Intraoperative imaging and localization techniques for part-solid nodules

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CENTRAL MESSAGE

Advances in imaging technology have increased the thoracic surgeon's armamentarium for identification of nonpalpable and central nodules intraoperatively.

With the implementation of guidelines for low-dose computed tomography (CT) scans for high-risk patients starting in 2011, combined with the overall increased use of computed axial imaging, solitary nodules are being detected more frequently, with a prevalence of up to 24% in high-risk smokers.[1,2] In appropriate patients, part-solid lesions with a solid component greater than 8 mm, as well as lesions with evidence of growth on serial CT scans, are high risk for metastases if left untreated and should be considered for excision for both diagnosis and treatment.[3] Minimally invasive wedge resection may often be the modality of choice to diagnose and treat small nodules, especially when nonsurgical CT-guided percutaneous or bronchoscopic biopsy is unattainable, nondiagnostic, or inconclusive in the high-risk setting. However, subcentimeter nodules and ground-glass opacities (GGOs) can be difficult to identify or discern with visual inspection or indirect instrument-based palpation alone, especially in the era of video-assisted thoracic surgery (VATS) and robotic lung resection. Often in this setting, preoperative and intraoperative tumor marking techniques may provide significant aid to the surgeon and decrease time in the operating room and potential morbidity in patients undergoing these procedures. With the availability of hybrid operating rooms, many of these localization techniques may be performed by the surgeon at the time of the operation and not as a separate procedure. Additionally, new radiologic and technical advancements in the last decade have expanded the number of intraoperative localization techniques that may be more widely available to the majority of practicing thoracic surgeons. Finally, emerging new modalities may combine molecular-guided localization and image-based diagnosis of pulmonary malignancies. This article will review the more common localization techniques (other than direct palpation or visualization), as well as discuss emerging image-dependent technologies.

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TRANSTHORACIC PERCUTANEOUS LOCALIZATION

Primarily with the aid of CT guidance, percutaneous localization techniques have been among the first adjunct modalities used preoperatively to aid the surgeon in identification of nodules. Needle localization techniques predominantly use CT guidance to locate a nodule and leave a marker such as a transpleural hookwire, microcoil or other fiducial marker, and vital inert dye in situ for the surgeon to "follow." In an early randomized controlled clinical trial, Finley and colleagues[4] described the preoperative CT-guided placement of platinum microcoils followed by intraoperative fluoroscopically guided identification of these markers in patients undergoing thoracoscopic resection for small peripheral nodules. Patients undergoing fiducial placement had higher successful diagnosis rates with wedge resection alone, decreased time to nodule excision, no difference in costs, and no clinically significant complications compared with those undergoing thoracoscopic resection alone.[4]

Pitfalls to these methods include marker/wire dislodgement, hemothorax, pneumothorax, and rarely air embolism. In the case of wire dislodgement (often secondary to lung collapse with single lung ventilation or postprocedure pneumothorax), if operating in a hybrid suite a CT scan be performed. Microcoils and fiducials have similar pitfalls as hookwires, although with a decreased propensity to migrate intraoperatively given their complete intraparenchymal position without fixation to the chest wall. However, this characteristic also requires the use of adjunct intraoperative imaging, most often fluoroscopy, to reliably identify their position. In a report of 63 patients undergoing CT-guided microcoil localization immediately preoperatively, Donahoe and colleagues[5] reported a 100% diagnosis rate with no significant complications attributed to the procedure. Mayo and colleagues[6] reported a 97% successful resection rate with fluoroscopically guided VATS wedge resection after CT-guided microcoil placement in 69 patients with a 3% rate of procedure related complications requiring intervention.

