Review Article

Image-guided techniques for localizing pulmonary nodules in thoracoscopic surgery

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Abstract: Low-dose computed tomography (LDCT) screening has increased the detection rate for small pulmonary nodules with ground-glass opacity (GGO) in the peripheral lung parenchyma. Minimally invasive thoracoscopic surgery for these lung nodules is challenging for thoracic surgeons, and image-guided preoperative localization is mandatory for their successful resection. Image-guided localization methods primarily include two imaging tools: computed tomography (CT) and bronchoscopy. These different methods may use different localized materials, including hookwires, dyes, microcoils, fiducial markers, contrast media, and radiotracers. Ultrasonography and near-infrared imaging are also used for intraoperative localization of lung lesions. In this article, we review different localization techniques and discuss their indications and limitations.

Keywords: Computed tomography (CT); electromagnetic navigation bronchoscopy; pulmonary nodule; video-assisted thoracoscopic surgery (VATS)

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Introduction

Lung cancer screening using low-dose computed tomography (LDCT) has been proven to reduce lung cancer mortality as well as all-cause mortality in high-risk patients, with a lung cancer detection rate of around 3% (1-4). Therefore, LDCT is accepted as an effective lung cancer screening tool for high-risk patients. However, 23–27% of the screening population has screening-detected indeterminate lung nodules and may need further management (5,6). Although there is no definitive gold standard for such management, several guidelines are available for the management of lung nodules found during LDCT screening (7-9). Nodule size, growth, and size of the solid component may predict the possibility of malignancy, and surgical biopsy for histological determination is required for patients with nodules that have a high possibility of malignancy (7-9).

With the advancements made in video-assisted thoracoscopic surgery (VATS) in recent decades, thoracic surgeries are increasingly performed using VATS because of similar long-term survival outcomes, better cosmetic results, shorter hospital stays, and less tissue injury compared with those for open surgery (10-12). Recently, uniportal VATS for major lung resection revolutionized the treatment of lung tumors (13-16). Gonzalez *et al.* reported the first uniportal VATS lobectomy in 2011 (13). Since then, more complicated procedures, including segmentectomy, pneumonectomy, tracheal resection, anastomosis, and even pulmonary vascular reconstruction, have been performed using uniportal VATS (14,16). Compared with those complicated thoracic surgeries, it may be more difficult to perform minimally invasive surgery for LDCT-detected nodules. These nodules are thoracoscopically invisible and impalpable with VATS. Therefore, VATS for these small, partially solid nodules with ground-glass opacity (GGO) is a challenge for thoracic surgeons. Accurate and effective preoperative or intraoperative localization techniques are helpful for successful VATS tumor excision and have become even more important than they were in the past.

Several localization methods have been described for small pulmonary nodules. The characteristics of an ideal localization technique include: (I) a high accuracy rate; (II) a low morbidity rate; (III) minimal patient discomfort; (IV) a short procedure time; (V) the ability to be applied to the whole lung field; (VI) the use of techniques that are available in most institutes with low additional equipment-dependent requirements; (VII) cost-effectiveness; (VIII) no radiation exposure to either the surgeon or the radiologist; and (IX) no need to transport the patient from the area in which the nodules are localized to the operating room. Recently, several studies have reported the efficacy and accuracy of performing localization in a hybrid operating room (17,18). Currently, there are many different localization methods available that use different guided systems and localized materials, and each has its advantage and disadvantages. Image-guided localization methods include two mainstream imaging tools: computed tomography (CT) and bronchoscopy. These different methods may use different localized materials, including dyes, hookwires, microcoils, metallic fiducial markers, contrast media, and radiotracers. Ultrasonography and near-infrared imaging are also used for intraoperative localization of lung lesions. In this article, we review the current commonly used localization techniques, as well as novel techniques for VATS lung nodule excision, and discuss the advantages and disadvantages of these techniques.

CT guided techniques

Hookwire localization

Localization with hookwire placement is the oldest and probably the most common method of nodule localization (19). The conventional mammographic hookwire system is most commonly used. The wire is usually placed just before the patient is sent to the operating room in order to avoid the patient's discomfort and complications, such as wire dislodgement and pneumothorax. Advantages of this method include an acceptable successful localization rate (93.6–97.6%) and a short localization duration (19-26). Additionally, surgeons can visually identify the localized site directly without intraoperative fluoroscopy and radiation exposure.

Hookwire dislodgement from a perinodular location is the major drawback of this method, and it may lead to the loss of any intraoperative reference to the tumor location. The reported dislodgement rate is 2.4–6.9% (20-26). Dislodgement may occur in three conditions during localization and surgery: when the patient is transported to the operating room, when the lung is deflated before surgery, and when the surgeons manipulate the lung during surgery. Therefore, surgeons should be very careful in such conditions to avoid dislodgement. Miyoshi *et al.* reported their modified method using a shorter, 1-cm-long hookwire with a firmly attached 30-cm-long 5-0 monofilament nylon suture (24). This method is more similar to microcoil placement with a suture, and it may reduce the incidence of dislodgement. Although initial localization failure was been noted in eight patients (8/125, 6.4%), all missing lesions and one remaining hookwire were recovered by additional resection.

