Intraoperative identification of pulmonary nodules during
minimally invasive thoracic surgery: a narrative review

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Background and Objective: The increasingly widespread application of computed tomography (CT) in the screening and follow-up of patients with lung disease has concomitantly increased the detection rate of pulmonary nodules. Currently, minimally invasive thoracic surgery (MITS) has become the preferred method of surgery for patients with pulmonary ground-glass nodules (GGNs) due to its advantages minimal invasiveness and rapid recovery. However, target nodule identification during MITS is sometimes challenging due to the inherent characteristics of these nodules, especially when they are small and distant from the pleura. This review details the many methods used for the intraoperative localization of pulmonary nodules.

Methods: Literature published in the Cochrane Library, PubMed, ClinicalTrials, and China National Knowledge Infrastructure from 1990 to 2022 were searched and analyzed to obtain a comprehensive review of the different methods of identifying pulmonary nodules. Literature related to animal testing were excluded.

Key Content and Findings: An overview of the recent progress in the clinical methods for intraoperative localization of pulmonary nodules [including CT-guided percutaneous placement of markers; bronchoscopy-guided placement of markers; intraoperative ultrasonography; three-dimensional (3D) printing technology; artificial intelligence (AI); and intraoperative molecular imaging (IMI)] was conducted. The advantages and disadvantages, as well as the complications associated with existing research methods, were summarized to assist doctors in the development of optimized clinical strategies.

Conclusions:Clinicians can communicate with the multidisciplinary team and select the appropriate positioning method according to each patient’s individual situation and the available support of the equipment and technology of the institution. Certain non-invasive and specific identification methods may have clinical potential in pulmonary nodule localization in the future.

Keywords: Lung cancer; pulmonary nodules; intraoperative identification; video-assisted thoracoscopic surgery (VATS); intraoperative molecular imaging (IMI)

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Introduction

Computed tomography (CT) is widely used in the screening and follow-up of lung disease; as a result, the detection rate of pulmonary nodules has increased. The annual incidence of pulmonary nodules in the United States is expected to rise with the current screening guidelines and advances in imaging technology, and has been reported to be 1.5 million (1). The nodules detected by CT can be single or multiple, solid or subsolid, and subsolid nodules can further be divided into ground-glass nodules (GGNs) and partially solid nodules. More importantly, when pulmonary GGNs continue to increase in size for more than 3 months, and are bigger than 10 mm in diameter, the probability of malignancy can range from 10% to 50% (2). The American College of Chest Physicians (ACCP) recommends surgical lung biopsy for indeterminate nodules that are >8 mm in diameter, are hypermetabolic or functional imaging tests positive, have a high malignant probability, when a non-surgical biopsy is suspicious for malignancy, or when a fully informed patient selects a definitive diagnostic procedure (3). Currently, minimally invasive thoracic surgery (MITS), including video-assisted thoracoscopic surgery (VATS) and robotic-assisted thoracic surgery (RATS), is the preferred method of surgery for patients with pulmonary nodules due to its advantages of minimal invasiveness and rapid recovery. However, when subsolid or GGNs are >15 mm in diameter and >10 mm from the pleura, the failure rate of intraoperative nodule identification is extremely high and conversion to thoracotomy is required (4). The current methods for assisting the localization of pulmonary nodules include CT-guided percutaneous placement of markers, bronchoscopy placement of markers, intraoperative ultrasound (US), three-dimensional (3D) printing, artificial intelligence (AI)-assisted identification, and intraoperative molecular imaging (IMI). Some studies have shown no differences in localization success among solid, subsolid, and pure ground glass lesions using hook wire, microcoil, and blue dye (5-8). This paper reviews the most commonly used intraoperative techniques for the localization of pulmonary nodules undergoing MITS. We present the following article in accordance with the Narrative Review reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-22-309/rc).

Methods

Literature published in the Cochrane Library, PubMed, ClinicalTrials, and China National Knowledge Infrastructure from 1990 to 2022 were searched to obtain a comprehensive review of the different marker placement methods used for pulmonary nodules. Literature related to animal experiments were excluded. The following search terms were used: lung neoplasms, pulmonary/lung nodule, peripheral lung lesion, ground-glass opacities, preoperative marking, intraoperative marking, thoracoscopic surgery, video-assisted thoracoscopic surgery, hookwire, microcoils, hydrogel plug, methylene blue, lipiodol, barium, fluorescence tracer, intraoperative ultrasonography, transthoracic, bronchoscopy, virtual bronchoscopy, electromagnetic bronchoscopy, 3D printing, artificial intelligence, and intraoperative molecular imaging (Table 1).