Likewise, contrast agents such as barium and lipiodol have also been percutaneously injected under CT guidance for localization. The disadvantage of barium is the inflammatory reaction it produces in lung tissue, which can alter histological analysis.[7] Lipiodol is advantageous in that it only diffuses to a small area and can last months within the lung parenchyma.[8] Lipiodol can also be identified with intraoperative fluoroscopy. The use of gamma-emitting radioisotopes has also been described, similar to sentinel node biopsy. This technique uses an intraoperative gamma probe to detect areas with the strongest signal after isotope injection.[9] Additionally, there have been multiple reports describing dual localization procedures to increase the success rate of nodule identification.[10]

Park and colleagues[11] compared the efficacy and safety of hookwire, microcoil, and lipiodol localization techniques in a large meta-analysis. They demonstrated the intraoperative localization rate of hook wires to be approximately 91% to 96%, microcoils at 95% to 98%, and lipiodol at 98% to 100%. Additionally, they found that pneumothorax and pulmonary hemorrhage was lowest for microcoil localization.

Of note, it is important to distinguish the use of CT versus intraoperative cone beam CT. The majority of available data in these procedures pertains to the use of preoperative CT, whereas little to no data yet exist comparing these modalities. While anecdotally there may be concern regarding the current quality of cone beam CT compared with CT, with concerns specifically revolving around adequate imaging and localization of GGOs, additional studies are needed to better evaluate the comparative effectiveness of these modalities in localization of pulmonary nodules.

A more recent technology uses mobile electromagnetic guidance and CT co-registration to virtually guide proprietary percutaneously introduced tip-tracked instruments and needles into lesions of interest (SPiN System, Veran Medical Technologies, St Louis, Mo). The technology potentially obviates the need for CT or hybrid cone-beam equipped operating rooms to achieve real-time transthoracic sampling and marking of pulmonary tumors by the surgeon immediately before surgery.[12] However, little reported data are currently available to assess the overall safety and efficacy of this technique.

NAVIGATIONAL BRONCHOSCOPY

Delivery of markers via electromagnetic navigational bronchoscopy is another method used intraoperatively before resection to localize nodules. This technology converts CT scan images into a 3-dimensional map of the airway and then enables real-time electromagnetic enabled navigation of the bronchoscope to target locations. The CT scan can be done preoperatively and systems are highly mobile, and thus there is no need for a hybrid operating room. The electromagnetic navigational bronchoscope has a steerable sensor probe at the tip, which allows the surgeon to traverse into distal airways to access and mark peripheral nodules not reachable by standard bronchoscopy.

Awais and colleagues[13] reported their initial experience with intraoperative navigational bronchoscopy and dye marking before minimally invasive resection with 29 of 29 lesions localized. The NAVIGATE trial was a multicenter prospective study assessing the use of electromagnetic navigational bronchoscopy in patients with lung lesions. Bowling and colleagues[14] reported data on a small subset of patients in the NAVIGATE trial who underwent electromagnetic navigational bronchoscopy assisted dye marking for surgical resection. In this study, the median nodule size was 10 mm, and the median distance from the pleura was 3 mm. They found that dye marking was acceptable for 91% of the surgical resections. Likewise, virtual bronchoscopy is a technology that creates virtual bronchoscopic images to guide the surgeon under direct bronchoscopic vision to targeted lesions. Virtual bronchoscopy is the basis for virtual-assisted lung mapping, which involves multi-spot dye marking to create a preoperative "lung map" for the surgeon to identify lesions for sublobar resections.[15] It has been shown to have a good safety profile and high degree of accuracy with a successful resection rate of 87.7%.[15,16] However, for tumors more than 30 mm from the pleural surface, virtual-assisted lung mapping is less effective in achieving the necessary resection margins.[17] For dye marking, the most commonly used agent is methylene blue. The disadvantage of this agent is the tendency for the dye to diffuse rapidly to the surrounding lung tissue or into the extrapleural space if delivered past the surface of the lung. Additionally, a rare complication is development of anaphylaxis to methylene blue.[9]

ULTRASOUND LOCALIZATION

Intraoperative ultrasound (US) has been in used in minimally invasive surgery for the past 30 years. Khereba and colleagues[18] identified 43 of 46 nodules in 45 patients using direct parenchymal intracavitary US in a prospective cohort of 45 patients. Similarly during VATS procedures, Kondo and colleagues[19] demonstrated the feasibility of intraoperative US for localization of ground glass opacities. This group was able to identify all preoperatively diagnosed

