**TITLE:**

Electromagnetic Navigation Transthoracic Nodule Localization for Minimally Invasive Thoracic Surgery

**AUTHORS AND AFFILIATIONS:**

Sohini Ghosh1, David Chambers1, Adam R. Belanger1, Allen Cole Burks1, Christina MacRosty1, Anna Conterato1, Jason Long2, Benjamin Haithcock2, M. Patricia Rivera1, Jason A. Akulian1

1Section of Interventional Pulmonology, Division of Pulmonary and Critical Care Medicine, University of North Carolina at Chapel Hill, NC, USA.

2Section of Thoracic Surgery, Division of Cardiothoracic Surgery, University of North Carolina at Chapel Hill, NC, USA.

**Corresponding Author:**

Jason Akulian (jason\_akulian@med.unc.edu)

Division of Pulmonary Diseases and Critical Medicine, Department of Medicine

University of North Carolina at Chapel Hill,

Chapel Hill, NC, USA

(o) 919-966-2531

(f) 919-843-9116

**E-mail Addresses of the Co-authors:**

Sohini Ghosh (Sohini.ghosh@unchealth.unc.edu)

David Chambers (David\_Chambers@med.unc.edu)

Adam. R. Belanger (Adam.Belanger@med.unc.edu)

Allen Cole Burks (acole\_burks@med.unc.edu)

Christina MacRosty (christina.macrsoty@unchealth.unc.edu)

Anna Conterato (anna.conterato@unchealth.unc.edu)

Jason Long (Jason\_long@med.unc.edu)

Benjamin Haithcock (Benjamin\_haithcock@med.unc.edu)

M. Patricia Rivera (patricia\_rivera@med.unc.edu)

**KEYWORDS:**

Electromagnetic navigation, lung nodule, transthoracic nodule localization, dye localization, minimally invasive thoracic surgery

**SHORT ABSTRACT:**

Presented here is a protocol for lung nodule localization using dye marking *via* electromagnetically navigated transthoracic needle access. The technique described here can be accomplished in the peri-operative period to optimize nodule localization and to successful resection when performing minimally invasive thoracic surgery.

**LONG ABSTRACT:**

The increased use of chest computed tomography (CT) has led to an increased detection of pulmonary nodules requiring diagnostic evaluation and/or excision. Many of these nodules are identified and excised *via* minimally invasive thoracic surgery; however, subcentimeter and subsolid nodules are frequently difficult to identify intra-operatively. This can be mitigated by the use of electromagnetic transthoracic needle localization. This protocol delineates the step-by-step process of electromagnetic localization from the pre-operative period to the postoperative period and is an adaptation of the electromagnetically guided percutaneous biopsy previously described by Arias *et al.* Pre-operative steps include obtaining a same day CT followed by the generation of a three-dimensional virtual map of the lung. From this map, the target lesion(s) and an entry site are chosen. In the operating room, the virtual reconstruction of the lung is then calibrated with the patient and the electromagnetic navigation platform. The patient is then sedated, intubated, and placed in the lateral decubitus position. Using a sterile technique and visualization from multiple views, the needle is inserted into the chest wall at the prechosen skin entry site and driven down to the target lesion. Dye is then injected into the lesion and, then, continuously during needle withdrawal, creating a tract for visualization intra-operatively. This method has many potential benefits when compared to the CT-guided localization, including a decreased radiation exposure and decreased time between the dye injection and the surgery. Dye diffusion from the pathway occurs over time, thereby limiting intra-operative nodule identification. By decreasing the time to surgery, there is a decrease in wait time for the patient, and less time for dye diffusion to occur, resulting in an improvement in nodule localization. When compared to electromagnetic bronchoscopy, airway architecture is no longer a limitation as the target nodule is accessed *via* a transparenchymal approach. Details of this procedure are described in a step-by-step fashion.

