Review Article

Perioperative identifications of non-palpable pulmonary nodules: a narrative review

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Abstract: Early detection of lung cancer is the key to improving treatment and prognosis of this disease, and the advent of advances in computed tomography (CT) imaging and national screening programs have improved the detection rate of very small pulmonary lesions. As such, the management of this sub-centimetric and often sub-solid lesions has become quite challenging for clinicians, especially for choosing the most suitable diagnostic method. In clinical practice, to fulfill this diagnostic yield, transthoracic needle biopsy (TTNB) is often the first choice especially for peripheral nodules. For lesions for which TTNB could present technical difficulties or failed, other diagnostic strategies are needed. In this case, video-assisted thoracic surgery (VATS) is the gold standard to reach the diagnosis of lung nodules suspect of being malignant. Nonetheless it's often not easy the identification of such lesions during VATS because of their little dimensions, non-firm consistency, deep localization. In literature various marking techniques have been described, in order to improve intraoperative nodules detection and to reduce conversion rate to thoracotomy: CT-guided hookwire positioning, methylene blue staining, intra-operative ultrasound and electromagnetic navigation bronchoscopy are the most used. The scientific evidence on this matter is weak because there are no randomized clinical trials but only case series on single techniques with no comparison on efficacy, so there are no guidelines to refer. From this standing, in this article we conducted a narrative review of the existing literature on the subject, with the aim of outlining a framework as complete as possible. We analyzed strengths and weaknesses of the main techniques reported, so as to allow the clinician to orient himself with greater ease.

Keywords: Indeterminate pulmonary nodule; pulmonary nodule management; video-assisted thoracic surgery (VATS); intraoperative lung nodule identification; computed tomography-guided localization

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Introduction

The incidence of indeterminate pulmonary nodules has markedly increased over the last two decades due to implementation of computed tomography (CT) screening for lung cancer and to extensively used CT exams for follow-up of cancer patients (1). These nodules can be solitary or multiple, small, solid or sub-solid, deep; more importantly, up to 50% of these could be malignant (2,3). Therefore, a rapid and precise histological diagnosis is usually mandatory.

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Traditional approaches for diagnosing suspicious difficult lung lesions by needle biopsy (endobronchial/transbronchial or percutaneous) are reported with a wide range of diagnostic yield; failure of needle biopsy to rule out malignancy is usually due to inadequate or missed tissue sampling (4-6).

Lung wedge resection by video-assisted thoracoscopic surgery (VATS) may be indicated for diagnosis of suspicious malignant pulmonary nodules, when less invasive biopsy procedures fail. However, target nodule identification during VATS is sometimes challenging, due to nodule site, size or consistency. Failure to localize pulmonary nodules results in conversion to thoracotomy in up to 54% cases and it reaches 63% for nodules <10 mm in diameter or located ≥5 mm deep from the pleura or with a prevalent subsolid component [semisolid or ground grass opacity (GGO) nodules] (7). Thus, nodules requiring a preoperative marking have usually the following characteristics: solid sub-centimetric, deeply located in the lung (depth from pleura/size ratio >1), GGO component (8). Several techniques have been proposed to overcome the difficulties of intraoperative pulmonary nodule identification and to attain successful VATS lung wedge resection: CT-guided insertion of localizer (hook-wire, microcoils, hydrogel plug), percutaneous injection of liquid agents (methylene blue, lipiodol, radionuclides), intra-operative ultrasound (US) and electromagnetic navigation bronchoscopy (ENB).

In this paper we review the most common perioperative techniques performed for localization of non-palpable lung lesions undergoing VATS resection.

We identified data by searching MEDLINE from 1990 to 2019 and from references cited in relevant articles. Search terms included pulmonary/lung nodule, localization/marking, hook wire, microcoil, hydrogel plug, methylene blue, lipiodol, radio, fluorescence tracer, intraoperative ultrasonography, electromagnetic navigation bronchoscopy. Limits specified English language papers with tag terms title/abstract.

We present the study in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/jtd-20-1712).