GGOs intraoperatively with the use of US. However, intraoperative US has been shown to be highly operator dependent. Additionally, intraoperative US may be less useful in patients with severe emphysema when the lung cannot fully deflate.[9]

NEAR INFRARED FLUORESCENCE IMAGING WITH INDOCYANINE GREEN

Near-infrared (NIR) fluorescence imaging uses fluorescent contrast agents that can be activated via laser light and detected with specialized cameras adjusted to detect wavelengths of light specific to a given fluorophore. Fluorescent agents absorb light at 1 wavelength and emit light at a longer wavelength. Currently, the only Food and Drug Administration (FDA)-approved agent is indocyanine green (ICG), which has traditionally had widespread clinical applications across several specialties.[20,21] In the setting of pulmonary nodule localization, ICG has been used most frequently as a marker injected directly into the peritumoral tissues via the previously discussed percutaneous or bronchoscopic techniques. While available and increasingly reported for the use of lung nodule localization by direct pulmonary parenchymal/tissue infiltration, it is important to note that this specific application of ICG is currently considered an off-label use by the FDA and must be used at the discretion of the surgeon with this in mind.

Abbas and colleagues[22] used navigation bronchoscopy to deliver ICG in 30 patients with tumors ranging from 0.4 cm to 4.4 cm with an average depth of 2.2 cm and had a localization rate of approximately 98% using a dedicated NIR fluorescence imaging thoracoscope. Ujiie and colleagues[23] used CT-guided percutaneous tumor injection of ICG. They showed a 90% localization rate intraoperatively. A more recent report in more than 450 patients by Li and colleagues[24] identified excellent localization rates (98%) with preoperative CT-guided ICG injection and a pneumothorax rate of 6%, with none requiring tube thoracostomy.

NEAR INFRARED FLUORESCENCE IMAGING AND INTRAOPERATIVE MOLECULAR IMAGING

As opposed to image-guided tissue injection, which is only as accurate as the technology guiding delivery of the marker to the target, intraoperative molecular imaging (IMI) relies on the use of tissue-specific markers (often detected by a coupled fluorescence agent) that bind to or sequester within tissues of interest at the cellular or molecular level. It is important to note that the agents and modalities described next remain investigational only and are not available for general clinical use outside the scope of clinical trials.

ICG is thought to potentially localize to tumors due to increased vascularity, and its utility via the intravenous route use for localization has been investigated in pulmonary tumors.[21] Okusanya and colleagues[25] demonstrated the use of systemic ICG injection 24 hours before surgery to identify lesions as small as 2 mm and 1.3 cm deep to the lung surface with a success rate of approximately 90%. However, localization was nonspecific, with a high rate of ICG uptake by nonmalignant nodules.

More recently, significant investigation has revolved around development of highly tissue specific dyes, including those with high specificity to tumor. One such agent is folate-fluorescein isothiocyanate, a folate-targeted dye in the visible light spectrum. Folate receptor alpha is highly expressed in more than 80% of pulmonary adenocarcinomas. Folate-fluorescein isothiocyanate localization is limited by its depth of penetration in lung tissues, as well as high background noise from surrounding tissues.[26] OTL-38 (On Target Laboratories, West Lafayette, Ind) is an investigational folate receptor binding molecule linked to a fluorophore with a detection spectrum within the NIR spectrum. Light in the NIR range (650-900 nm) has deeper tissues penetration due to less absorption by hemoglobin and water, and thus less autofluorescence by surrounding tissue.[27]