CT-guided percutaneous placement of markers

CT-guided percutaneous solid markers

Hookwire

After long-term practice, the percutaneous situation of localizers is viewed as a generally safe and effective method (9). At present, the most widely used method in clinical practice is CT-guided hookwire placement (10), which was first reported by Mack in 1992 (11). Hookwire is especially effective when the node is superficial to the lung. The process is based on CT-guided lung biopsy, and thus, it is associated with similar complications to CT-guided lung biopsies. A common complication is pulmonary hemorrhage, with a reported incidence of 31.38% (342/1,090), and includes lower-grade (24.4%, 266/1,090) and higher-grade hemorrhage (6.97%, 76/1,090) (12). The most fatal complication is air embolism (13). However, CT-guided hookwire placement also has its drawbacks, such as pneumothorax, hemothorax, subcutaneous emphysema, and wire shedding (14,15), in addition to life-threatening complications caused by air embolism, such as cerebral infarction, epilepsy, temporary and permanent paralysis, shock, and cardiac arrest (14,16). In 2002, Japanese researchers conducted a Hookwire marking and auxiliary suture system in 168 lesions of 150 patients and observed complications of asymptomatic pneumothorax in 54 cases (32.1%), intrapulmonary hemorrhage in 25 cases (14.9%), and hemothorax in 1 case (0.6%). The failure marking of 4 patients was due to superficial puncture, and none of the participants experienced major complications (17). Iguchi et al. also reported that 2 in 500 patients experienced retained Hookwires. One of the cases was due to the Hookwire being placed at a considerable distance from
the target and the other was due to a wedge resection performed from the interlobar fissure side (18). Other studies and reviews have shown similar rates of relatively minor complications (10,19-23). However, this method has been banned in Japan due to the possibility of death due to air embolism (24).

Microcoils

Another widely used CT-guided intraoperative implanted is the microcoil. Mayo et al. reported the safety and efficacy of VATS guided by microcoils for the resection of 75 pulmonary nodules (4–24 mm). In their study, the microcoil displacement complication rate was 3%, and the diagnostic rate of fluoroscopy-guided resection was 97% (25). In a randomized trial, Finley et al. reported that microcoil localization of pulmonary nodules less than 15 mm in diameter had a success rate of 93% (27/29), without associated complications (26). The conversion rates for thoracotomy due to failure of nodule identification during VATS ranged from 0 to 6.6% (25,27). Small needle-pleura angle (≤30°), pleura-microcoil distance (≤20 mm), and the presence of pleural indentation during the procedure were identified as significant risk factors contributing to microcoil pleura marking failure (28). Compared to Hookwire, microcoil localization has a corresponding successful operative field targeting rate of 97% to 94%, a successful VATS rate of 97% to 96%, and a lower complication rate (9,29). Xu et al. reported microcoil localization in 47 patients (48 pulmonary nodules) covered by the scapulae, and the rates of successful targeting and localization were 95.8% (46/48) and 89.6% (43/48), respectively (30). The most common complications were asymptomatic pneumothorax (4–13%) and microcoil displacement (0–5%) (26,31).

Hydrogel

To overcome complications such as pneumothorax caused by localizers, cylindrical hydrogel plugs have been proposed for intraoperative marking of pulmonary nodules (32-34). In this method, after CT-guidance of the lung tissue puncture, the dry hydrogel is used to enter the lung nodule. When the delivery system with the guide needle is withdrawn from the chest wall, the dry hydrogel is rapidly hydrated due to the contact with the parenchyma nearby. The needle tract is sealed, and the expanded hydrogel protrudes from the parenchymal pleura and marks the location of the inferior nodule. Imperatori et al. recently reported the use of this method to identify 28 pulmonary nodules, with 89% (25/27) of the nodules detected by hydrogel plug localization, and the other 11% discovered by palpation or pleural puncture.

Table 1 A summary of the literature search strategy

| Items                                      | Specification |
|--------------------------------------------|---------------|
| Date of search (specified to date, month, and year) | 10/03/2022 |
| Databases and other sources searched       | Cochrane Library, PubMed, ClinicalTrials, and China National Knowledge Infrastructure |
| Search terms used (including MeSH and free text search terms and filters) | MeSH: lung neoplasms, Free text search terms: pulmonary/lung nodule, peripheral lung lesion, ground-glass opacities, preoperative marking, intraoperative marking, thoracoscopic surgery, video-assisted thoracoscopic surgery, Hookwire, microcoils, hydrogel plug, methylene blue, lipiodol, barium, radionuclide, fluorescence tracer, intraoperative ultrasonography, transthoracic, bronchoscopy, virtual bronchoscopy, electromagnetic bronchoscopy, 3D printing, artificial intelligence, and intraoperative molecular imaging. |
| Timeframe                                  | 1 January 1990 to 10 March 2022 |
| Inclusion and exclusion criteria (study type, language restriction, etc.) | Inclusion: clinical trials, retrospective study, case reports. Exclusion: animal testing. Literature published in any language were included |
| Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.) | A comprehensive literature search was independently conducted by two authors (Lu Tang and Yiheng Zhang) to identify the relevant published studies |
| Any additional considerations, if applicable | None |