Other complications have included minor pneumothorax (7.5–40%), lung parenchyma hemorrhage (13.9–36%), and subcutaneous emphysema (5%). A large amount of hemothorax and massive air embolism are rarely reported (20-26). Moreover, there are some anatomical locations that would be a limitation for the procedure, including apical localization, diaphragmatic localization, and location near the great vessels. Surgeons should consider other localization techniques for such nodules.

Dye localization

Localization of pulmonary nodules by methylene blue dye injection was first reported 20 years ago (27). The success rate is high, and it has a short localization procedure time. This procedure can be easily performed in most institutes with CT-guided biopsy technical components and equipment without additional costs. There is almost no anatomical limitation compared to that for hookwire localization. Additionally, radiologists and surgeons are not exposed to radiation.

The major disadvantage of this procedure is that the blue dye may rapidly diffuse into the surrounding lung parenchyma. Therefore, the localization procedure requires immediate surgery upon completion. One method using methylene blue-stained autologous blood was reported to avoid rapid dye diffusion (28). Lin *et al.* first reported using patent blue vital dye for localization, and their results showed high accuracy and safety (29). Other minor complications have included minimal pneumothorax and intrapulmonary hemorrhage. Anaphylaxis to dye is a lethal complication, but it is rarely reported (30).

Microcoil and fiducial marker placement

Unlike localization with a hookwire, no wire is left protruding extracorporeally after CT-guided localization with metallic microcoils and fiducial markers (31-36), and it may decrease the discomfort of patients during the waiting time to enter the operating room. The size of platinum microcoils is about 15–80 mm in length and 4–5 mm in diameter, and the size of gold fiducial markers is 1.2 mm × 3 mm (31-36). The procedure is similar to that for hookwire localization. The microcoil is passed through a coaxial needle and deployed into the lung parenchyma distal to the needle. Compared to direct visualization of the localized site with hookwire and dye localization, this localization technique requires fluoroscopic guidance during the VATS procedure and increases radiation exposure for surgeons. The success rate is 93–98.4%. Microcoil and fiducial marker migration leads to localization failure and may occur in 3–10% of patients (31-36). Other complications include air embolism, fiducial marker embolization, focal intrapulmonary hemorrhage, pneumothorax, and hemothorax.

Contrast medium injection

Instead of using metallic materials to localize the lung nodule, some physicians inject a water-insoluble contrast medium, such as barium or lipiodol, within or around the lung nodule for localization (37,38). These contrast media can be injected by CT-guided needle injection or by CT-guided bronchoscopy injection. Then, the labeled nodules can be intraoperatively detected by fluoroscopy. Because barium may be interpreted as a lesion on pathologic examination and also may cause inflammatory changes in the lung parenchyma, using barium localization may influence pathological diagnosis. Therefore, some authors suggest using lipiodol rather than barium (38). Lipiodol can be retained in the lung parenchyma for a long time, up to 3 months after injection. In addition, lipiodol also diffuses to a very small area in the lung parenchyma. Therefore, the patient does not need to hurry to the operating room immediately after localization in the radiology unit. Nodules are easily identified during fluoroscopy, and the reported success rate is 100% (37,38).

As for other CT-guided percutaneous marking procedures, complications include pneumothorax, minimal hemothorax, and air embolism. The contrast medium could also induce embolisms because it is water-insoluble. Therefore, the injection site should be checked to avoid intravascular injection, and the suggested injection amount is <0.5 mL (38).

Radiotracer-guided localization

Radiotracer-guided localization uses gamma-emitting radioisotopes (technetium 99, Tc99m) attached to large albumin molecules for localizing lung nodules with CT-guided needle injection (39-42). Post-procedure scintigraphy is usually performed to confirm the location of the radiotracer. Gamma-ray emissions can be detected intraoperatively by a probe converting them into digital counts as well as audio signals. The area with the strongest signal can be identified as the lesion site. This technique was first reported by Chella and colleagues in 2000 (39). Thirty-nine patients were included, and their results revealed a 100% successful resection rate (39). The radiotracer can remain stable for up to 24 hours. Therefore, surgeons can use the probe continuously to localize lung nodules during the operation. The disadvantage is that this technique is highly facility-dependent due to the radiotracer, gamma probe, and radiation protection equipment. Surgeons and radiologists may be exposed to the radiation. Other complications are the same as those previously described for CT-guided percutaneous marking procedures, including pneumothorax, hemothorax, and focal intrapulmonary hemorrhage.

Dual localization

Most institutes may use a single technique for lung nodule localization. Kang and colleagues reported their experience using dual localization with a hookwire and radiotracer/lipiodol for needlescopic resection of small lung nodules (43,44). The purpose of dual localization is to avoid failure from hookwire dislodgement and to improve the successful resection rate. The time required for their dual localization was 10.8–13.1 minutes, and the success rate was 100%. They demonstrated that the dual-marking technique is safe, accurate, and not time-consuming.

