



Placement of markers to assist minimally invasive resection of peripheral lung lesions

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Contributions: (I) Conception and design: All authors; (II) Administrative support: K Harris, L DeLorenzo; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: With development of lung cancer screening programs and increased utilization of radiographic imaging there is significantly higher detection of smaller lung nodules and subsolid lesions. These nodules could be malignant and pose a diagnostic challenge. Video-assisted thoracoscopic surgery and robotic-assisted thoracoscopic surgery (RATS) represent minimally invasive methods for tissue sampling. Intraoperative identification of these lesions maybe difficult, requiring marking prior to surgery. We review different techniques for the placement of markers to assist in the resection of peripheral lung lesions (PLL).

Keywords: Peripheral lung lesions (PLL); bronchoscopy; markers; tattoo

Submitted Mar 18, 2019. Accepted for publication Mar 20, 2019.

doi: 10.21037/atm.2019.03.50

View this article at: <http://dx.doi.org/10.21037/atm.2019.03.50>

Introduction

Pulmonary nodules are well-circumscribed lesions that are surrounded by pulmonary parenchyma and measure <3 cm. These nodules can be solitary or multiple, solid or subsolid (1,2), and more importantly, have the potential of being malignant. The incidence of pulmonary nodules in the United States has been reported to be 1.5 million and is expected to rise with current screening guidelines and advances in imaging technology (3).

Peripheral lung lesions (PLLs) are lung nodules located in the periphery of the lung and are typically difficult to biopsy. Their incidence in the general population has not been described, but they also have malignant potential.

Current guidelines for solid nodules recommend tissue sampling for single indeterminate lesions that are ≥ 8 mm in some low and high-risk patients, and in those patients

in which there is evidence of nodule growth during the recommended follow up period (4). The American College of Chest Physicians (ACCP) recommend surgical lung biopsy for indeterminate nodules that are >8 mm in diameter, have a high probability of malignancy, are hypermetabolic or positive by functional imaging tests, when a non-surgical biopsy is suspicious for malignancy, or when a fully informed patient prefers a definitive diagnostic procedure (5). Surgical biopsy is also recommended as an option for part solid (>50% ground glass) nodules that are >0.8 cm in diameter that persist 3 months after an initial CT scan and those part solid nodules that are >1.5 cm in diameter (5).

Tissue sampling techniques include CT guided needle aspiration, bronchoscopy with transbronchial biopsy, either by conventional fluoroscopy or guided with electromagnetic navigation bronchoscopy (ENB), radial endobronchial

ultrasound (EBUS), or a combination of these. Surgical lung biopsy is the gold standard for the diagnosis and treatment of PLLs.

Minimally invasive thoracic surgery (MITS) is the preferred approach for surgical resection of PLLs. MITS includes video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracoscopic surgery (RATS). Compared to open thoracotomy for surgical resection of PLLs, MITS has lower complication and mortality rates and is associated with less pain and a decrease in length of stay (6-8). RATS may have better outcomes than VATS but at a higher cost and operative time. This debate is an active area of investigation, with some evidence suggesting that there is no difference between VATS and RATS lobectomy and wedge resection (8-11).

Lung cancer continues to be the leading cause of cancer deaths, and the second most diagnosed cancer in the US. The use of low-dose chest CT scans for lung cancer screening has led to the detection of more PLL (12). Many of these lesions will undergo surgical resection for diagnosis and cure of early-stage lung cancers. Small PLL and those that are ground glass or semisolid or lesions that are not close to the visceral pleura may represent a challenge during VATS or RATS. Ground glass lesions or those not near the visceral pleura maybe difficult to locate (12). Various modalities have been developed to facilitate PLL identification during MITS by marking PLL.

We searched the Cochrane library and PubMed from 1990 to 2019 to obtain a comprehensive review of the different methods of placement of markers and tattoos for PLL. We used the following search criteria: Lung nodule, peripheral lung lesion, preoperative marking, thoracoscopic surgery, fiducial, dye, transthoracic, bronchoscopy, Virtual bronchoscopy, electromagnetic bronchoscopy.

Percutaneous placement of markers

Percutaneous techniques for the placement of lung markers for PLLs have proven to be effective and relatively safe (13). They are mostly performed under CT guidance. Local anesthesia and moderate sedation are frequently necessary for patient comfort and accuracy of marker placement.

Table 1 describes the profile for the most common percutaneous methods while *Table 2* summarizes some of the landmark studies for each.

Percutaneous fiducials and microcoils placement

Fiducial markers are small metal spheres (typically gold), that can be placed in or near PLLs and can be localized intraoperatively under fluoroscopy. The technique of fiducial marker placement is similar to that of image-guided percutaneous biopsy (14) with a success rate of 95–98% (14,15). Microcoils for pleural marking consist of placing a coil with the distal end adjacent to the nodule and the proximal end coiled in the pleural space. This technique assumes that the surgeon will resect the tumor and coil together.

General complications of the percutaneous marker placement techniques include pneumothorax and hemothorax. Specific complications of fiducial markers are low, and the procedure is generally well tolerated (15). Fiducial embolization, migration, and parenchymal hematoma have been reported (14,15,28). One strategy to lower the rate of pleural migration is to deploy the marker into the parenchyma through longer path and not through the closest path to the pleura (15).