MeSH, Medical Subject Headings.
displaced. Only 1 in 28 cases (4%) required drainage due to pneumothorax during hydrogel plug labeling, and no other complications were reported (35). Qian et al. also reported similar results using medical glue to locate 15 pulmonary nodules: 1 case of pneumothorax, 5 cases of chest pain, and 6 cases of cough were reported (36). Wang et al. used blue-stained glue in 20 patients with a 100% success rate for intraoperative localization, and 9 cases of pneumothorax and 4 cases of minor pulmonary hematoma were detected (37).

In addition to research innovations in implants, recently, cone beam CT (CBCT)-guided percutaneous approaches or DynaCT combined with intraoperative CT in the hybrid operating room (HOR) in the lung have been reported. In cases of simultaneous localization of difficult lesions, advantages such as less discomfort, fewer complications, and lower VATS conversion rates have been reported (38-40).

**CT-guided percutaneous injection of liquid marker**

**Methylene blue (MB)**

MB is one of the most commonly used dyes in clinical practice, and MB localization is a relatively safe and inexpensive method. The procedure is well tolerated by the patient as there is no foreign body implantation. The thoracoscopic identification rate of pulmonary nodules after MB localization is 90–100% (41,42). However, an important disadvantage of MB labeling is that the dye diffuses into the surrounding lung parenchyma, preventing accurate identification of pulmonary nodules (10), with a failure rate of up to 8% (43). Furthermore, in rare cases, MB can cause allergic reactions (44). In cases such as when anthrax hyperpigmentation is present in the lung parenchyma, the dye may not be distinguishable from the surrounding lung during thoracoscopy (41,44). Some researchers have suggested that VATS should be started within 120–150 minutes after localization to reduce the spread of MB to the surrounding tissues (43). To prevent this shortcoming of rapid diffusion, many researchers have developed improved methods, such as MB-stained autologous blood (45), MB mixed with contrast agents and collagen (46), and MB-stained glue (37). The same dye localization method also uses patent blue V (PBV) dye (47,48) and agar (49).

**Lipiodol and barium**

Lipiodol injection is another widely accepted localization method. Mogi et al. used CT-guided lipiodol to mark 56 patients during VATS. The candidates for lipiodol marking had lesions ≤10 mm in diameter and/or with a distance to the nearest pleural surface of >10 mm that were also localized in the outer third of the lung parenchyma. A total of 55/56 patients (98.2%) successfully underwent the resection (50). With regards to complications, pneumothorax, hemorrhaging, chest pain, blood in sputum, and pneumothorax were noted (50-52). Barium is another imaging agent for the localization of pulmonary nodules. Lee et al. reviewed 10 patients with pulmonary nodules who underwent CT-guided barium sulfate preoperative localization. Postoperative CT scans showed that the localization success rate was 100%. Besides 2 cases of pneumothorax after the operation, no other complications were detected (53). However, the barium suspension forms round or oval barium balls in the lung tissue, and the density is very different from that of lung tissues, which can cause a severe acute inflammatory reaction and even pulmonary edema or pulmonary fibrosis, and thus, should be used with caution (53).

**Radionuclide**

Radionuclide injection under CT guidance is mainly based on the injection of $^{99m}$Tc-labeled human serum albumin at the lung nodules, followed by intraoperative probe detection of gamma rays converted into digital counts and audio signals (54). The advantage of radiotracers is that they remain in the body for more than 24 hours, can be well tolerated by patients, and can detect deep nodules. However, its disadvantage is that it is facility-dependent, requires special equipment (radiotracer, gamma probe, and radiation protection equipment), and increases radiation exposure. Ambrogi et al. used this method on 211 patients with a success rate of 98.6% (208/211). Only 1 case of pneumothorax during the labeling procedure was detected, where some radio-tracer had expanded into the pleural space, which suggested that this method is safe and effective (55).

**Indocyanine green (ICG)**

Currently, CT-guided localization using the fluorescent tracer ICG is popular due to its clear visualization (56). Zhang et al. reported the use of CT-guided percutaneous injection of ICG to localize 35 patients, with a success rate of 94.3% (33/35). No severe adverse reactions were found during the procedure (57). Although ICG can realize the detection of pulmonary nodules, the method has certain limitations, including the requirement for fluoroscopy equipment to detect ICG fluorescence. In addition, the
diffuse or insufficient injection of ICG may seriously affect the ability of the operator to locate the nodule.

