Review Article

Hybrid theatre and alternative localization techniques in conventional and single-port video-assisted thoracoscopic surgery

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Abstract: Management of pulmonary nodules in terms of diagnosis and intraoperative localization can be challenging, especially in the minimal invasive video-assisted thoracoscopic surgery (VATS) approach, and may be even more difficult with single port VATS with limited access. The ability to localize small lesions intraoperatively is particularly important for excisional biopsy for diagnostic frozen section, as well as to guide sublobar resection. Some of the common techniques to aid localization include preoperative percutaneous hookwire localization, colour dye or radio-dye labelling injection of the nodule or adjacent site to allowing visualization or detection by radioactive counter intraoperatively. The use of hybrid operating room (OR) for intraoperative localization of lung nodules was first reported in 2013, and was called image guided VATS (iVATS). Subsequently, we have expanded the iVATS application for single port VATS major lung resection of small or ground-glass opacity lesions. By performing an on-table cone-beam CT scan, real-time and accurate assessment of the pulmonary lesion can be made, which can aid the localization process. Other types of physical or colour marker that can be deployed percutaneously in the hybrid OR immediate before surgery can enhance haptic feedback and sensitivity of digital palpation, as well as provide a radiopaque nidus for radiological confirmation. In the past decade, the electromagnetic navigation bronchoscopy (ENB) technology had developed into a useful adjunct technology for the localization of peripheral lung nodules by injection of marking agent or deployment of fiducial to the lesion through the endobronchial route causing much lower marking agent diffusion and artefacts. Recently, the combination of hybrid OR and ENB for lung nodule localization and marking has further increased the accuracy and applicability of the technology. The article will be exploring the latest development of the above approaches to lung nodule localization, and discuss some of the techniques' advantages and flaws.

Keywords: Pulmonary nodule; hybrid theatre; localization; single-port; video-assisted thoracoscopic surgery (VATS)

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Introduction

Approximately 27% of "at-risk" patients who undergo chest computed tomography (CT) screening are found to have pulmonary nodules larger than 4 mm in size according to a recent national lung screening trial (1). Despite the fact that the majority of these nodules may not actually be malignant, biopsy and/or surgical intervention along with follow-up CT to confirm or support their indolent characteristics is recommended for nodules greater than 1 cm in diameter (2). Single-port video-assisted thoracoscopic surgery (VATS) has become an increasingly popular modality and provides a minimally invasive approach to the removal of pulmonary nodules (3,4). However, this technique also raises additional issues compared with conventional three-port VATS. During single-port VATS, the surgical instruments and camera need to be located within a single incision, thus making intraoperative localization of these lesions perhaps even more challenging (5). Furthermore, manual palpation may well be impossible for single-incisional subxiphoid VATS approach (6). Small pulmonary lesions of 1 cm, for instance, or those located at a distance from the periphery of the lung, particularly when they are at a depth greater than 2.5 times the lesion diameter, can be difficult to locate intraoperatively using palpation alone. Localization becomes more problematic when dealing with part-solid lesions with high ground-glass opacity (GGO), which are hard to palpate even if they are substantial or near the periphery.

Classically, the use of preoperative CT-guided marking by dye, contrast medium, radio nucleotide labelling, or hookwire/microcoil localization has been useful in aiding the intraoperative localization of small lesions. Occasionally, however, such methods lead to complications. Recent studies have demonstrated the efficacy of identifying pulmonary lesions immediately before or during surgery using a hybrid operating room (OR) with intraoperative CT to implant a hookwire or metallic fiducial, intraoperative localization using ultrasound, or electromagnetic navigational bronchoscopy (ENB)-guided localization. In this paper, we review the development of techniques for localizing small pulmonary nodules and discuss some of their advantages and limitations, with a particular emphasis on approaches that can be used in single-port VATS.