Microcoils are usually platinum-based and can be placed in or near the lesion of interest and then identified by fluoroscopy. Like fiducials, they differ from hookwires, in that there is no thread left protruding outside the skin, making fluoroscopy necessary for their identification during MITS. Finley *et al.*, prospectively randomized 60 patients with lung nodules (≤ 15 mm) to either microcoil localization (29 patients) or no localization (27 patients). Four patients did not undergo surgery. The coil group had a higher rate of successful diagnosis with VATS than wedge resection alone (27/29 *vs.* 13/27; $P < 0.001$), decreased operative time to nodule excision (37 \pm 39 *vs.* 100 \pm 67 minutes; $P < 0.001$), and reduced stapler firings (3.7 \pm 2.0 *vs.* 5.9 \pm 3.1; $P = 0.003$) with no difference in total cost [\$4,903 \pm 2,518 (median, \$3,930; range, \$2,366–11,952) *vs.* \$5,803 \pm 2,615 (median, \$5,363; range, \$1,975–11,282)]. Four patients in the microcoil group had a pneumothorax as a complication, but none of them required chest tube placement (16).

Percutaneous placement of methylene blue (MB)

PLL localization by MB is a safe and inexpensive procedure compared to other modalities. The technical aspects and the equipment needed for the procedure are similar to those of CT-guided needle aspiration (17,28). The closest distance

Table 1 The most common percutaneous modalities for placement of markers for peripheral lung lesions

Localization modality	Advantages	Disadvantages	Specific complications*
Fiducial and microcoils	Well tolerated by patients; easily placed by radiologists; greater flexibility with time and approach to surgery	Radiation exposure	Embolization; migration; parenchymal hematoma
Methylene blue/PBV [†]	Similar to CT-guided biopsy technical components and equipment with no additional cost; no foreign body is left in the lung, doesn't affect histopathology; well tolerated by patients	Dye might diffuse to the surrounding parenchyma; immediate surgery is required; less reliable in cases of extensive anthracotic pigmentation	Anaphylaxis (rare)
Hookwires	High success rate (98–100%)	Hookwire dislodgement; patient discomfort; immediate surgery is required	Pneumothorax; parenchymal hemorrhage; subcutaneous emphysema; air embolism (rare)
Barium	Well tolerated by patients; stable and doesn't diffuse into the lung parenchyma easily; flexible time between localization and surgery; easily recognized intraoperatively (palpation, visualization, fluoroscopy)	Barium causes inflammation and can affect the quality of the sample, hence it is advised not to inject directly into the nodule; radiation exposure	Lung inflammation and pneumonia (when used in large doses)
Radiotracer (Tc99m)	Flexible time between localization and surgery; well tolerated by patients	Facility-dependent and requires special equipment (radiotracer, gamma probe, and radiation protection equipment); radiation exposure	Non-specific: pneumothorax, hemothorax, and parenchymal hemorrhage
Lipiodol	Well tolerated by patients; stable and can last for months; well demarcation of the lesion hence prevents over-resection of normal lung parenchyma; doesn't affect histopathology	Radiation exposure	Systemic embolization (lipiodol is insoluble in water)

[†], PBV: patent blue V; *, complications related to the CT-guided needle introduction is applied to all modalities (i.e., pneumothorax, hemothorax, etc.).

between the chest wall and the nodule is identified and the dye is injected into or around the margins of the nodule and along the needle tract (lung, pleura and chest wall) during the withdrawal of the needle (18). Patients tolerate the procedure well as there is no foreign body left inside the lung parenchyma (17). Thoracoscopic identification rate of the nodule is 90–100% (17,18).

An important disadvantage of MB marking is diffusion of the dye into the surrounding lung parenchyma preventing precise identification of PLLs (17,18,22). Thoracoscopy should therefore begin soon after the localization procedure, ideally within 120–150 minutes (18). To prevent rapid diffusion, modified approaches have been described such as MB-stained autologous blood (29) and MB mixed with contrast and collagen (30).

An additional limitation of MB marking may occur when anthracotic pigmentation of the lung parenchyma is present.

In these cases the dye may not be distinguishable from the surrounding lung during thoracoscopy (17). Anaphylaxis induced by MB has been reported but is extremely rare (31).

Percutaneous placement of hookwire

Hookwire placement is the oldest and the most common method used for PLL localization (22). The wire is introduced and deployed percutaneously and a thread is left outside the chest wall. The surgeon follows this tract in order to reach the lesion. Given the risk of pneumothorax, wire dislodgment, as well as patient discomfort and pain, the wire placement is usually performed right before the planned surgery. Some authors reported successful experience with leaving the wire in place for longer periods (20). The presence of interstitial lung disease is associated with increased risk of wire dislodgement (13,23).