**CT-guided percutaneous dual localization**

Some markers can be combined for clinical applications. For example, Zhang et al. performed CT-guided labeling of 153 pulmonary nodules in 140 patients which were smaller than 2 cm with a mixed method of tissue adhesive and iohexol (58); Jiang et al. used medical glue and MB to mark 383 nodules in 346 patients (59); Doo et al. used Hookwire and $^{99m}$Tc to mark 36 nodules in 34 patients (60); Wang et al. used $^{99m}$Tc and MB to mark a patient successfully (61); and Brady et al. localized 75 nodules with Hookwire combined with MB injection in 74 patients (62). Although these combined applications have also been associated with complications, it is presumed that they can also effectively improve the overall surgical recognition rate.

**Bronchoscopy-guided placement of markers**

An alternative to the percutaneously-mediated approach is the bronchoscopy approach. The latter appears to be an improvement in terms of complications such as pneumothorax and hemothorax. Furthermore, percutaneous CT marking can be complicated by air embolisms, yet there have been no reports of air embolism caused by bronchoscopy. In addition, bronchoscopy can be used in areas that are not accessible by percutaneous methods, including the interlobar fissures and areas facing the mediastinum, diaphragm, and scapula. Bronchoscopy labeling methods including instillation of barium mixtures (63-65), blue or fluorescent dyes (66-71), and placement of microcoils (72,73), all of which have a similar success rate as CT-guided percutaneous labeling. The implementation of these techniques is performed under CT fluoroscopy or virtual bronchoscopy.

**Electromagnetic navigation bronchoscopy (ENB)**

ENB is a technique proposed in recent years for the evaluation of small peripheral lung lesions. It combines virtual and conventional bronchoscopy with the aim of guiding the diagnosis and/or localization of pulmonary nodules with dye-labeled instruments. The ENB diagnosis rate of pulmonary nodules can reach 90–100% (67,74–76). Compared with other percutaneous markers, ENB-guided dye labeling for intraoperative VATS localization is safe and has fewer complications (70,75–78). A meta-analysis of 15 studies, including 681 procedures, demonstrated that diagnostic ENB is safe: 40 cases of pneumothorax, 7 cases of minor or moderate bleeding, and 2 cases of post-procedural respiratory failure were reported, with none requiring specific treatment (79).

**Virtual-assisted lung mapping**

The 3D localization of lung nodules is represented by virtual assisted lung mapping (VAL-MAP), which traditionally provides multiple markers on the lung, as well as geometric information, or X, Y, and/or Z axes on the lung surface. Importantly, multi-label two-dimensional (2D) or 3D information replaces single-dimensional localization that may cause inaccurate incisal margins, and CT repositioning after VAL-MAP ensures accurate or reproducible information. The Japanese researcher Sato published a series of reports on VAL-MAP labeling, with the methodology changing from 2D to multi-dimensional, from MB to visualization in dye, and from traditional CT to CBCT (24,74,80–84). Furthermore, VAL-MAP was associated with a low risk of pneumothorax (6.6% per case; 2.1% per mark), with no hemothorax (80).

Similarly, some cases of bronchoscopy combined with intraoperative use of cone-beam CT or ENB have been successfully performed, with bronchoscopy dye labeling of small pulmonary nodules (38,66).

**Intraoperative ultrasonography**

US technology has been used to locate pulmonary nodules since the 1990s. It has the advantage of being safe and effective in locating unpalpable nodules in real time without causing damage to the lung parenchyma, thus eliminating the risk of pneumothorax and hemoptysis. However, it has certain limitations. For example, to avoid artifacts, lung US requires complete deflation of the lungs, which is more difficult in patients with emphysema. Ground-glass opacities (GGOs) are difficult to identify by US due to their density being close to that of normal lung parenchyma. However, the study by Kondo et al. showed that experienced clinicians can safely and effectively localize these nonpalpable nodules by intraoperative US (85). Other studies have confirmed that the success rate of intraoperative US identification of pulmonary nodules can reach 93–98% (86–89). An US provides access to most of the visceral pleural surface. During VATS, US can almost completely explore the
visceral pleura, and a 1 cm length US probe can enter areas of the lung that cannot be reached by finger palpation. In addition, the US can be positioned to compensate for the failure of intraoperative CT-guided marking.