Common techniques to localize pulmonary nodules without the need for palpation

Multiple methods, mostly performed under the guidance of preoperative CT, have been developed to assist the identification of pulmonary nodules. In general, they can be classified into three categories: implantation of metallic substances, injection of vital dye visualized by colour or intraoperative fluoroscopy, and radionuclide labelling detected by an endoscopic probe.

Metallic implantation

Although lacking an official standard, preoperative CT-guided hookwire placement is currently the most common method used to localize small pulmonary lesions and has a relatively high success rate. The wire is often placed several hours before the commencement of surgery. Any displacement of the wire can lead to a failure of localization in approximately 9.5% of patients (7), though this may be partly resolved by the use of a spiral wire (8) or addition of a suture system (9). The problem of displacement mainly occurs during the transportation of the patient to the OR or during the surgical procedure itself, either when the lung is deflated after general anaesthesia or through the gentle retraction of the wire by the surgeon. Likewise, migration of the microcoil, which is normally implanted preoperatively via percutaneous route and detected through intraoperative fluoroscopy in the lung parenchyma, during the period between coil insertion and operative resection can occur in 3% to 10% of cases (10,11). Other complications, such as pleuritic pain, pneumothorax, hemothorax, or air embolus, can arise due to the invasive puncture of the visceral pleura.

Dye or contrast medium injection

The injection of methylene blue tattooing (12) or another water-soluble contrast medium with lipiodol or barium sulphate (13) under CT guidance close to the tumour site assists the surgeon in locating the lesion during surgery either by direct sight or through intraoperative fluoroscopy. Apart from pleural-related complications, the diffusion of the dye within the parenchyma and at time spillage into the pleural space can lead to a failure in localizing the lesion. Thus, the time between labelling and thoracoscopy must be as short as possible; otherwise, an excessive amount of dye will diffuse beyond the target region. Moreover, the possibility of anaphylaxis and the potential risk of embolism may be non-negligible if this material accidently reaches the systemic circulation (14). In addition, there are physical limitations to the use of intraoperative fluoroscopy in the deflated lung when the patient is in the decubitus position.

Radionuclide labelling

The technetium-99 (99TC) radiotracer, after injection into the tissue surrounding the lesions, can remain stable for up to 24 hours, thereby increasing the time frame between labelling and surgery (15). Perhaps more importantly, the technique enables the continual localization of nodules during surgery via a gamma probe, thus allowing for their accurate excision. However, centres must have the correct equipment and radiation protection procedures in place to offer this method. In addition, this technique may not be suitable for deep and posterior nodules because of the structure of the probe, which is not able to be moved freely within the chest (7,16). Other complications relating to percutaneous injection are similar to those given for the methods listed above.

Although these preoperative methods facilitate thoracoscopic sublobar resection, most of them require the patient to be transferred to two different locations or departments to complete the entire resection: one to localize the lesion and one for surgery. This may be time-consuming and uncomfortable for patients.

Simultaneous localization and resection of pulmonary nodules

The simultaneous localization of pulmonary nodules and surgical resection, especially after anaesthesia in the OR, could help to minimize complications such as pneumothorax and wire displacement resulting from patient transfer and procedural delays, as well as reduce patients' discomfort. Recent studies to investigate the use of hybrid OR, which combines localization techniques with immediate single-port VATS, have shed new light on minimally invasive thoracic surgery.

Image-guided video-assisted thoracoscopic surgery (VATS) in hybrid operating room (OR)