Table 2 Summary of landmarks studies in percutaneous localization of peripheral lung lesions

Study/year	Modality used	Patients/nodules	GGO nodules (%)	Nodule size [range], mm	Nodule depth [range], mm	Duration of localization procedure [range], minutes	Time between localization and surgery [range]	Operative time [range], minutes*	Success rate [†] (%)	Malignant nodules (%)	Complications
Sancheti et al. (14)/2014	Fiducial markers	58/65	NA	9.9 [3–24]	18.7 [2–35]	NA	NA	58.7 [30–120]	98	79	Pneumothorax 5%, intervention for pneumothorax 0%, pleural migration 2%, parenchymal hemorrhage 2%, fiducial embolization 2%
Sharma et al. (15)/2017	Fiducial markers	19/20	45	11 [6–19]	9 [1–32]	NA	7 [1–123] days	NA	95	85	Pneumothorax 25%, parenchymal hemorrhage 10%
Finley et al. (16)/2015	Microcoil	60/29 [†]	NA	12.7±4	22.5±10.3	29±9	NA	37±39	93	75	Pneumothorax 14%, intervention for pneumothorax 0%
Lenglinger et al. (17)/1994	Methylene blue	15/15	NA	16 [8–33]	10 [0–21]	32 [18–47]	120 minutes	NA	100	33	Pneumothorax 33%, intervention for pneumothorax 0%, parenchymal hemorrhage 20%
Vandoni et al. (18)/1998	Methylene blue	51/54	NA	NA	18 [12–45]	NA	162 [75–270] minutes	51 [30–150]	92	59	Pneumothorax 25%, intervention for pneumothorax 2.1%
Tseng et al. (19)/2016	Patent blue V (PBV) dye	100/217	46	8 [3–22]	7 [0–39]	50±20	NA	134±73	99	70	Pneumothorax 40%, intervention for pneumothorax 0%, parenchymal hematoma 24%, anaphylaxis 1%
Ichinose et al. (20)/2013	Hookwire	417/500	36	GGO 11.8±5.3, solid 9.1±4.6	GGO: 9.9±7.8, solid: 13.9±11	14 [9–19]	27 [5–138] hours	NA	100	78	Pneumothorax 68%, intervention for pneumothorax 4.6%, parenchymal hematoma 10%, air embolism 0.24%, dislodgment 0.4%

Table 2 (continued)

Table 2 (continued)

Study/year	Modality used	Patients/nodules	GGO nodules (%)	Nodule size [range], mm	Nodule depth [range], mm	Duration of localization procedure [range], minutes	Time between localization and surgery [range]	Operative time [range], minutes*	Success rate [†] (%)	Malignant nodules (%)	Complications
Hanauer et al. (21)/2016	Hookwire	181/187	4	10.3 [9–29]	11.6 [0–45]	NA	224 [54–622] minutes	60 [18–135]	98	59	Pneumothorax 39%, intervention for pneumothorax 2.1%, parenchymal hematoma 5.9%, dislodgment 3.7%
Li et al. (22)/2018	Hookwire	86/86	29	14 [6–22]	7.3 [2–19]	19 [10–30]	NA	49 [28–89]	100	90	Pneumothorax 24%, intervention for pneumothorax 0%, parenchymal hematoma 21%
Kang et al. (23)/2011	Hookwire and lipiodol	32/36	25	7.5 [3–17]	7.3 [0–35]	13 [7–23]	NA	34.4 [18–75]	100	42	Pneumothorax 25%, intervention for pneumothorax NA, parenchymal hematoma 8%, dislodgment 3%
Brady et al. (24)/2018	Hookwire and methylene blue	74/75	20	14.6 [6–39]	23.2±13.4	NA	NA	NA	86	70	Pneumothorax 13%, intervention for pneumothorax 1%, parenchymal hematoma 41%, dislodgment 9%
Lee et al. (25)/2012	Barium	10/10	60	7.6 [3–14]	8.4 [0–23]	25.6 [15–48]	13.2 [2–24] minutes	NA	100	60	Pneumothorax 20%, intervention for pneumothorax 10%
Watanabe et al. (26)/2006	Lipiodol	150/174	26	10 [2–30]	10 [0–30]	NA	1.7 [1–7] day	NA	100	61	Pneumothorax 17%, intervention for pneumothorax 6%, hemoptysis 6%, chest pain 11%, hemopneumothorax 0.6%
Chella et al. (27)/2000	Tc99m	39/39	NA	8.3 [4–19]	13 [6–30]	NA	130 [60–190]	50 [20–100]	100	46	Pneumothorax 16%, intervention for pneumothorax 0%

[†], 27 patients (control group) had no localization modality, 4 patients didn't undergo surgery; ^{*}, defined as ability to identify the target lesion intraoperatively; ^{*}, range or ± standard deviation (SD); NA, data not available; GGO, ground-glass opacity.

Pneumothorax risk is high (24–68%) but when it occurs, it is usually asymptomatic and only 0–4.6% requires an intervention (20–22). Factors that increase the risk of pneumothorax include the presence of emphysema, localization of several targets, and a smoking index greater than 400 (20,22). Parenchymal hematoma is another common complication (5.9–21%) and this risk is increased in lesions deeper than 25 mm (20).

Kleedehn *et al.* compared preoperative transthoracic hookwire with MB marking for PLLs. One hundred and two patients underwent 109 localization procedures: 52 hookwire insertions and 57 MB injections. Localization success was 98% and 100%, respectively. There was however, a trend toward more frequent and severe complications in the hookwire insertion group: pneumothorax (38% *vs.* 25%) and perilesional hemorrhage (12% *vs.* 4%). Hookwire dislodgement occurred in 7 out of 52 patients (13%) without affecting the localization rate, as the nodules were localized through visualization of the parenchymal puncture sites. There was one death secondary to systemic air embolism (32).