Lachkar et al. reported the use of radial endobronchial ultrasound (r-EBUS) for virtual bronchoscopy of endoscopic pleural dye-labeled biopsy of pulmonary nodules (90). Ost et al. conducted a multicenter clinical study and found a diagnostic rate of 63.7% with either r-EBUS nor ENB, 57.0% with r-EBUS alone, 38.5% with ENB alone, and 47.1% with both ENB and r-EBUS. These results differed significantly from expectations, and prospective studies are warranted to further assess the efficacy and cost/benefit ratio of these modalities (91).

### 3D printing technology

Currently, 3D printing is an evolving manufacturing technology. When percutaneous placement of markers is used in combination with preoperative 3D-assisted printing and localization technology, it can effectively reduce unnecessary radiation exposure that occurs during conventional localization process. A study by Fu et al. involving 37 patients used CT scans to build models, and 3D printed models were then used for intraoperative percutaneous localization to help identify small lung nodules. After a learning curve, the localization success rate was as high as 95.6% (92). Zhang et al. randomized 190 patients into the groups in a 1:1 ratio and compared percutaneous localization with 3D template and CT-guided percutaneous localization. There was no deviation between the two groups of localizers, with patients in the 3D template group showing better localization time and less radiation dose (93).

### AI

In this golden age of rapid advances in AI, researchers and surgeons are realizing that AI can contribute to every aspect of healthcare, especially surgery. In terms of pulmonary nodule localization, the use of CT-guided 3D reconstruction, virtual reality (VR), augmented reality (AR), and mixed reality (MR) have all been explored.

The VR technology can assist in the generation of immersive, completely artificial computer-simulated images and environments that allow for real-time interaction. Jensen et al. developed a VATS lobectomy assessment tool (VATSAT) which provides supervisors and assessors with a procedure-specific assessment tool for evaluating VATS lobectomy performance and helps to determine when a trainee is ready to work unsupervised (94). Ujiie et al. developed a VR surgical navigation system using head mounted displays (HMD) to improve preoperative planning and contribute to the safety and accuracy of anatomic resection (95). Qin et al. developed a training system (VatsSim-XR) which includes customized haptic-enabled thoracoscopic instruments, a VR helmet set, endoscope kit with navigation, and a patient-specific corresponding training environment (96).

The AR technology superimposes computer-generated imagery onto a real-life view. Peng et al. constructed a model using pigs and selected 30 native lung structures to simulate solitary lung nodules. Using the Microsoft HoloLens AR system (Microsoft Corp., Redmond, WA, USA), the points picked in the model could be accurately marked. The results showed an average success rate of 76.67% within a diameter of 1 cm around nodules, and 100% within a diameter of 2 cm around nodules. Therefore, HoloLens AR-assisted pulmonary nodule localization may be a promising technique to improve the surgical treatment of early-stage lung cancer (97).

Combining AR and VR gives rise to MR, where digital and physical objects interact in real-time. Perkins developed a software application and medical image processing pipeline for the Microsoft HoloLens to incorporate patient-specific data and provide a mixed-reality tool to explore and manipulate chest anatomy with a custom-designed user interface featuring gesture and voice recognition. This may facilitate the accurate and rapid identification of small lung lesions during minimally invasive surgeries and reduce the need for additional invasive preoperative localization procedures (98).

Although AI technology is still in the initial stages of research, it has broad prospects. For example, the simplification of operations is conducive to the training of young doctors. However, there are also many challenges, such as the diversification of surgical operations, the inability to achieve the unity of computer simulation, and some anatomical variations that may lead to errors in AI recognition. The effective integration of AI with thoracic surgery remains a challenging research topic.

### IMI

Currently, IMI emerging as a new technique that uses targeted optical contrast agents in combination with...
imaging devices during surgery to identify resected lung cancer tissue. The commonly used imaging systems include Artemis (the Netherlands), PINPOINT (Canada), Firefly (USA), Karl Atorz Photodynamic Diagnostics (PPD; Germany), and DPM (China). Most of the research in this area has been performed by Professor Singhal of the University of Pennsylvania. Okusanya et al. first tried to locate pulmonary nodules by intravenous administration of ICG in 2014. They administered 5 mg/kg of ICG 24 hours before surgery and successfully identified the 16 pulmonary nodules in 18 patients, and an additional 5 sub-centimeter nodules were found, making this the first in-human trial using near-infrared (NIR) imaging to identify pulmonary nodules during thoracic surgery (99).