CT-guided percutaneous fiducial marker placement

Hook wire

The commonly used pulmonary nodules localization technique is CT-guided hook wire localization, which was first proposed by Mack in 1992 (9). A spiral-CT of the chest region of interest is performed, with the patient in the supine/prone position, according to the nodule location. The skin overlying the biopsy site is sterilized and injected with local anaesthetic. Under CT guidance, a 20 or 21-Gauge needle introducer loaded with a flexible hook wire is introduced into the lung and carefully advanced until it is confirmed to be placed close to the nodule. Then the introducer is withdrawn, the hook wire horn is released and remains anchored to the lung parenchyma next to the nodule. Immediately after hook wire placement, chest CT is obtained to confirm proper position of the marker and to rule out complications. Then the semi-rigid wire emerging form the skin is cut approximately 1 cm long and protected by sterile gauze covering. Retrospective studies have shown lung nodule localization rates up to 94% with the hook wire (10-12). The most common complications associated with this procedure include pneumothorax and pulmonary hematoma. The rate of pneumothorax occurring during hook wire localization ranges between 7.5% to 40%, with a majority of cases treated conservatively (13). After hook wire insertion, parenchymal bleeding with lung hematoma has infrequently been reported (2.5%) and its entity does not generally impact on patient's clinic. Massive air embolism is a rare complication that has sporadically been described in case reports and with a rate of 0.6% in a large case series (14). Hook wire dislodgement occurs in 2.5–13% of cases (15,16). Hook wire dislodgement occurs in three situations. First, during patient transportation to the operating table, the hook wire can inadvertently be pulled and displaced. Second, dislodgement may occur when the lung deflates. The third chance of displacement materializes when the hook wire is pulled by the surgeon to tent the lung and perform wedge resection.

Microcoils

Microcoils preoperatively inserted into the lung under CT guidance have been used to identify intraoperatively lung nodules. Patient position (supine, prone, or lateral) on the CT table is chosen to allow the desired needle insertion route, based on the initial CT scan. Under local anaesthesia, a 20-Gauge coaxial introducer is percutaneously advanced into or close to the lung nodule. After CT confirmation that the introducer tip is placed at the desired site, the introducer stylet is removed and microcoil is inserted. Follow-up CT is obtained to verify the proper placement

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of microcoil and to identify any procedure-related complications. After CT-guided microcoil placement, the patient is transferred without delay to the operating room for fluoroscopically guided VATS resection of the nodule. Mayo *et al.* reported on the safety and efficacy of microcoil-guided VATS resection of 75 small (4–24 mm) lung nodules. The microcoil placement complication (dislodgement) rate was 3% and the diagnostic yield of fluoroscopically guided resection was 97% (17). In a randomized trial, Finley *et al.* reported successful localization rate with microcoils of 27/29 (93%) of nodules <15 mm in size, without relevant complications (18). Conversion rate to thoracotomy due to nodule identification failure during VATS ranges from 0 to 6.6% (17,19). The most common complications are asymptomatic pneumothorax (4–13%) and microcoil displacement (0–5%) (18,20).

Hydrogel plug

A cylinder hydrogel plug, originally developed for pneumothorax prevention during percutaneous pulmonary biopsy, has also been proposed for the purpose of preoperative marking of lung nodules (21-23). The patient is positioned prone or supine on the CT table, based on nodule location. An initial CT scan is acquired to verify correct patient position and to exactly measure the chest wall thickness at the puncture site (distance between skin and pleura). After local anaesthesia injection, the tip of a 19-gauge needle introducer is advanced into the pulmonary nodule, under fluoroscopic guidance. The plunger stylet of the hydrogel plug delivery system, set to account for the skin-to-pleura distance, is pushed down for a 25-mm dry hydrogel plug progression into the lung nodule. The delivery system with introducer needle is withdrawn from the chest wall and the dry-hydrogel plug rapidly expands by hydration due to contact with the parenchyma, sealing the needle tract. Plug expansion is completed within few minutes, reaching 50 mm in length. The expanded hydrogel plug sticks out of the parenchymal pleura and marks the site of the underlying nodule. We recently reported the use of this method to identify 28 lung nodules (24). All these nodules were intraoperatively identified: 89% by hydrogel plug; 11% by palpation and pleural puncture hole visible after plug displacement. Only 1 of 28 (4%) hydrogel marking procedures caused a pneumothorax requiring drainage. No other complications were reported after hydrogel plug marking of the lung. An advantage of this procedure is the possibility of marking the nodule after its percutaneous biopsy, as a second step of the same procedure. Moreover, hydrogel plug marking offers the opportunity of delaying surgery up to 60 days, because the plug stays in place for several weeks (24).