In a study by Predina and colleagues,[28] IMI was used for localization of GGOs using the folate-NIR combination intraoperatively. The study subjects were given OTL38 systemically before resection, and no toxicity was observed. Of the 21 GGOs, 20 had accumulation of the OTL-38. A total of 15 of 21 lesions were identified with NIR imaging compared with 10 of 21 with just VATS alone. OTL-38 was highly specific in identification of tumor and in 1 case identified tumor where frozen section did not. Although the level of evidence is preliminary and anecdotal, conceptually these findings suggest a novel additional expansion of these technologies in molecular image-guided diagnosis of malignancy (ie, if it glows, it is primary lung cancer). It was noted from this study that lesions less than 2 cm in diameter and less than 1.5 cm from pleural surface were most effectively identified with NIR imaging.[28] A recently reported multi-institutional phase 2 trial of OTL-38 given intravenously preoperatively suggested clinically significant changes in the course of operation in approximately 25% of patients due to identification of index nodules not seen by standard white light imaging, real-time identification of positive tumor margins, or synchronous occult nodules found by the technology alone.[29] A randomized phase 3 multi-institutional trial is currently ongoing. Currently, no studies comparing NIR and IMI with other more established modalities for lung nodule localization have been reported.

DISCUSSION

New technology and localization methods have increased the surgeon's options for intraoperative lung nodule identification. However, more data are needed to determine what methods are best suited in terms of accuracy, efficacy, and safety. Currently, several viable options for preoperative localization of lung nodules before surgery remain available to surgeons. The choice of modality likely remains a function of individual and institutional experience, availability of technology, and preference.

Transthoracic markers such as wires, fiducial coils, or dyes remain the most "traditional" options, although additional refinements in these methods continue to emerge. As an example, a recent first in human report of CT-guided placement of a radiofrequency identification tag and accompanying detector system has been described with potentially highly precise localization of a small lung nodule.[30] Likewise, a recent case report described the use of novel nonradioactive radar localization technology (SAVI SCOUT, Cianna Medical Inc, Aliso Viejo, Calif) for intraoperative nodule localization. This technology has been FDA approved for breast tumor localization, and in 2018 was cleared for soft tissue use as well. Cornella and colleagues[31] describe the first case of successful localization of a pulmonary nodule with the SCOUT system. The SCOUT technology uses a long-term implantable radar reflector that can be delivered percutaneously via CT guidance. Intraoperatively, the hand piece and console can be used to identify the reflector in the target lesion. The SCOUT technology claims to provide a range of 6 cm detection with 1-mm accuracy.[31] While these reports are promising, it is important to note these emerging technologies remain investigational only for use in the lung, and larger studies need to be done to assess their safety and efficacy for widespread use in pulmonary nodule localization.

Bronchoscopy-based techniques, usually with placement of standard or fluorescence-based dyes, are also increasingly reported. These procedures appear to have good utility and safety profiles, likely decrease the rate of pneumothorax, and allow the surgeon to perform the procedure immediately before surgery with the potential to mark more than 1 lesion.[32] A meta-analysis by Yanagiya and colleagues[33] including 25 studies using various bronchoscopy-based techniques, including electromagnetic navigation, virtual lung mapping, use of standard and NIR dyes, and a range of other similar techniques, identified approximately 100% pooled success rates for complete resection combined with a less than 2% rate of pleural injury or hemorrhage.

As discussed, intraoperative NIR imaging using ICG as a the "fiducial" marker for tumor localization has gained significant popularity. There are an increasing number of reports suggesting high success rates combined with low morbidity, regardless of the modality used to introduce the fluorophore (ICG). Likewise, IMI techniques with tissue/tumor-specific fluorescent based markers represents a more recent development still under study. It is important to recognize that these techniques remain largely in the investigational stage with access to these modalities restricted to ongoing clinical trials.

CONCLUSIONS

With the rise in minimally invasive techniques to thoracic surgery, localization of the small pulmonary nodule will continue to be a challenge to the thoracic surgeon. This may be especially apparent with the rise in surgical robotics in which direct manual palpation of the lung is further limited. Also, although little data yet exist, recent advancements in robotic bronchoscopy may hold significant potential to alter the accuracy and efficacy of localization methods. With these emerging new technologies and increased sophistication of imaging modalities, ideal localization techniques will likely move toward those that are noninvasive, operator independent, less time-consuming, cost-effective, and safe for our patients.

Conflict of Interest Statement

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