Kim et al. demonstrated that ICG can locate pulmonary nodules in resected lung specimens at a dose of 1 mg/kg; just 2 false positives were seen in patients with no residual tumor after neoadjuvant treatment (100). Mao et al. also labelled 36 patients with intravenous administration of ICG. In 36 patients, 76 nodules were resected, and 68 nodules were found during in vivo exploration by ICG fluorescence imaging (101). Researchers have also applied ICG intravenous injection to detect lesions in patients with sarcoma lung metastases, and to identify colon cancer lung metastases during surgery, with some occult lesions detected in their studies (102, 103). In addition to systemic administration, Quan et al. tested 6 patients through respiratory tract administration of ICG, and the results showed that the fluorescence mainly localized in non-cancerous tissues, and the edge of the tumor could be clearly displayed, which represents a method of reverse exploration (104).

Due to the limitations of ICG with poor specificity, including accumulation in areas of inflammation, researchers have sought a targeted molecular imaging agent that can specifically bind to and identify lung adenocarcinomas (LUADs). The folate receptor (FR) is a highly expressed target in LUAD. There are 4 members in the FR family, but only FRα and FRβ bind folic acid with high affinity. Approximately 80–90% of LUADs express apical luminal FRα (1–3 million receptors per cancer cell), and thus, bind greater amounts of serum folate than normal lung epithelial cells (105–107). Therefore, FRα may be a potential molecular target for the diagnosis of LUAD. Keating et al. designed a compound named EC17 (C42H34N10Na2O10S), which is produced by binding folic acid hapten (vitamin B9) and fluorescein isothiocyanate (FITC) through an ethylenediamine spacer. Patients were administered 0.1 mg/kg EC17 dissolved in 10 mL of normal saline 2 hours before surgery via peripheral vein injection lasting 10 minutes. Fluorescence imaging during surgery revealed that the lung nodules of all 3 patients showed green fluorescence, with no adverse reactions (108). Predina et al. conducted further studies on the imaging conditions. Due to the non-specific accumulation of contrast agents in non-cancerous tissues, lung parenchyma, granulomas, edema tissues, and others, the fluorescence signals may be similar to those of some tissues which have biological chromophores, such as hemoglobin, collagen, and porphyrin. The tumor-to-background ratio (TBR) can be improved by modifying the exposure time on the imaging capture device (109). Okusanya et al. reported using EC17 4 hours before surgery in 50 patients, with 92% sensitivity for pulmonary adenocarcinomas. Only 14% of nodules were identified with intraoperative fluorescence imaging (IFI) in vivo (105). Kennedy et al. also applied EC17 4 hours before surgery and achieved 100% specificity for pulmonary adenocarcinomas. These results indicated that optical biopsy may be more accurate than frozen section for the identification of pulmonary adenocarcinomas (110).

Since the success rate of nodules targeted by FITC is related to the distance from the pleura, the team developed another material, OTL38. OTL38 is a folate analog conjugated to the NIR dye S0456 with excitation and emission maxima at 776 and 796 nm, respectively. Due to light scattering reduction and reduced blood absorption, the depth of penetration into solid organs increases and autofluorescence decreases (111). Keating et al. first studied OTL38 in cells, followed by animal and human experiments. After intravenous injection of 0.025 mg/kg OTL38 2 hours before surgery, fluorescence was detected in all 3 lung nodules. The results of this study support the use of NIR thorascopic surgery with an appropriately targeted NIR contrast agent for the investigation of early stage non-small cell lung cancer to delineate tumor margins and identify metastatic lymph nodes (111). Predina et al. conducted a series of clinical trials and demonstrated that OTL38 has a sensitivity of 69.2–100% for the in vivo localization of pulmonary nodules in FR-positive patients, and the depth of pulmonary nodules from pleura can reach 2 cm (112–114). The mechanism is shown in Figure 1.

In summary, NIR imaging has several unique advantages compared with other techniques, including no requirement for radiation, better imaging through organs, no requirement for advance knowledge regarding the location of the nodule, ease of interpretation, real-time, and intuitive...
use for the observer. Therefore, this technology will likely become the treatment trend in the future. A summary of the clinical trials examining IFI for pulmonary nodules can be found in Table 2.

**Limitations**

There were several limitations to this review. First, good quality data was not available for some of the topics covered. Second, some relevant articles may have been missed. Third, a formal quality assessment of the included articles was not performed.

**Summary**

Currently, a variety of techniques are available for the identification of intraoperative pulmonary nodules. This article summarized the advantages and disadvantages of existing research methods and their clinical progress, so as to assist doctors in providing optimized clinical strategies. Clinicians can communicate with the multidisciplinary team and decide upon the appropriate positioning method according to each patient’s circumstances and the support of the existing equipment and technology of the institution. The various methods, instruments, and modalities described in this paper each have their own shortcomings and limitations (Tables 3,4), and further research to identify improved solutions is warranted.