**INTRODUCTION:**

With the increasing use of CT scans of the chest for diagnostic and screening purposes1, there is an increased detection of subcentimeter pulmonary nodules requiring diagnostic evaluation2. Percutaneous and/or transbronchial biopsy have been successfully used to sample indeterminate and high-risk nodules. These lesions often make for challenging targets due to their distal parenchymal location and small size3. When indicated, surgical excision of these lesions should be performed, using a lung-sparing resection *via* minimally invasive thoracic surgery (MITS), such as video- or robot-assisted thoracoscopic surgery (VATS/RATS)4. Even with advances in surgical technique, there remain intra-operative challenges to resection, despite direct visualization of the lung parenchyma during MITS. These challenges are primarily related to difficulties with nodule localization, especially with ground-glass/semisolid nodules, subcentimeter lesions, and those more than 2 cm from the visceral pleura5,6. These challenges are exacerbated during MITS due to a loss of tactile feedback during the procedure and can lead to more invasive surgical methods, including diagnostic lobectomy and/or open thoracotomy5. Many of these issues with intra-operative nodule localization can be mitigated by the use of adjunct nodule localization methods *via* electromagnetic navigation (EMN) and/or CT-guided localization (CTGL). This protocol will first highlight the benefits of using electromagnetic transthoracic nodule localization (EMTTNL). Secondly, it will delineate in a step-by-step fashion how to replicate the process prior to MITS.

Electromagnetic navigation helps to target peripheral pulmonary lesions by overlapping sensor technology with radiographic images. EMN first consists of using available software to convert CT images of the airway and parenchyma into a virtual roadmap. The patient’s chest is then surrounded by an electromagnetic (EM) field within which the exact location of a sensory guide is detected. When a guide instrument (*e.g.*, magnetic navigation [MN]-tracked needle) is placed within the patient’s EM field (endobronchial tree or skin surface), the location is superimposed on the virtual roadmap, allowing for navigation to the target lesion identified on the software. EMN can be performed *via* either transthoracic needle approach or bronchoscopy. EMN bronchoscopy has previously been described for use in both biopsy and fiducial/dye localization7-11. A number of other localization techniques have been developed with varying success rates, including CT-guided fiducial placement, CT-guided injection of dye or radiotracer, intraoperative ultra-sonographic localization, and EMN bronchoscopy12. A recently introduced EMN platform has incorporated an electromagnetically guided transthoracic approach into its workflow. Using the CT roadmap, the system allows the user to define a point of entry on the chest wall surface through which they will pass a tip-tracked EMN-sensed needle guide into the lung parenchyma and lesion in question. Through this needle guide, biopsies and/or nodule localization can then be performed7.

Prior to the EMN localization of nodules for MITS, CTGL using dye marking or fiducial (*e.g.*, microcoils, lipoidal, hook-wire) placement was the primary method employed. A recent meta-analysis of 46 studies of fiducial localization showed high success rates among all three fiducials; however, pneumothorax, pulmonary hemorrhage, and the dislodgement of fiducial markers remained significant complications13. A CT-guided tracer injection with methylene blue has had similar rates of success, but with fewer complications when compared with hook-wire fiducial placement14. One of the primary limitations of using dye for lung nodule localization has been diffusion over time15. Patients undergoing CTGL with dye marking have the localization performed in the radiology suite, followed by transport to the operating room, during which time dye diffusion can occur, making this technique less attractive. Some centers have mitigated this time lapse with the use of hybrid operating rooms with robotic C-arm CTs16,17; however, radiation exposure can be higher with the repeated images and use of fluorosocope15. The use of EMN bronchoscopy allows for peri-operative nodule localization. This, however, has been plagued by prolonged bronchoscopy times and an inability to navigate to those lesions without airway access. EMTTNL allows for a rapid percutaneous nodule localization followed by MITS in one location (*i.e.*, the operating room), therefore decreasing time between the localization and the surgery18. In addition to EMN bronchoscopy, Arias *et al.* described using EMN for percutaneous biopsy7. An adaptation of this procedure for nodule localization is described below.