Combined percutaneous modalities for placement of markers

Although most institutions use a single modality for PLL localization, some authors reported using combined methods to overcome the shortcoming of using one single method (23,24). Kang *et al.* reported a success rate of 100% by combining hookwire and lipiodol marking without significant increases in procedure time or complications (23). Brady *et al.* combined hookwire and CT-guided MB techniques and reported that MB was helpful in identifying the lesion intraoperatively when wire dislodgment occurred (24).

Hookwire and Tc-99m (33), Tc-99m and MB (34), and hookwire and navigational bronchoscopic-guided MB injection (35) are other combined methods described in the literature.

Bronchoscopic placement of markers to assist resection of peripheral lung lesions

With the emergence of virtual bronchoscopy (VB), electromagnetic navigational bronchoscopy (ENB) and other bronchoscopic modalities such as radial EBUS, the placement of marking and tattooing of the PPLs has been

gaining popularity worldwide. Bronchoscopic placement of markers using devices such as fiducials, and dye agents (tattoos) have been used to facilitate wedge resection of PPLs. *Table 3* summarizes studies using bronchoscopic placement of markers prior to MITS.

Virtual bronchoscopy is a modality that utilizes helical CT scan images and computer software to reconstruct a 3D simulation of the tracheobronchial tree. This can be manipulated in 3D space, allowing the user to navigate the airways and obtain a real-time bronchoscopic perspective (51). With this development and the aid of ultra-thin video bronchoscopes, the technical difficulties of transbronchial marking of PPLs have been ameliorated. The development of ENB has broadened the opportunity for new diagnostic and therapeutic modalities. ENB uses an electromagnetic tracking system and a position sensor during bronchoscopy to guide navigation through the bronchial tree. The information obtained is combined with previously acquired CT images to create 3-D virtual images and a real-time navigation “route” leading to the lesion of interest, making sampling and/or marking of peripheral lung lesions possible (52–55). An important advantage is that it can be performed during the same operative session as the thoracic surgery. The inefficiency of transporting the patient from one place to another, coordinating different teams and the operating room and repeated exposures to anesthetics or sedatives can also be avoided.

Bronchoscopic placement of barium

Early methods of marking using bronchoscopic assistance for thoracic surgery were somewhat laborious and time consuming. Barium has been used with a good success rate for localization. It remains in place for a prolonged period of time, allowing for safe resections, even days after the localization of PLLs (36,37,39).

In 1997, Kobayashi *et al.* developed CT-guided bronchoscopic barium marking for patients undergoing fluoroscopy-assisted thoracoscopic surgery (36). In 2001 Okumura *et al.* reported the results of marking 21 lesions in 20 patients using the same method (37). Under local anesthesia with 4% lidocaine, thin video-bronchoscopes were orally inserted followed by tracheobronchial examination. A transbronchial aspiration cytology (TBAC) needle was inserted and directed to the lesion of interest using fluoroscopic guidance. With the needle in position, the patient was transferred to the CT scanner

Table 3 Summary of landmark studies using endobronchial modalities for the localization of peripheral lung lesions

Study/year	Modality	Patients/ nodules	Nodule size mm [range]	Nodule depth mm [range]	Marking time min [range]	Time between localization and surgery [range]	Operative (thoracoscopy) time minutes	Success rate (%)	Malignant nodules	Complications	Comments
Kobayashi <i>et al.</i> , 1997 (36)	CT-guided bronchoscopic barium marking with fluoroscopy	1/1	11	N/A	25	7 days	N/A	100	1	None	First transbronchial barium injection
Okumura <i>et al.</i> , 2001 (37)	CT-guided bronchoscopic barium marking	20/21	N/A	6.5 (mean) [6–18]	30 (mean) [15–60]	30 (mean) [1–12] min	N/A	100	15	None	One mini- thoracotomy
Sakamoto <i>et al.</i> , 2001 (38)	Bronchoscopic dye injection (IC) with CT fluoroscopy	6/6	11 (mean) [5–15]	N/A	30 (mean)	1–3 days	N/A	100	N/A	None	First transbronchial dye use
Asano <i>et al.</i> , 2004 (39)	VB, UTB, barium injection, CT	23/31	7 (median) [5–10]	7 (median) [1–20]	23.5 (median) [8.3–49.9]	9 (median) [1–22] days	N/A	100	17	None	Suggested that CT scan confirmation was unnecessary N/A
Endo <i>et al.</i> , 2004 (40)	CT-fluoroscopy bronchoscopic dye (IC) injection	17/17	9.8 (mean) [5–17]	14.8 (mean) [0–30]	35 (mean) [25–45]	Performed on the day before surgery in 94% of patients	N/A	100	15	None	N/A
Miyoshi <i>et al.</i> , 2006 (41)	CT guided, VB, bronchoscopic metallic coil marking	9/11	10 (mean) [5–17]	8.5 (mean) [0–15]	32 (mean) [15–60]	7 (mean) [1–30] days	58 [25–95]	100	10	None	One mini- thoracotomy. Expensive coil
Krimsky <i>et al.</i> , 2014 (42)	ENB bronchoscopic pleural dye injection (IC or MB)	21/21	13.4 (mean) [7–29]	N/A	N/A	Same day but not done in the OR setting	N/A	87	13	None	Diffuse staining in 1 patient and no dye identified in 3 patients
Bolton <i>et al.</i> , 2014 (43)	ENB bronchoscopic pleural dye injection (MB)	19/19	18 (mean) [8–40]	N/A	28 (median) [17–40]	Intraoperative localization	N/A	100	15	None	Performed localization at the same surgical setting. Retrospective
Anayama <i>et al.</i> , 2015 (44)	ENB bronchoscopic dye (ICG) plus iopamidol, infrared fluorescence	Animal model	N/A	N/A	N/A	N/A	N/A	100	N/A	None	Developed an animal model for the use of ENB and ICG for preoperative localization of PLLs