The integration of real-time on-table image guidance technology into clinical practice is well established in other specialties, including cardiology and vascular surgery. However, the use of hybrid OR, termed image-guided VATS (iVATS), for the intraoperative assessment and localization of lung nodules was first reported by the Brigham and Women's Hospital group in 2013. In their prospective clinical trial (17), 23 patients with a mean pulmonary lesion size of 1.30±0.38 cm underwent placement of two T-shaped fiducials using intraoperative C-arm CT followed by standard thoracoscopic resection. Briefly, after general anaesthesia and placement of the patient into a lateral decubitus position, a C-arm CT scan was conducted during an end-inspiratory-hold manoeuvre according to the pre-determined field. Two T-bar fiducials were then implanted for localization under the guidance of fluoroscopy. Notably, the T-bars were successfully implanted in 20 (87.0%) cases and normally required only one CT scan. The average and total procedure radiation doses were low (median: 1,501 mGy × m^2; range, 665–16,326). The total amount of time needed for the procedure was also found to be acceptable because the median length of time required for placing the two T-bars was 39 min. Narayanam *et al.* (18) similarly demonstrated that the combination of lung tattooing and immediate VATS was safe for children in an interventional radiology suite and avoided the need for open thoracotomy to provide a definite diagnosis. Ohtaka *et al.* (19) introduced an O-arm intraoperative CT scan system integrated with a novel "intraoperative stamping" method (20) for localizing pulmonary lesions. However, the centre of the O-arm in this case may require adjusting more than once due to the lack of a pre-determined scanning field, thus increasing the potential radiation exposure to the patient. Moreover, although the "stamping" method avoids puncturing of the visceral pleura, an additional incision is required to place the dye-containing gauze ball, making its application difficult in single-port VATS.

We subsequently expanded the iVATS method to include single-port VATS in major lung resections of small or GGO lesions, known as image guided single-port VATS (iSPVATS) (21). In our method, the hookwire is inserted within 30 min under the guidance of on-table cone-beam CT (DynaCT) in the OR, thus guaranteeing the accuracy of the localization process (*Figure 1*). A single-port VATS procedure can then be performed immediately. If the hookwire is dislodged during lung deflation, a salvage CT scan can be performed to re-hookwire or re-localize the lesions although that was never necessary in our experience. Moreover, DynaCT provides essential information for resection margins even in cases unsuitable for hookwire insertion.

Use of our hookwire iSPVATS approach may reduce the risk of complications associated with the transportation of the patient and delay of the procedure such as prolonged

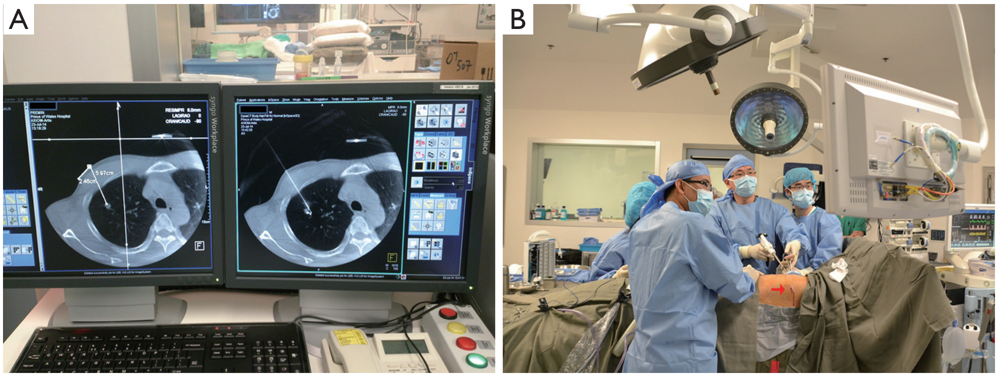

Figure 1 Hybrid OR hookwire guided single port VATS lung resection. (A) Percutaneous hookwire insertion in hybrid operating room with CT guidance; (B) single port VATS resection of hookwire (Red arrow) located lesion in hybrid theatre room with DynaCT arm in parked position (not in view). OR, operation room; VATS, video-assisted thoracoscopic surgery.