A 79-year-old male with a 40 pack-year history of tobacco use and bladder cancer was found to have a new PET fluorodeoxyglucose-avid lung nodule of size 1.0 cm x 1.1 cm in the left lower lobe by surveillance imaging (**Figure 1**). Given the lesion’s size and position, wedge resection was considered challenging and the patient’s pulmonary reserve made him a less than ideal candidate for diagnostic lobectomy. It was decided that he would undergo EMTTNL to aid in the MITS resection of the lung nodule.

**PROTOCOL:**

The procedure is performed in accordance with standard of care expectations and follows the guidelines of the human research ethics committee at the University of North Carolina at Chapel Hill.

**1. Pre-operative Preparation**

* 1. Review prior chest computed tomography (CT) imaging to ensure that the patient undergoing nodule localization has a peripheral pulmonary nodule suitable for minimally invasive thoracic surgery (MITS).
  2. On the day of or a day prior to the procedure, perform a noncontrast chest CT scan with the patient in the lateral decubitus position with the lung ipsilateral to the nodule positioned up to mimic the position during the dye injection. Obtain both expiratory and inspiratory images to account for nodule movement.

Note: The CT should be formatted per EMTTNL system specifications7.

* 1. Use the navigation system planning software to digitally segment the target lesion.
  2. If the target lesion is radiographically “pure” ground-glass in nature, the segmentation software may fail to properly identify the lesion. In this case, place a virtual target in the center of the target lesion.
  3. Once the target lesion has been successfully marked, use the planning software to delineate the percutaneous site for needle entry. The percutaneous entry site should be located between two ribs, taking care to avoid the intercostal neurovascular bundle on the inferior border of the rib, and represent the shortest track from skin entry to nodule acquisition.

1. **Peri-operative Preparation and Registration**

2.1. Transfer the patient to the operating room and have the appropriate personnel induce general anesthesia with paralysis.

Note: General anesthesia should be only administered by certified personnel and the dosing of the drugs is at the discretion of the anesthesia provider.

2.2. Once anesthesia and paralysis have been achieved (as confirmed by the loss of muscle tone and the cessation of spontaneous chest wall motion), establish an orally inserted airway using a double lumen endotracheal tube (DL-ETT) as opposed to a traditional single lumen endotracheal tube.

Note: This is placed by the anesthesia providers, and any size required based on the patient’s specifications is acceptable. This will allow for procedural positioning, single-lung ventilation for the surgical resection and EMN system registration.

2.3. Perform a white light bronchoscopy (WLB) examination of the tracheobronchial tree to the segmental level, assessing for occult endobronchial disease.

2.4. After performing a WLB examination of the airway, position the patient in the lateral decubitus position, mirroring as closely as possible the patient’s positioning during CT. Attach three electronic reference point pads to the patient’s chest, placing them on the ipsilateral chest wall to the nodule and out of the way of the chosen point of entry (**Figure 2**).

2.4.1. For example, if the chosen point of entry is the left anterior thorax, place the pads on the left chest, at least 5 cm away from the point of entry. Then, plug the pads into the EMN system.

2.5. Perform system registration for the patient with system calibration by first positioning the EMN field generator over the reference pads. Fine-tune the position using prompts provided by the EMN system. Once the field generator is in position, using the EMTTNL platform, take a virtual “snapshot” of the reference pads.

2.6. Following the snapshot, insert the proprietary EMN-tracked disposable scope catheter (DSC, 3.2 mm in outer diameter, working channel 2.0) into each lumen of the DL-ETT in order to generate a data point cloud delineating the extent of the main airways (**Figure 3**). Align the catheter on the main carina and, then, pull back slowly into the trachea until prompted by the system to stop (green checkmark). Then, drive the DSC into the right lung—specifically, the right lower lob—until prompted to stop (green checkmark).

2.7. Once the data point collection is halted, remove the DSC from the right lung lumen of the DL-ETT and insert it into the left lung lumen of the tube. Drive the DSC into the left mainstem bronchus 2 - 3 cm proximal to its bifurcation into the left upper and lower lobes. Resume the data collection at this point and drive the DSC into the left lower lobe until prompted to stop (green checkmark). Once the full data point cloud is collected, proceed to EMTTNL.