Table 3 (continued)

Table 3 (continued)

Study/year	Modality	Patients/ nodules	Nodule size mm [range]	Nodule depth mm [range]	Marking time min [range]	Time between localization and surgery [range]	Operative (thoracoscopy) time minutes	Success rate (%)	Malignant nodules	Complications	Comments
Awais et al., 2016 (45)	ENB bronchoscopic dye injection (MB)	29/33	10 (median) [4–27]	13 (median) [3–44]	9.7 (mean)	Intraoperative localization	N/A	100	19	None	Retrospective
Tay et al., 2016 (46)	ENB bronchoscopic pleural dye injection (IC or MB) with fluoroscopy	6/6	21.2 (mean) [15–25]	2.2 (mean) [0–10]	N/A	Performed 24 hours prior to VATS	N/A	100	6	None	Small sample with big lesions. Radial EBUS was used in some lesions
Marino et al., 2016 (47)	ENB bronchoscopic dye injection (MB)	70/72	8 (median) [4–17]	6 (median) [1–19]	N/A	Intraoperative localization	N/A	97.2	58	None	Retrospective Extravasation of methylene blue (×2)
Abbas et al., 2017 (48)	ENB bronchoscopic pleural dye injection (MB and/or ICG)	51/54	13.3 (mean) [4–44]	22 (mean) [4–38]	29.1 [12–45]	Intraoperative localization	212 [140–290]	98.1	43	None	Retrospective
Munoz- Largacha et al., 2017 (49)	ENB bronchoscopic pleural dye injection (MB) with fluoroscopic confirmation	17/19	9 (mean) [4–32]	9.5 (mean) [1–40]	N/A	Intraoperative localization	N/A	79	15	None	Dye not visualized in 2 cases and extravasation into pleural space. Retrospective. No significant difference in identification of solid or GGO PLLs
Ng et al., 2019 (50)	ENB triple contrast dye marking (iohexol, MB, ICG)	6/6	[2–12]	N/A	N/A	Intraoperative localization	N/A	100	N/A	None	Case reports. Explains the process of triple dye marking

CT, computed tomography; EBUS, endobronchial ultrasound; IC, indigo carmine; ICG, indocyanine green; ENB, electromagnetic navigational bronchoscopy; MB, methylene blue; VB, virtual bronchoscopy.

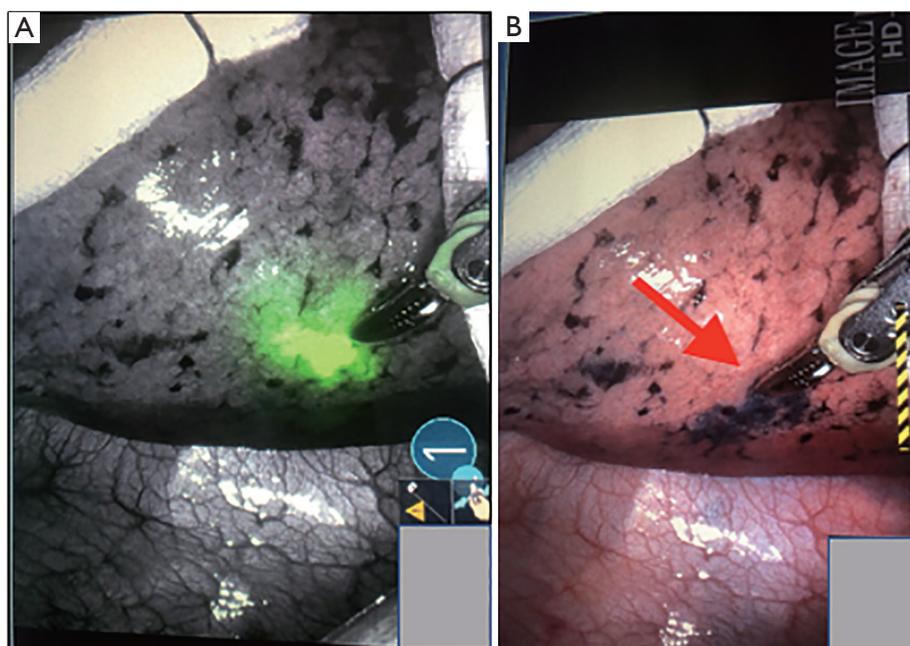


Figure 1 Robotic assisted thoracoscopic surgery: methylene blue and ICG dyes were used to place a tattoo using electromagnetic navigational bronchoscopy. (A) ICG tattoo; (B) the methylene blue tattoo was difficult to identify (arrow) due to visceral anthracosis. ICG, indocyanine green.

to confirm its location and correlation with the lesion. If the needle was correctly located, 0.1 to 1.0 mL of 50% to 100% w/v barium sulfate was infused and then confirmed under fluoroscopy. The mean procedure time for the CT-guided bronchoscopic marking was 30 minutes. VATS resection, under general anesthesia, followed between 1–12 days of the barium injection with a mean operative time of 78 minutes. This method was found to be effective and reliable (100% identification rate) without the complications derived from the transcutaneous route, such as hematomas and pneumothorax. Nonetheless, it was technically difficult.