Percutaneous injection of liquid agents

Methylene blue, lipiodol, radio or fluorescence tracer

Preoperative localization of small and/or non-palpable pulmonary nodules has been effected also by injection of liquid agents, including methylene blue, lipiodol, and fluorescence/radio tracer (radioisotope attached to albumin). The marking is performed on the day of surgery (before the procedure), in the CT unit. After CT identification of target pulmonary lesion and local anaesthesia in sterile condition, a 20–25-gauge needle is inserted into/close to the nodule. The skin puncture point is chosen to minimize the skin-to-nodule needle tract. After checking by CT scan the needle tip position, the liquid tracer is injected into or adjacent the nodule. This procedure allows to mark the nodule, the surrounding parenchyma, the overlying visceral pleura and the chest wall needle tract. After marking, a CT scan is performed, to rule out complications. Delay between labelling and VATS must be as short as possible. During surgery, the liquid agent is located by different lung colouring or by fluoroscopy. Guidance with use of liquid materials has been evaluated in several studies (25-28). All liquid markers are limited by their potential to diffuse widely away from the nodule, therefore the interval between marking with the liquid localizer and surgical resection of nodule must be minimized.

Localization of small nodules with the injection of methylene blue has yielded sub-optimal results, as this method showed a failure rate up to 8% (29). The methylene blue dye diffuses rapidly, therefore nodule excision must be completed as quickly as possible after dye injection, otherwise the localization of non-palpable nodules is doomed to fail. Furthermore, the methylene blue dye may cause anaphylactic reaction and may be difficult to identify in lungs with heavy anthracotic pigmentation (30). The injection of lipiodol, an oil-based iodinized contrast medium, has the advantage of not being a time-sensitive procedure, as the marking may last for several weeks in the lung parenchyma. Using lipiodol marking, Watanabe *et al.* in their study of 174 nodules with mean size of 10±6 mm, described a successful fluoroscopic localization rate of 100%. Reported complications of marking with lipiodol

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were chest pain (11%), hemosputum (6%), pneumothorax (17%), and hemo-pneumothorax (0.6%). Six percent of patients with pneumothorax required drainage (31). Notably, these complications were associated with needle insertion into the lung, not to lipiodol contrast medium. Air embolism during percutaneous needle insertion into the lung is reported to be 0.02% to 0.07% (32,33). Lipiodol itself poses a potential risk of embolism because it is water insoluble.

Injection of radiotracer aggregates (radionuclides) under CT guidance has been used to successfully localize nodules (34). This technique utilizes gamma-emitting radioisotopes (technetium 99, Tc99m) attached to large albumin molecules with CT-guided needle injection. Then, an intraoperative probe detects gamma ray emission translated into digital counts and audio signals. Radiotracer remains stable for 24 hours. Applicability of this procedure is limited by diffusion of the agent in the lung parenchyma if surgery is delayed, and by the need of nuclear medicine equipment and staff in the operating room.

Localization with a fluorescence tracer, indocyanine green (ICG), has also been performed (35). Zhang *et al.* in a recent study reported a successful localization rate of 94.3% using CT guided percutaneous ICG injection and fluorescence. No adverse effects were seen during the procedures (36). Application of ICG fluorescence can implement the detection of lung nodules, but this method has limitations. Detection of ICG fluorescence requires fluoroscopy equipment, and leakage or insufficient ICG injection may significantly impair the operator ability to localize the nodules.

Intraoperative ultrasonography

Ultrasonography (US) techniques have been used for localizing lung nodules since the 1990s. Many authors have suggested that US is a safe and effective method allowing successful intraoperative identification of pulmonary nodules in up to 93% of cases (37-42). US probes for VATS generally are 10 mm in diameter. Ultrasonography of the lung mandates that the lung be completely deflated, to avoid artifact imaging; accordingly, in patients with emphysema the US localization of nodules is more difficult. Moreover, US is highly operator-dependent (38,41). A solid lung nodule appears as a hyperechoic lesion with a hypoechoic shadow in the underlying tissue. GGO nodules are difficult to identify by US, as their density is similar to that of adjacent normal parenchyma. However Kondo *et al.* showed that experienced clinicians can safely and effectively localize also these non-palpable nodules with intraoperative US (43). The advantages of US are real-time localization of non-palpable nodules and the absence of injury to the pulmonary parenchyma, that eliminates the risk of pneumothorax and haemoptysis. Furthermore, US provides access to most of the visceral pleural surface. During VATS the visceral pleura, including the surface of complete fissures, can be explored almost completely by US. The US probe can access areas of the lung that are impossible to reach by finger palpation. Moreover US can localize nodules that are challenging for preoperative CT-guided marker placement. Khereba *et al.* reported an additional intraoperative US localization of 43% of nodules that were not identified by palpation or visualization, and an operative time of 74±34 minutes (40).

