAB for ICG dye-marking in a cone-beam CT hybrid operating room (81), albeit with a small study size of five cases. Bawaadam *et al.* reported the use of RAB with an ICG-soaked fiducial coil, which allowed fluoroscopic visualization multiple days later, to achieve 100% localization in a series of four patients (*Figure 3*) (82). Some groups have also described the completion of RAB and RATS under a single anesthetic setting (83). As the technology evolves, patients with metastatic lung lesions can potentially benefit from robotic approaches for metastasectomies.

Systemic targeting strategies

Advancements in NIR imaging have led to the development of methods that can localize a nodule by systemically infusing molecular substances intravenously prior to

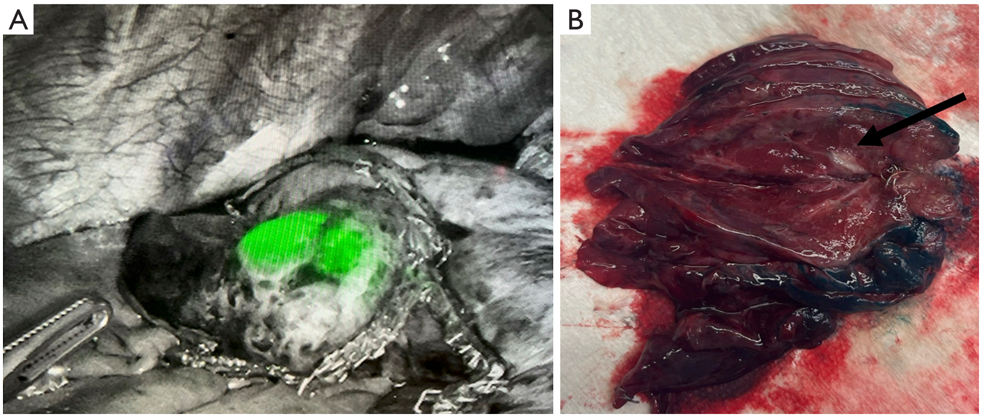

Figure 3 ICG soaked coil localization. The ICG coil can be seen under near-infrared light during robotic assisted thoracoscopic surgery (A). The coil can then be identified in the resected specimen (arrow) confirming the excision of the target metastatic lesion (B). ICG, indocyanine green.

surgery. The molecules accumulate in tumoral regions and have fluorescent tags or innate fluorescent properties that facilitate visual detection with greater ease and accuracy than white light. Inhalation of targeting agents have also been reported. Molecular marking via systemic targeting allows for intraoperative detection of malignant lesions that have been previously identified radiologically as well as radiologically occult disease.

Systemic-ICG targeting

High-dose ICG systemic infusion has been reproducibly shown to preferentially accumulate in multiple types of malignant lesions (84). A dose of 5 mg/kg with NIR imaging 24 h later has been shown to be optimal (85). The mechanism that allows ICG localization to cancer deposits is known as the enhanced permeability and retention effect (86). Increased pressure gradients and abnormally leaky capillaries in the peri-tumoral region facilitates ICG dye accumulation. NIR optical imaging built into thoracoscopes and robotic camera systems detect the fluorescence and allow for identification of known lesions as well as occult tumor deposits. There are minimal side effects and a low toxicity profile to high dose ICG infusion (84,85,87,88). ICG-infusion has been shown to be safe and effective in a pediatric population (89). The main limitation is not size of the lesion but depth from the pleural surface; a depth less than 2 cm is favorable (85,87). In addition to systemic infusion, Wang *et al.* reports ICG inhalation as a feasible and safe method for detection, successfully localizing 88% of studied pulmonary nodules (90). More cohort studies are needed to evaluate the efficacy of inhaled agents in comparison with other localization techniques.

Specific targeting molecules

Investigators have developed more specific molecules linked with fluorescent tracers that can be delivered systemically to aid in nodule detection using NIR optical cameras. Pafolacianine is a folate analogue with an ICG-like conjugate that binds to folate receptors that are present on approximately 85% of pulmonary malignancies. This molecule is infused between 1–24 h prior to surgery and exhibits mild infusion reactions and no serious adverse events (91). The advantage of this molecule is that it has less autofluorescence than ICG and a better depth of penetration for detection, although a false positive rate of 15–25% was reported in the ELUCIDATE trial (91). The molecule was shown to identify numerous tumor types including colorectal, breast, renal, melanoma, spine, ovarian, prostate, sarcomatous, and neuroendocrine histologies. Another folate receptor targeting molecule known as OTL38 demonstrated ability to optically fluoresce osteosarcoma deposits (86).