discomfort, hookwire displacement, and pneumothorax. However, a special multidisciplinary team comprising surgeons, radiologists, and anaesthetists requires special training. The DynaCT system also needs experience in positioning for the decubitus lie when conducting thoracic surgery. The procedure would work well for lesions adjacent to the chest wall or near the periphery even if of subcentimetre size, but may not be suitable when the wire has to cross extensive lung tissue to localize a very deep lesion. Furthermore, the lesion may not be accessible percutaneously in areas around the apical, diaphragmatic, or mediastinal regions of the lung because it is shielded or too dangerous to approach (22). In addition, it may be more challenging to "mark" multiple lesions, particularly during pulmonary metastasectomy, using this technique. Currently, there are no large studies providing data on indications for iSPVATS in intra-operative localization of small pulmonary nodules. For experienced surgeons, lesions 1cm or more in size can usually be palpated in SPVATS.

Intraoperative ultrasound localization

In completely deflated lungs, the structures of the pulmonary arterioles and venules are identified as homogeneous hypoechoic areas and the bronchioles as hyperechoic spots. In contrast, pulmonary nodules can be visualized by intraoperative ultrasonography as a hypo-/hyperechoic nodule or a hyperechoic shadow beneath the nodule. It has been reported that pulmonary nodules that underwent wedge resection and that can be successfully located by ultrasound were located at a depth of around 30 mm on CT scan, which corresponds to approximately less than half that distant when the lung is deflated (23). Therefore, ultrasonography would be of use if it were able to detect a lesion at a depth of 15 mm from the surface of an entirely deflated lung. In previous studies, ultrasonography showed a sensitivity of more than 90% in localizing pulmonary lesions (24,25), with a procedural time in VATS ranging from less than 1 to 13 (mean, 4.07±3.99) minutes (26). Perhaps more importantly, the echo-Doppler function was able to reveal details regarding the vascularisation of the nodule and could thus help to predict the nature of the lesion (27). This technique offers a time-saving and less invasive method of localization with almost no reported complications.

The careful placement of the port for thoracoscopic ultrasound is reportedly a crucial factor for successful localization (28), mainly because the linear-type probe without optics has been adopted during VATS in previous reports (16,27). A design such as this may decrease the ability of ultrasound to access lesions in the posterior segment or lateral to the spine (26) and hence hamper its potential use in single-port surgery. In 2011, Rocco *et al.* (29) described their initial experience using a 10-mm ultrasound probe along with a 5-mm, 0-degree video-thoracoscope and an articulating grasper to identify two peripheral nodules via single-port VATS. Although it has been noted in the past that a high frequency of 12 MHz will allow the near visualisation of targets at a greater depth (for instance, 15 mm in deflated lungs) (23), a frequency of 5 to 10 MHz was adopted with success by Rocco's team.

Apart from the benefit of a non-invasive approach, ultrasonography in VATS may be simpler than other techniques that require a potentially rapid learning curve. More importantly, in a previous study, ultrasonography was reportedly able to identify two occult lesions that may not have been detected by preoperative spiral CT (24). Wada *et al.* (23) recently introduced a prototype convex ultrasound thoracoscope that was able to visualise targets over a much wider range of lungs in an animal model. Additionally, they added a real-time fine-needle aspiration system to the probe through a single port to enable surgeons to take a diagnostic biopsy of the nodules in advance of diagnostic resection. These features could be particularly important when dealing with multiple pulmonary lesions. Fundamentally, intraoperative ultrasonography requires the complete collapse of the lung for accurate imaging, which makes it difficult and time-consuming in patients with emphysema or pleural adhesions (27). Low-pressure CO_2 insufflation (<10 mmHg) during VATS does not have an adverse haemodynamic impact on the clinical setting (30) and may help to expedite the collapse of the lungs, however, further investigation is warranted.

The main criticism of intraoperative ultrasound localization is that the technique is highly operator-dependent and thus cannot be applied without a specialist in ultrasonography with extensive experience. The procedure is extremely difficult to carry out when the intraoperative localization of subcentre lesions with air filled cavity is required. Nevertheless, it should be pointed out that ultrasound localization is possibly the only available "salvage" technique should one be caught out intraoperatively by an unexpectedly difficult to localize pulmonary nodule, since no prior preparations are required for its use.