Electromagnetic navigation bronchoscopy

Electromagnetic navigational bronchoscopy (ENB) is a technique proposed in recent years for evaluating small, peripheral pulmonary lesions. ENB combines virtual and conventional bronchoscopy, with the purpose of guiding diagnostic and/or dye marking instruments for localization of pulmonary nodules (44,45). The ENB procedure is performed under general anaesthesia, with endo-tracheal tube ventilation. The patient lies supine on the electromagnetic board. The dedicated bronchoscope is introduced into the lumen of the segmental bronchus of interest. The electromagnetic locatable guide is carefully advanced toward the target lesion under navigational pathway with virtual 3D airway based on preoperative CT scan on the ENB console screen. Then the dye/contrast medium is injected close to the lesion. Compared with the conventional percutaneous approach, localization of small lung nodules by ENB was shown to significantly reduce dye diffusion and the occurrence of pneumothorax as the visceral pleura is not violated. The reported ENB diagnostic yield for small, peripheral pulmonary nodules ranges between 59% and 94% (45-47). The safety of ENB-guided dye marking for intraoperative VATS localization of lung nodules has been documented (48,49). ENB-guided dye marking was also shown to be associated with fewer complications in comparison with other percutaneous marking procedures (50). Marino *et al.* reported successful localization in 97% of 70 lung lesions (median size: 8 mm; median distance from pleural surface: 6 mm), and failure rate of 2.9%, markedly lower than that of other percutaneous marking techniques (51).

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Krimsky *et al*. used ENB-guided dye marking of 21 lung nodules with indigo carmine and methylene blue, and obtained successful localization of 81% of the lesions. No ENB-related complications were reported (48).

Hybrid operating room

Hybrid thoracic surgeries are performed in dedicated operating rooms where CT-guided localization of lesion and surgical excision take place in a single multidisciplinary procedure. The incidence of complications such as pneumothorax, wire dislodgement or dye diffusion correlates with time elapsed between nodule marking and surgery. Thus, intraoperative CT-guided (IOCT) VATS may reduce these complications by minimizing the time interval from localization to excision of non-palpable lung lesions, a step forward compared to the usual methodology that involves patient transportation from the CT suite to the operating room (52).

Hybrid operating rooms seem to be more cost-effective than traditional surgical suites, as imaging and surgical equipment are all in one place rather than in separate rooms. In the hybrid operating room equipped with a surgical table and an imaging system such as C-arm cone-beam computed tomography (CBCT) (53), multiple detector CT (MDCT) (54) or mobile O-arm CBCT (55), the patient undergoes lesion localization immediately before the VATS procedure. After induction of general anesthesia, the patient is positioned according to lesion localization. An initial CBCT acquisition for surgical planning is performed. The needle trajectory is identified and CBCT or fluoroscopy is used to confirm appropriate needle positioning. Markers such as hook-wire or coils are then inserted through the needle percutaneously and deployed at the edge of the lesion. Localization of the nodule is confirmed by post-procedural CBCT scan or fluoroscopy. Another device that needs to be considered in the setting of the hybrid operating room is (ENB. Application of ENB for marking peripheral pulmonary lesions with dye in the context of a hybrid procedure is relatively recent. Using a virtual three-dimensional (3D) bronchial map acquired from a preoperative CT scan, ENB allows to utilize the bronchoscope to mark peripheral lung nodules for immediate VATS resection (56).

Conclusions

Several techniques are available for preoperative/intraoperative localization of small, non-palpable lesions, the most difficult ones to identify during VATS wedge resection procedures. Adoption of preoperative localization techniques for management of non-palpable pulmonary nodules allows to reduce operating time and to minimize the rate of conversion to thoracotomy. An ideal method for intraoperative localization of all difficult lung nodules does not exists. As the management of non-palpable nodules should be multidisciplinary, choice of the localization method among those locally available should be made after discussion at the multidisciplinary team meeting.

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