Monoclonal antibodies have been combined with NIR probes to facilitate the intraoperative identification of pulmonary nodules. Colorectal pulmonary metastatic lesions were enhanced with SMG-101, a tracer that combines a monoclonal antibody to carcinoembryonic antigen (CEA) with a NIR fluorescent tracer (92). This targeting molecule was successful at fluorescing colorectal pulmonary metastatic deposits but was similarly limited by depth of penetration. In a murine model, a HER2/NEU antibody conjugated with a fluorescing tracer was shown to accurately identify pulmonary nodules expressing HER2/NEU (93).

In an effort to increase the accuracy of identifying malignant targets, a pH-activated NIR fluorescent nanoprobe consisting of a dye IR780 conjugated with calcium phosphate has been studied (89). This compound takes advantage of the extracellular acidity common to solid tumors where the conjugate breaks down in the acidic environment enhancing differentiation between normal tissue and tumor (94).

The advancements in NIR optical technology and synthesis of fluorescing agents will likely continue to increase a surgeon's ability to visually identify metastatic and primary lung lesions without requiring an initial invasive procedure such as percutaneous or bronchoscopic labelling.

Emerging technologies

In addition to the more established techniques described above, there are emerging technologies being evaluated in animal models and early pilot studies. This includes augmented reality and navigational systems, in which pre-operative CT-scans and localization markers are used to generate a 3D projection of the lung and an associated nodule, which can be viewed on a surgeon worn headset during the resection (95). This technology has shown promise in animal models and human trial with a 70% success rate (96). It has the advantage of streamlining the localization process but its cost and benefit over existing technologies has not yet been evaluated.

The use of artificial intelligence is also being evaluated. This technology is already used in the radiologic identification of pulmonary nodules, but may soon be available for intraoperative assessment (97,98). Broadly, this technology can aid surgeons by predicting intraoperative pathology and helping ensure adequate margins (98). It has been used in neurosurgery and endocrine surgery to help identify residual malignancy and the likelihood for nodal metastasis (99-101). The introduction of artificial intelligence to thoracic surgery is likely eminent, although the exact manner in which it will be employed is uncertain.

Critical assessment of the literature

To date, there are more than a dozen described techniques for localizing pleural metastasis that have been used in conjunction with minimally invasive metastasectomy. The reported effectiveness of these techniques is generally >95%. This leads to the dilemma: what is the optimal localization technique? To answer this question, it is important to note the context of these studies. While thorough and well performed, the vast majority of studies represent case reports, small case series, and retrospective cohort studies. They are often heterogenous in nature and include primary lung cancer, metastatic disease, and indeterminate ground glass opacities. Despite the best intentions of the authors there is undoubtedly an element of selection bias. Metanalysis has been performed for more established techniques like hook-wire, microcoil, and lipiodol injection as well as ICG localization, but it remains difficult to compare between these varied approaches (7,57). There are randomized trials evaluating individual techniques against standard light detection, but robust studies comparing disparate methods are lacking. A further concern is cost with little data to help guide the surgeon or hospital administration.

Given these limitations, the choice of localization remains at the discretion of the surgeon and their institutional practice. As with many surgical techniques, surgeon comfort/familiarity with a particular procedure may be the greatest driver of success. The authors favor use of radiotracer as it is easy to adapt to both a RATS or VATS approach. Alternatively, if the approach is solely RATS then ICG soaked microcoils can be extremely effective and may be performed as a single or staged procedure (82). Given the growing acceptance of systemic techniques, head-to-head trials including cost analysis will be of particular value.

Conclusions

The decision to proceed with minimally invasive pulmonary metastasectomy should be based on a patient's individual risk factors, likelihood of successful local control, absence of other sites of systemic disease, and tumor biology. Minimally invasive pulmonary metastasectomy in conjunction with localization procedures is associated with a >95% success rate. The choice of localization technique is at the discretion of the surgeon and their institutional practice. Understanding the advantages and disadvantages of different methods can help guide the thoracic surgeon towards better patient outcomes based on the available resources. Direct comparison of systemic targeting and traditional image-guided labeling through randomized trials is needed to determine the optimal modality.

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Footnote

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