Limitations include the increased radiation exposure from using CT and fluoroscopy, transporting patients to different settings and the need for coordination between radiology, anesthesia, the operating room, as well as pulmonary physicians and surgeons. It has been stated that barium injection can induce a mild acute inflammatory reaction within hours followed by bronchopneumonia, and eventually granulomatous inflammation, which may confound the pathologic examination (56). At the same time, given the small amount of injected Barium, these complications are unlikely to occur (25).

Bronchoscopic placement of tattoos using dye agents

Indigo carmine (IC), MB and indocyanine green (ICG) have been used to mark PLLs before VATS or RATS (Figure 1). They are safe and effective and can be injected in a similar fashion (38,40,42). IC can be seen up to 3 days of injection (38), whereas MB diffuses within hours into the tissues (42). Therefore, the selection of the dye depends on the time between the localization procedure, and the surgical resection. If the localization is done immediately before resection, then, both can be used without affecting the outcomes. ICG has also been used for identification of other cancers and evaluation of lymph nodes. It can be visualized using near infrared (NIR) technology (36,39,54) in those cases where damaged lungs, anthracosis or hemorrhage make it difficult for the targeted tissue to be differentiated using MB (Figure 1B) (44,50,57).

Sakamoto *et al.* developed a bronchoscopic dye injection technique for the localization of small pulmonary nodules prior to VATS. Six patients were included with a total of six lesions, and a mean size of 11 mm. The subsegment containing the nodule was located using a high-resolution

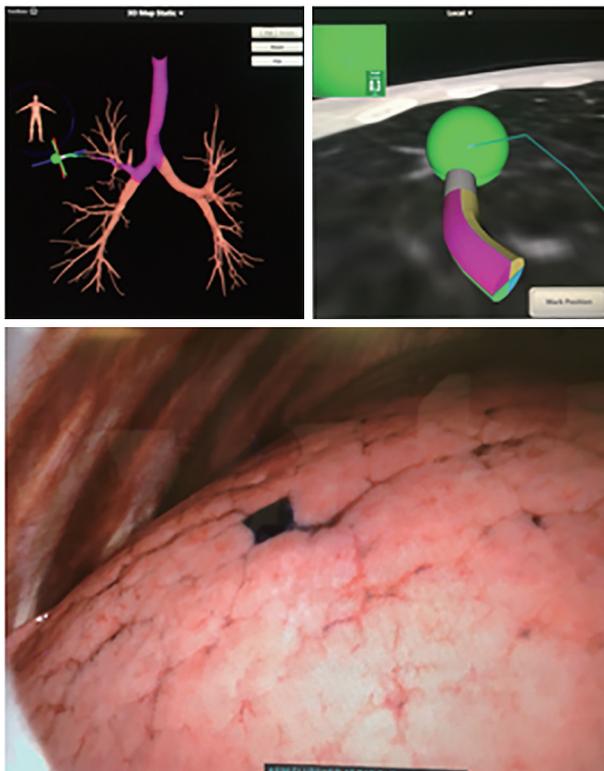


Figure 2 Tattoo placement to localize a right upper lobe nodule: the upper panels showed the electromagnetic navigational bronchoscopy planning. The lower panel shows the methylene blue tattoo during robotic assisted thoracoscopic surgery.

CT. A bronchoscope was then inserted into the related subsegmental bronchus and a teflon sheath was advanced through the bronchiole beyond the tumor to the visceral pleura using CT fluoroscopy guidance. When the catheter approached the visceral pleura 0.5 mL of IC was injected. A CT was then performed to confirm the location of the injected site, which appeared as an obscure mass. The average injection time was 30 minutes and the time between the IC injection and VATS was 1–3 days. The mean operative time for VATS was not reported. None of the procedures were converted to open thoracotomy and there were no complications reported (38).

The first ENB guided intraoperative dye injection method for marking PPLs was reported by Bolton *et al.* They retrospectively evaluated the safety and effectiveness of ENB alone as a localization strategy for pulmonary nodules. A total of 19 patients and 19 lesions underwent ENB (SuperDimension, Minneapolis, MN, USA) localization of PPLs prior to RATS (da Vinci robotic

resection) in the same operative setting. All patients received general anesthesia and ENB was performed to localize the lesion. In some instances, transbronchial needle biopsies were obtained. Once the lesion was localized, 0.5–1.0 mL of MB was injected. The catheter was then guided to the pleural surface where 0.5–1.0 mL was injected in each of two separate locations. The bronchoscope was then removed and RATS was performed. The mean nodule size was 18 mm (range: 8–40 mm) with a median marking time of 28 minutes. All lesions were identified and there were no adverse effects associated with the placement of dye for localization. No conversions to VATS or thoracotomy occurred.