This article provided a detailed summary of IMI, which is non-invasive, simple to operate, and does not increase the difficulty nor risk of surgery. However, all the associated target markers are nonspecific or target LUADs, and thus, the development of fluorescent nanomaterials with new targets may be the direction of future developments.

**Figure 1** OTL38, a folate analog conjugated to the NIR dye S0456, is an agent that selectively targets the FRα on tumor cell membranes. When study participants received intravenous OTL38 (0.025 mg/kg) 3 to 6 hours before resection, in situ, real-time fluorescent imaging was performed using an iridium system, and the tumors displayed in situ fluorescence. NIR, near-infrared; FR, folate receptor.
| Principle investigator | Year | Disease | Surgical approach | Drug | Dose | Method | Time from injection to imaging | Imaging system | No. of patients | No. of nodules | Sensitivity for malignancy | Size of the smallest nodules detected | Maximum depth of detected nodules | TBR (range) | SUVmax |
|------------------------|------|---------|------------------|------|------|--------|-------------------------------|----------------|----------------|---------------|-------------------------------|-------------------------------------|------------------------------------|----------------|--------|
| Okusanya (99)          | 2014 | Lung cancer | Thoracotomy      | ICG  | 5 mg/kg | Systemic injection | 24 h | BioVision | 18 | 23 | 95.5% (21/22) | 0.2 cm | 1.3 cm | 1.5–4.4 | 0–11 |
| Kim (100)              | 2016 | Lung cancer | VATS             | ICG  | 1 mg/kg | Systemic injection | 24 h | PINPOINT | 11 | 11 | 88.9% (8/9) | 0.3 cm | 1.4 cm | NR | 0.8–9.6 |
| Mao (101)              | 2017 | Lung cancer | VATS             | ICG  | 5 mg/kg | Systemic injection | 24 h | D-Light P, SUPEREYE | 36 | 76 | 88.7% (63/71) | 0.1 cm | 1.3 cm | 1.43–11.9 | 3.29±1.81 (mean) |
| Newton (102)           | 2018 | Colon cancer lung metastases | VATS | ICG  | 3 mg/kg | Systemic injection | 24 h | Iridium | 1 | NR | 100% (1/1) | 0.2 cm | NR | NR | NR |
| Predina (103)          | 2019 | Sarcomas lung metastasis | Thoracotomy | ICG  | 5 mg/kg | Systemic injection | 24 h | Iridium | 10 | 16 | 87.5% (14/16) | 0.3 cm | 1.3 cm | 2.7–4.2 | NR |
| QUAN (104)             | 2020 | Lung cancer | VATS             | ICG  | 0.75 mg/mL | Respiratory inhalation | 1 h | Pinpoint | 6 | 6 | 100% (6/6) | 0.2 cm | 1.0 cm | NR | NR |
| Keating (108)          | 2016 | Lung cancer | NR              | EC17 | 0.1 mg/kg | Systemic injection | 2 h | NR | 3 | 3 | 100% (3/3) | 2 cm | NR | 3.3–3.6 | 5.2 |
| Okusanya (105)         | 2015 | Lung cancer | Thoracotomy      | EC17 | 0.1 mg/kg | Systemic injection | 4 h | Artemis or FluoCam | 50 | 50 | 92.3% (48/52) | 0.3 cm | 0 | 2.0–14.7 | 0–19 |
| Kennedy (110)          | 2015 | Lung cancer | VATS             | EC17 | 0.1 mg/kg | Systemic injection | 4 h | FluoCam | 30 | 30 | 100% (19/19) | 0.7 cm | 0 | 4.8–6.3 | 1.8–6.1 |
| Keating (111)          | 2017 | Lung cancer | Thoracotomy      | OTL38 | 0.025 mg/kg | Systemic injection | 3 h | Karl Storz | 3 | 3 | 100% (3/3) | 3.4 cm | NR | 2.2–3.4 | NR |
| Predina (112)          | 2018 | Lung cancer | NR              | OTL38 | 0.025 mg/kg | Systemic injection | 2.8–4.5 h | Iridium | 20 | 21 | 100% (24/24) | 0.1 cm | 0.39 cm (mean) | 2.1–4.2 | 2.8–10.0 |
| Predina (113)          | 2018 | Lung cancer | VATS             | OTL38 | 0.025 mg/kg | Systemic injection | 3.4–5.1 h | Iridium | 12 | 13 | 69.2% (9/13) | 1.1 cm | 1.2 cm | 2.2–3.7 | 3.5–8.9 |
| Predina (114)          | 2017 | Lung cancer | MITs             | OTL38 | 0.025 mg/kg | Systemic injection | 3–6 h | Iridium | 50 | 66 | 95.6% (65/68) | 0.2 cm | NR | 3.2±0.8 (mean) | 6.5±3.7 (mean) |