CT-guided localization in a hybrid operation room

Currently, the previously described common localization techniques are primarily performed preoperatively in the radiology unit. Patients feel discomfort because they have to undergo an invasive procedure with only local anesthesia or with no anesthesia. The subsequent starting time for the operation is often unpredictable. Transportation of patients may also increase the duration from localization to surgery and increase the possibility of complications, such as pneumothorax and hemothorax. Therefore, it is ideal to use a hybrid operating room for the intraoperative assessment and localization of the indeterminate small lung nodule. Another advantage is that even if the first localization failed, a salvage CT scan can be performed and a second localization procedure performed immediately. Intraoperative CT scans can also provide information on the resection margin. Preoperative localization of lung nodules in a hybrid operating room was first reported in 2013 (17). Zhao *et al.* reported their experience of image-guided single-port VATS in a hybrid operating room in 2016 (18). The only concern is the availability of facilities. Most institutes may have only one or two hybrid operating rooms. It is not possible to perform VATS lung resection for all patients with indeterminate lung nodules in only one hybrid operating room. Therefore, the hybrid operating room should be reserved for difficult cases.

Bronchoscopic-guided techniques—electromagnetic navigation bronchoscopy

Flexible bronchoscopy is limited in that it is unable to guide instruments directly to peripheral lesions. Therefore, electromagnetic navigation bronchoscopy (ENB) with a steerable instrument has been proposed and its feasibility approved for the biopsy of peripheral lung nodules for one decade (45-47). The ENB bronchoscope consists of four components, including a sensor probe with a steering mechanism that is able to navigate the bronchial tree, an extended working channel that can carry either the sensor probe or a flexible instrument, an electromagnetic location board, and computer software that converts thin-cut CT scans into images with three-dimensional virtual bronchoscopy reconstruction and a planned navigation route (45). It enables real-time navigation to the peripheral lung nodules that are invisible on flexible bronchoscopy and subsequent biopsy through the working channel.

Anantham and colleagues reported their early experience using ENB-guided fiducial marker placement for Cyberknife radiosurgery of lung tumors (48). They demonstrated the safety and accuracy of this technique. The fiducial markers were successfully deployed in eight of nine patients. Recently, ENB was used for intraoperative localization of lung tumors (49,50). The entire procedure and surgery is performed in the operating room. The localization procedure is performed under general anesthesia. Therefore, patients do not experience discomfort associated with these invasive preoperative procedures.

ENB-guided dye localization has been proven to be a safe and effective technique (49). Anayama and colleagues reported an animal study that used ENB and a near-infrared fluorescence thoracoscope for the resection of lung nodules (50). They showed the possibility of this technique to localize multiple lung nodules. ENB can precisely localize peripheral lung lesions in the general operating room without the requirement of a CT scan system, which is required for a hybrid operating room. The ENB localization procedure is performed just before surgery begins. Therefore, the common complications of pneumothorax and hemothorax are not of concern.

Other techniques

Intraoperative ultrasonography

The use of thoracoscopic ultrasonography for the localization of lung nodules has been reported since the beginning of thoracoscopic surgery in the 1990s (51-57). The thoracoscopic ultrasound probes are usually 10 mm in diameter and are either rigid or flexible. In a completely deflated lung, the lung nodule can be identified as a hyperechoic lesion with a hypoechoic shadow beneath the nodule (57). This technique can be applied to any pleural surface in the thoracic cavity. Small hard nodules can be easily identified. Although ground-glass nodules are more difficult to localize using this method, Kondo *et al.* demonstrated that intraoperative ultrasonography performed by experienced sonography specialists can both safely and effectively localize ground-glass nodules in a completely deflated lung (57). However, the procedure is highly operator-dependent and can only be used successfully by experienced ultrasonography specialists. Additionally, localization using intraoperative ultrasonography requires complete collapse of the lung, which is often not possible in patients with emphysema. These disadvantages may limit the use of intraoperative ultrasonographic localization in current minimally invasive thoracoscopic surgery.

Intraoperative near-infrared imaging

Recently, Keating *et al.* reported a novel technique of using intraoperative near-infrared imaging (NIR) to identify lung cancer (58). The patient received indocyanine green injection 4 hours before surgery. Using NIR imaging during VATS, the surgeon could detect the invisible and impalpable nodules and resect them with a negative margin. It provided real-time information to the surgeons during the operation. The disadvantages may include false-positive and negative fluorescence, as well as limitations regarding tissue penetration. This novel technique may improve oncologic outcomes by facilitating early intraoperative detection of small, invisible multiple lung malignancies.

Conclusions

Each localization method has its advantages and disadvantages. It may not be possible to establish a gold standard for localizing indeterminate lung nodules since there is lack of comparative clinical trials. In addition, physicians may also choose different techniques in different institutes based on the limitations of their facilities. The key point is for surgeons to understand the advantages and disadvantages of each technique, and to select the appropriate one for different patients with different tumor locations. The use of a hybrid operating room for intraoperative localization of indeterminate lung nodules could avoid patient transport, reduce patient discomfort, and may become a trend in the future.

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Footnote

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

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