Electromagnetic navigation bronchoscopy (ENB) in hybrid operating room (OR)

The clinical use of ENB-guided biopsy to obtain tissue for the diagnosis of peripheral lung lesions dates back almost a decade (31,32), and with its many advantages over percutaneous CT-guided procedures is rapidly gaining acceptance (3). Bolton *et al.* (33) studied 19 patients who underwent robotic pulmonary surgery immediately after dye marking through ENB under fluoroscopic guidance in the OR. Methylene blue was injected at the site of the lesion and at two other separate locations beneath the pleura, meaning it could be identified more precisely during thoracoscopy. Dye placement by ENB could therefore lower the incidence of marker diffusion from the nodule and the difficulty with visualisation in patients with extensive anthracotic pigmentation. Moreover, the median time for ENB-guided dye placement was 28 min, which provided a limited extension to the total operating time.

ENB can also be a useful adjunct technology for the localization of peripheral lung nodules by the deployment of fiducials to the lesion via the endobronchial route, leading to a much lower production of artefacts than the conventional percutaneous approach. Fiducials are dense markers several millimetres in size and made of either gold or platinum; they are used by stereotactic radiosurgery systems to achieve the real-time tracking of tumours (34). Previously, fiducials are placed under CT guidance via a transthoracic approach, facilitating the subsequent detection and removal of small nodules with intraoperative fluoroscopy (35). The fiducials are associated with negligible risk of allergic reaction and are often placed hours to days before surgery. However, migration of the fiducials is not uncommon with prolonged delay. Fiducials can also be placed using navigation bronchoscopy. Anantham *et al.* (36) placed 39 fiducials via ENB into nine patients for radiotherapy. However, they found a 10% migration rate after placement, most likely due to coughing. Implantation of the fiducials under ENB after general anaesthesia immediately prior to surgical resection may solve this problem.

Novel ENB-associated technologies that allow for homing-in on lung lesions are currently under development and will, in the future, provide further options for thoracic surgeons. Anayama *et al.* (37) recently reported their initial experience in a porcine model using ENB-guided transbronchial indocyanine green (ICG) injection. They were able to detect an artificial nodule at a depth of less than 24 mm in the inflated lung using a near-infrared (NIR) fluorescence thoracoscope. The ICG spot was shown to remain at the injection site for more than 6 hours *in vivo*, and the specific wavelength of ICG fluorescence could be detected by NIR regardless of the colour or texture change of the visceral pleura by anthracosis or other diseases. In addition, ICG was found to be safe with the added advantage that it does not adversely affect the pathological examination. The limitations of this technique were similar to other dye-marking techniques, particularly when treating patients with severe pulmonary emphysema because ICG may diffuse among the alveolar space.

The combination of endobronchial ultrasound (EBUS)

Figure 2 Patient in the hybrid operating theatre undergoing DynaCT scan image guided electromagnetic navigational bronchoscopic biopsy of small lung nodule.

and ENB would improve the lesion localization rate to 93% (38), but these techniques may not sufficiently identify subcentimetre lesions with a high GGO content because of the common navigational error range of 4 to 6 mm. Navigational errors of the system and movement of the biopsy tool during its deployment can adversely affect the success of the biopsy or marking. To further increase the accuracy and applicability of this technology, we recently reported the successful use of integrated DynaCT and ENB in a hybrid OR, providing unparalleled real-time images to guide and confirm the successful navigation and biopsy to an 8-mm lesion located in the right middle lobe (39) (*Figure 2*). The image from the DynaCT revealed its superior accuracy over fluoroscopy or EBUS in determining the direction of the catheter tip. Normally, two intraoperative scans are required: one to identify any minor misdirection and the second to confirm the biopsy after any necessary adjustment has taken place. Thus, the radiation exposure from this technique is similar to a preoperative percutaneous centesis procedure. Hopefully, this hybrid technique will allow more precise placement of marking dye or fiducials, of which we are currently investigating.