**3. Procedure**

3.1. Align a tracked percutaneous needle at the chest wall skin entry site using the EMN platform for guidance. Mark the skin at the entry point to the chest cavity, taking care that the entry point should be just superior to the rib and avoid any known vasculature or osseous structures (*e.g.*, clavicle, subclavian vessels).

3.2. Clean and prepare the skin with a 2% chlorhexidine solution for a minimum of 15 s and allow it to dry for a minimum of 30 s. Drape the field using sterile technique.

3.3. Once a sterile field has been created, don sterile gloves and a sterile gown and inject 1 - 2 mL of 1% lidocaine subcutaneously at the entry point for local anesthesia. Use a #10 blade surgical scalpel to make a superficial skin incision (5 mm) at the entry site through the epidermis.

3.4. Place the sterile 19-G electromagnetic needle on the marked entry point. Using the transverse and coronal views on the electromagnetic system screen, adjust the angle of entry so that it lines up with the center of the target lesion (**Figure 4**).

Note: Crosshair markings should overlap in at least two different planes.

3.5. Once the angle of entry is confirmed, stabilize the EMN-tracked needle against the chest wall and firmly advance through the chest wall, while the anesthesia team holds the patient in exhalation. Positive end-expiratory pressure (PEEP) is maintained at 5 cm of water.

3.6. Once reaching the distal side (from the chest wall) of the target lesion, remove the tracked stylet without moving the needle and cover the needle hub with a finger. **Use extreme caution so as to not dislodge the needle**. If, at any time during the following steps, there is concern about needle movement, reinsert the tracked stylet to confirm needle placement.

3.7. To the needle, connect a syringe containing either 2 - 3 mL of undiluted methylene blue, or 2 - 3 mL of a 1:1 mixture of methylene blue and the patient’s blood.

Note: The patient’s blood should be drawn just prior to mixing it to minimize clotting and can be drawn off with either a peripheral IV or from a fresh needle venipuncture.The mixture is recommended as it thickens the solution and limits dye diffusion and/or “splashing” of dye within the pleural space during needle retraction.

3.8. Inject 0.5 mL of the dye or the dye:blood mix within the target lesion. Gradually and continuously deposit another 0.5 mL of the dye or the dye:blood mixture while slowly withdrawing the needle to create a track.

**4. Post Procedure**

4.1. After EMTTNL (**Figure 3**), perform MITS using the dye marking to localize and resect the lung nodule19-23.

Note: Post-procedure patient care will be at the discretion of the thoracic surgeon as this protocol does not have any specific post-operative requirements.

**REPRESENTATIVE RESULTS:**

The patient was prepared per the protocol noted above. Following this, EMTTNL was performed with an injection of a total of 1 mL of a 1:1 methylene blue:patient blood mixture. Upon removal of the needle, the patient was prepped and draped for MITS. Robot-assisted thoracic surgery was performed using the four-arm technique with a robotic surgical system using five total ports. Four ports are placed along the eighth intercostal space (each 9 cm apart) anteriorly from the midclavicular line extending posteriorly to the scapular tip using one 12-mm robotic stapling port (most anterior port) and three 8-mm robotic ports. One additional 12-mm robotic port is placed posteriorly one intercostal space above the diaphragm for the assistant. The robotic surgical system is docked to the patient using all four robotic arms for camera driving with an 8-mm, 30° scope, a right and a left arm for bipolar energy and dissection, and the “third” arm for lung retraction. Following the deflation of the lung, the localization dye marking was identified, and diagnostic wedge resection was undertaken (**Figures 5**). A pathologic frozen section revealed transitional cell carcinoma (bladder cancer), the margins were deemed clean, and no further resection was performed.

**FIGURE LEGENDS:**

**Figure 1: FDG-avid left lower lobe nodule which requires localizations prior to surgical excision.** (**A**) Positron Emission Tomography (PET) scan; (**B**) Chest Computed Tomography. Note the FDG-avid left lower lobe nodule (arrow).

**Figure 2: Electronic reference pad placement.** Three reference pads should be placed on the chest wall ipsilateral to the nodule, and out of the way of the chosen point of needle entry.