No., number; TBR, tumor-to-background fluorescence ratio; ICG, indocyanine green; VATS, video assisted thoracoscopic surgery; NR, not reported; MITS, minimally invasive thoracic surgery.
| Modality                  | Method          | Time to surgery | Advantages                                                                 | Disadvantages                                                                 | Complications                                                   |
|--------------------------|-----------------|-----------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------|
| Hookwires                | Percutaneous    | ≤3 h            | High success rate; easy to operate                                         | Hookwire dislodgement; patient discomfort; immediate operation; difficult to locate pulmonary nodules in some areas | Pneumothorax; parenchymal hemorrhage; subcutaneous emphysema; retained; air embolism (rare) |
| Microcoils               | Percutaneous    | Days            | Well tolerated; easy to operate; flexibility with time to surgery          | No direct mark on the pleural surface results; radiation exposure increased   | Embolization; migration; parenchymal hematoma                    |
| Hydrogel plugs or medical glue | Percutaneous; ENB | Weeks          | Sealing up the needle track, decreasing the rate of puncture-related complications; non-toxic; good biosafety; long duration in body | Pungent smell                                                               | Irritating cough                                                 |
| Methylene blue/PBV       | Percutaneous    | ≤3 h            | Cheap and easy to get; no foreign body left in the lung; well tolerated; no anatomic limitation; no effect on pathology | Dye diffusion; immediate surgery; less reliable in anthracotic pigmentation lung | Anaphylaxis (rare)                                              |
| Lipiodol                 | Percutaneous    | Months          | Easy to operate; well tolerated; flexibility with time to surgery; well demarcation; no effect on pathology | Radiation exposure; pneumothorax; hemorrhaging in the lung parenchyma          | Systemic embolization; allergy                                  |
| Barium                   | Percutaneous    | Months          | Easy to operate; well tolerated; stable and no diffusion; flexibility with time to surgery; easy to recognize | Effect on pathology; radiation exposure                                       | Lung inflammation and pneumonia                                 |
| $^{99m}$Tc               | Percutaneous;   | ≤24 h           | Easy to operate; well tolerated; deep detection                           | Spillage into the pleural; half-life 6 h; special equipment required; radiation exposure | Unremarkable                                                   |
|                           | ENB; intravenous|                 |                                                                           |                                                                               |                                                                  |
| ICG and target molecular fluorescent dye | Percutaneous; ENB | 24 h            | Dyeing durable; safe; visible fluorescence; cheap and easy to get; no foreign body left in the lung; well tolerated; no anatomic limitation; no effect on pathology; easy to operate | Controlling the injection dose; complex imaging system needed; limited depth of penetration | Allergy (rare)                                                  |
| Intravenous              |                 | 2–24 h          | Detecting unidentified nodules                                             | Only useful for pulmonary adenocarcinoma; high false positive rate            | Unremarkable                                                   |
| Inhalation               |                 | 1 h             | Only accumulation in the lung; convenient; application during the operation; low allergic reaction | Reverse imaging; complex imaging system needed                                | Unremarkable                                                   |

PBV, patent blue V; ICG, indocyanine green; ENB, electromagnetic navigation bronchoscopy.
Table 4 Advantages and disadvantages of different instruments used in assisting the localization of lung nodules

| Instrument | Advantages | Disadvantages |
|------------|------------|---------------|
| CT         | Easy to operate; short operation time; high success rate; low cost | Pneumothorax; parenchymal hemorrhage; subcutaneous emphysema; difficult to locate pulmonary nodules in some areas |
| Bronchoscopy | Reduce pneumothorax and bleeding and can locate some positions that are difficult to puncture anatomically | Limited localization accuracy; complicated localization procedure; higher localization costs; pneumothorax; minor or moderate bleeding |
| ENB        | High success rate; safety | Expensive; complex operation process; high technical requirements |
| VAL-MAP    | Better determination of the surgical margin; safety; effectiveness | Expensive; complex operation process; high technical requirements; cumbersome process; immediate surgery is required |
| AI         | Reducing surgical fatigue; removing the lesions under direct vision | Expensive; high technical requirements; recognition error |
| Hybrid operation room | Shorten the time period from localization to VATS; one anesthesia for the operations | Expensive; high technical requirements |
| US         | Safety; real time locating; without any material in lungs | Complete deflation of the lungs; normal lung parenchyma density nodules not identifiable; poor mobility and limited depth |

CT, computed tomography; ENB, electromagnetic navigation bronchoscopy; VAL-MAP, virtual assisted lung map; AI, artificial intelligence; US, ultrasound; VATS, video assisted thoracoscopic surgery.

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