Conclusions and perspectives

Various techniques have been introduced over the past few decades to help thoracic surgeons identify pulmonary nodules during minimally invasive surgery when detection by manual palpation may be challenging or difficult. Although many small nodules can still be comfortably palpated during VATS or SPVATS, marking of certain lesions, especially subcentimetre or small GGO nodules, may allow the surgeon to more confidently locate the target and define the margin. Most of these techniques require localization to be performed in the radiology suite followed by surgery in the OR. This inevitably takes a considerable amount of time, and patients might experience discomfort due to various complications. In contrast, a hybrid theatre can provide real-time imaging and enhance the possibility of success for hookwire placement or ENB, and also serve as a useful adjunct in the intraoperative ultrasonography technique during uniportal VATS. Other types of physical markers that can be deployed percutaneously in the hybrid OR include the microcoil and standard metal (gold) fiducials, which can enhance haptic feedback and the sensitivity of digital palpation as well as provide a radiopaque nidus for radiological confirmation. DynaCT-guided percutaneous injection of a marking agent (dye, barium, or lipiodol) immediately before surgery can similarly provide a radiopaque beacon to guide resection. A hybrid theatre can also provide relatively simple image guidance by assessing the relationship of the surgical instruments to the lesion. In the future, a combination of ENB-guided metal fiducial placement and hybrid operating theatre image-guided localization may further improve the accuracy and safety of resection, especially for multiple lung lesions in iSPVATS.

Since no comparative studies have yet been performed, it is difficult to conclude which technique should be applied under what circumstances and which technique would be most effective (*Table 1*). The evolutionary change in the localization techniques discussed in this review may eventually shift the treatment paradigm toward the patient-centralized caring concept whereby only a single anaesthetic regimen is needed for both localization and resection of the pulmonary nodule(s), iSPVATS would potentially avoid complications, eliminate disruptions from anaesthetic induction, and shorten hospital stay, providing a more cost-effective approach. Finally, we look forward to a brighter future in which greater numbers of pulmonary malignancies are able to be identified at an earlier stage through these advances, thus lowering patient mortality.

Table 1 Brief summary of pulmonary nodules localization techniques without the need for palpation

Techniques	Traditional route	Advantages	Complication	Potential contraindication	Potential integration in hybrid OR
Hookwire	Percutaneous placement	Widely used	Puncture-associated complication; dislodgement	Apical, diaphragmatic, or mediastinal regions; multiple lesions	Real-time adjustment by DynaCT
Metallic fiducials	Percutaneous placement/ENB	Multi-site localization	Puncture-associated complication; fiducials migration	No	Accurate placement by intraoperative ENB and/or DynaCT
Dye marking	Percutaneous placement	Easy to perform	Puncture-associated complication; contrast medium migration	Deep and posterior nodules	Accurate placement by intraoperative ENB and/or DynaCT, ICG fluorescence thoracoscopy
Radionuclide labelling	Percutaneous placement	Multi-site localization; also locates sentinel node	Puncture-associated complication; contrast medium migration; radiation exposure	Deep and posterior nodules	Accurate placement by intraoperative ENB and/or DynaCT
Ultrasound	Intraoperative use	Noninvasive; detect occult nodule; helps to define pathology	No	Operator dependent; emphysema	Cross-check with DynaCT

OR, operation room; ENB, electromagnetic navigation bronchoscopy; DynaCT, on-table cone-beam computed tomography; ICG, indocyanine green.

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Footnote

Conflicts of Interest: ZR Zhao and RW Lau have no conflicts of interest to declare. CS Ng has an electromagnetic navigational bronchoscopy system SuperDimension Version 7 on loan from Medtronic.

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