Marino *et al.* retrospectively reviewed a total of 70 patients and 72 lesions who underwent ENB immediately followed by VATS between 2011 and 2014. Patients underwent general anesthesia and the nodules were localized using the SuperDimension navigation system. After nodule localization with ENB, the electromagnetic guide was removed and an ECW was left in place. A bronchoscopic needle was deployed with fluoroscopic guidance and used to inject 0.5 mL of MB into the nodule. If the nodule was >5 mm from the pleura surface, an additional injection of 0.5 mL was used to mark the pleural surface. The needle and the bronchoscope were removed and VATS resection was performed. The median nodule size was 8 mm and the median distance to the pleural surface was 6 mm. The mean time of the bronchoscopic marking was 28 minutes. The success rate was 97.2% with only 2 nodules not marked successfully.

ENB and endobronchial injection of dye (MB, IC, ICG) have proven to be an effective method of localization, and studies have shown the ability to identify smaller lesions, with mean localization times as low as 9.7 minutes (45). The technique is safe and effective and has the advantage of being performed in the same setting with surgical resection of PLLs (28) (Figure 2). The success rate has been reported to be between 79–100% (38,40,42,44–50). It should be noted however, that all of these studies have been retrospective, most of them have been small, and some (with a 100% success rate) were done on patients that had a high risk for malignancy. ENB-guided dye marking can, on rare occasions, be limited by dispersion of dye into the pleural space. This may occur if the needle penetrates the visceral pleura. There were no complications reported with any of the dyes used.

Combinations of dyes have been used to facilitate localization. MB and ICG were combined with iohexol,

a radiopaque material, to facilitate the localization with fluoroscopy. The addition of this marker is useful if MB is not localized, it disperses or if ICG cannot be located under NIR (44,50).

In 2015, Anayama *et al.* described an animal model of localization of pulmonary nodules using ENB and a near-infrared fluorescence thoracoscope. Under general anesthesia, ICG was injected into the lung parenchyma of live porcine by transthoracic approach. After euthanasia, the geographic distribution of ICG was examined. In the same study, ENB guided ICG injection and intraoperative localization was performed. A sub centimeter pulmonary nodule was created as the objective “pulmonary nodule” by injecting 0.3 mL of 5% agar containing iopamidol into the lung parenchyma of live porcine. ENB with the cylindrical sensor (5 mm long, 0.8 mm diameter) (Aurora, Northern Digital, Waterloo, Ontario, Canada) was then used to localize the nodule and 0.1 mL of a mixture of ICG and iopamidol was injected using an Olympus transbronchial needle. The position of the injected ICG was confirmed with CT scan and was followed by VATS 6 hours later. It was found that the transbronchial application of ICG fluorescence dye can be used to localize small sized pulmonary nodules during MITS (44).

Tay *et al.* reviewed a retrospective cohort of consecutive patients undergoing ENB-guided pleural tattoo followed by VATS wedge resection of PPLS. Six patients underwent ENB and tattoo placement with a 25 G needle passed through an EWC under fluoroscopic guidance. When the needle was in position, 1 mL of IC was injected in 5 out of six patients and 1mL of MB was injected in one patient. The marking procedure was performed 1 day before VATS and all lesions were identified. An important feature of this study showed that the use of a radial probe EBUS was used to localize the lesions was possible (46).

Abbas *et al.* described a retrospective study on 51 patients and 54 nodules. Patients under general anesthesia, underwent ENB (SuperDimension) for localization. A needle was inserted through the extended working channel (EWC) and fluoroscopy was used to confirm its location. One mL of a marker solution was injected into the nodule. If the nodule was deeper than 20 mm from the pleura, a second injection of 0.5 mL was injected close to the overlying pleura. MB was used with fiducials for the first 2 patients. No added benefit from the fiducials was identified and the next 19 patients received only MB. Since MB tended to diffuse into the surrounding lung parenchyma and the added ability to monitor the injection under fluoroscopy,

the marking solution was switched to 1–2 mL of a mixture of Isovue, MB and ICG injected bronchoscopically into or adjacent to the nodule. Most patients underwent RATS but only two had VATS resection of the PLLs, all immediately after the marking procedure. The tattooing mean time was 29.1 minutes and the mean operative time after marking was 212 minutes. The dye was visible in 100% of nodules with a localization success rate of 98.1%. No adverse events were identified (48).

Bronchoscopic placement of coils

Intrabronchial coil marker placement is a modality that was found to be effective when performed in combination with virtual bronchoscopy, flexible bronchoscopy and the subsequent CT confirmation of coil position. Miyoshi *et al.* prospectively evaluated 9 patients with 11 lesions. All patients had a CT chest performed and the images were transferred to a workstation (Alatoview, Toshiba, or Virtual Place Worksite) Reconstructed VB images were generated to one sixth generation bronchi. The VB images were used to simulate the branches of the bronchus leading to the lesions. Thin video bronchoscopes were orally inserted under local anesthesia. A transbronchial coil-feeding catheter (Boston scientific) was inserted in the bronchus and fluoroscopically guided to the lesion site. At this point a high-resolution scan was performed to assess the location. When the tip of the coil-feeding catheter had reached the lesion, a fibered platinum coil (Boston scientific) was instilled into the bronchus with CT fluoroscopic guidance. Coils used were similar to coils used for blood vessel embolism. Lung resections via VATS, as late as 30 days after the localization procedure were performed. The mean localization procedure time was 32 minutes There were no complications related to the localization procedure which had a success rate of 100% (41). Since resections can occur several days after the PLLs are marked, coordinating with the OR is more efficient. Drawbacks include the high cost of the coil, the need to transport the patient to different settings, and the higher radiation exposure when compared to some of the other bronchoscopic techniques.