**Figure 3: Virtual rendering of airways reconstructed from the procedure CT scan.** This image is re-constructed using data from the CT scan after collecting data points within the airways.Note the data points within the airway tree as well as checkmarks denoting completion of airway data collection

**Figure 4: Snapshot with alignment of percutaneous needle entry in transverse, coronal and sagittal views.** This electromagnetic system screenshot shows an example of needle alignment in multiple views with the target lesion centered just prior to needle insertion (Image courtesy of Veran Medical).

**Figure 5: Images of the lung during and after resection.** (**A**) Intra-operative images of the lung after injection of 1:1 methylene blue/blood mixture. Arrow identifies the exit point of the percutaneous dye needle. **(B)** Successful wedge resection of the dye localized lung. Forceps identify the exit point of the percutaneous dye needle.

**DISCUSSION:**

Peri-operative transthoracic nodule localization under EMN guidance is a novel application of a recently introduced EMN platform.The critical steps in the performance of EMTTNL are a proper point cloud registration of the device and attentiveness to the percutaneous insertion site and the angulation of the needle. Visualization and maintenance of the angle of entry on multiple planes of the CT scan (HUD, oblique 90, and oblique) are crucial to the success of the procedure.

Some of the following modifications have been adapted due to trouble-shooting frequently occurring issues. One modification to this technique includes CT performed in the lateral decubitus position instead of the supine. This change was adopted due to registration errors after pronounced patient repositioning and/or shifting of the reference pads. Another modification is the mixing of the dye in a 1:1 concentration with the patient’s blood. During initial efforts, there was excessive splattering of dye within the chest cavity, as well as dye diffusion, despite short intervals to surgical port placement. The mixture has, since, led to decreased diffusion and less dye soiling of the pleural space.

Limitations of this technique may include the localization of multiple nodules (oligometastases) due to the possibility of pneumothorax development between needle passes. A pneumothorax after the first needle pass would distort the anatomy and result in improper dye injection. That said, we have overcome this limitation in at least one instance where we left the initial localization needle anchored in place by an assisting physician and then localized another target with a separate needle. Once both targets were needle-localized, the injection of the dye and the needle retraction were performed simultaneously, resulting in the successful EMTTNL of two separate ipsilateral targets. Another limitation is the location of the nodule itself. EMTTNL is an excellent option for peripheral nodules; however, the transthoracic approach is not ideal for central lesions, nor for those inaccessible due to the scapula or other bony/vascular structures. Additional limitations of the technique include user and system errors, such as the potential for excess dye injection causing dye spillage and/or an inability of the surgeon to pinpoint the site of the lesion. Errors may also occur with use of the EMN system, including misregistration and reference PAD malposition.

This technique draws on the existing practice of CTGL. EMTTNL is a significant advancement due to its ability to be performed in the peri-operative setting. Previous use of CTGL has been limited due to complications, radiation exposure, the time from CTGL to transport to surgery, and dye diffusion14,15. Bronchoscopic dye marking has also been described with varying degrees of success10,11,18; however, bronchoscopic access to nodules is limited by airway architecture24. This is typically not an issue with EMTTNL as the transthoracic approach is not restricted to the airways.

Future applications of EMTTNL may include the use of other marking agents, including gold fiducials, hydrogel plugs, or indocyanine green coupled with near-infrared fluorescence. Multi-centered prospective trials of EMTTNL to aid in MITS would be useful to determine optimal nodule and patient characteristics for the application of this technique.

**ACKNOWLEDGMENTS:**

This work is supported by T32HL007106-41 (to Sohini Ghosh).

**DISCLOSURES:**

Jason Akulian and Jason Long have received institutional educational grants for CME activities and consulting fees from Veran Medical Technologies. No financial assistance was provided for the development of this manuscript. Sohini Ghosh, David Chambers, Adam R. Belanger, Allen Cole Burks, Christina MacRosty, Anna Conterato, Benjamin Haithcock and M. Patricia Rivera have no disclosures related to this project.

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