Bronchoscopic placement of fiducials

Fiducial markers have been successfully used to guide stereotactic body radiotherapy. They can be placed percutaneously or with ENB (58-60). Belanger *et al.* performed a retrospective review of ENB cases between

June 2015 and April 2017. All patients were considered for biopsy and possible fiducial marker placement. The procedures were performed under general anesthesia with endotracheal intubation or laryngeal mask airway. Airway inspection and EBUS-guided evaluation of mediastinal and hilar lymph nodes with transbronchial needle aspiration, when indicated, was performed. In cases without an established diagnosis, ENB (SPiNDrive, Veran Medical, Saint Louis, MO, USA) was subsequently performed with ENB-guided tip-tracked TBNA biopsies. If the rapid onsite evaluation of the biopsies was inconclusive then Electromagnetic-guided transthoracic needle aspiration (EMTTNA) was done. After the biopsies were obtained, fiducial marker placement was done with a tracked brush, in which the fiducial marker was loaded and then guided to the lesion or next to it and inserting it into the lung parenchyma. The fiducial markers used bronchoscopically were 0.8 mm × 3.5 mm gold seed with an attached 4 mm nitinol wire. For EMTTNA a 0.5 mm × 5 mm linear gold wire was used. Fiducial marker placement was done in 65 patients with a total of 133 markers placed. ENB was used for 131 markers and EMTTNA for only 2 of them. Migration of the marker was noted in 1 case but 2 other markers remained intact in the patient, allowing for the performance of SBRT. There were no complications related to the fiducial marker placement. In the same study, ENB was successful for PLLs biopsy with a diagnostic yield of 78% and when combined with transthoracic needle aspiration the yield increased to 87% (58). Bolton *et al.* reported lower rates of complications using ENB compared with CT-guided marker placement (59). In both studies fiducials were used to guide therapy and not as markers prior to MITS.

Combined percutaneous and bronchoscopic modalities for placement of markers

Sun *et al.* proposed a combination of ENB guided injection of MB combined with percutaneous Hookwire placement. In his case report a 50-year-old female with a 0.6 cm × 0.5 cm lesion was targeted with ENB. MB 0.6 mL was injected through an EWC. The time required to complete the procedure was 14 minutes and 25 seconds. The injection was followed by a CT chest to determine the optimal needle path, sterilization of the skin and local anesthesia. The hookwire was inserted through the chest wall and placed as close as possible to the lesion. A repeat CT chest was done to confirm the placement and identify possible

complications. No complications were identified with a total time for this procedure of 16 minutes. The patient was transported to the OR and VATS was performed within one hour.

To our knowledge, there are no other reports of combined percutaneous and bronchoscopic modalities.

Other modalities

Zhao *et al.*, used cone beam CT and ENB in a Hybrid operating room, which can provide real-time images that aid the navigation, identification and biopsy. The use of image guided percutaneous localization in the hybrid operating room has also been described (61,62).

The Brigham and Women's Hospital iVATS evaluated 23 pulmonary lesions of size 1.30±0.38 cm which received conventional thoroscopic surgery after the placement of two T-shaped fiducials (Kimberly-Clark, Roswell, GA, USA) under intraoperative C-arm CT. In this study, a 5-second end-inspiratory-hold 200° rotation with a 0.36 mGy/projection scanning protocol for the pre-determined field was able to identify the nodule by CBCT. Two T-bar fiducials were implanted afterwards for localization under fluoroscopic guidance according to the trajectory provided by the syngo iGuide needle guidance software. Twenty-two lesions were found to be malignant. Zhao *et al.* performed 19 real-time image-guided hookwire localization immediately followed by VATS resections. The mean operative time was 128 min. A total of five patients had a pneumothorax as a complication of hookwire insertion, but none required intervention (62). With this technique, the radiation exposure is not significantly higher than with other fluoroscopic techniques but the cost and complexity of the equipment maybe a challenge (61).

Lachkar *et al.* reported successful dye marking using VB biopsy of PPLs with radial endobronchial ultrasound (EBUS) (63). Combined radial EBUS and ENB has a diagnostic yield of 47.1% for PPLs (64). This suggests that radial EBUS can be used in combination with ENB to assist in PLLs marking before MITS. Prospective studies evaluating the efficacy and cost/benefit of these modalities are needed.

Conclusions

Pulmonary nodules have malignant potential. With the increased use of CT scans, advances in technology, and lung cancer screening guidelines, smaller and an increased

number of smaller lesions are being detected. This can be challenging for the thoracic surgeon during MITS. Multiple modalities have been developed to assist in the localization of lesions, resulting in the reduction of the operating time and conversion to thoracotomy. Transthoracic marking has been popular in the past. Bronchoscopic techniques with similar efficacy and lower complication rates are attractive since they can be performed intraoperatively without major technical complications.

Acknowledgments

None.

Footnote

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

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Cite this article as: Velasquez R, Martin A, Abu Hishmeh M, DeLorenzo L, Dhillon SS, Harris K. Placement of markers to assist minimally invasive resection of peripheral lung lesions. *Ann Transl Med* 2019;7(15):360. doi: 10.21037/atm.2019.03.50