



Advances in techniques for identifying small pulmonary nodules

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Abstract

Since the introduction of video-assisted thoracoscopic surgery, the demand for its use in resecting small pulmonary nodules has increased. In parallel, the development of high-resolution computed tomography has led to an increase in the detection of the early lung cancers appearing as nodules with ground-glass opacity. Several techniques to resect these small lesions have been devised, the most familiar of which is the use of a computed tomography-guided percutaneous hook wire. We recently developed virtual-assisted lung mapping to achieve safer and more reliable resection of these lesions. Virtual-assisted lung mapping is carried out using three-dimensional computed tomography, bronchoscopy, and fluoroscopically guided navigation to mark the lung surface with dye. A prospective study showed that this technique was safe and had a high success rate. Multiple marking around the targeted lesion allows for a sufficient surgical margin at resection. We recently introduced an electromagnetic navigation bronchoscopy system to confirm the sites to be marked by virtual-assisted lung mapping in the operating room prior to video-assisted thoracoscopic surgery. We are now studying a method to enable minimally invasive, safe, and reliable resection of lesions located deep in the lung parenchyma.

Keywords Pulmonary nodule · Video-assisted thoracic surgery · Virtual-assisted lung mapping

Background

Video-assisted thoracic surgery (VATS) has been commonly used in the surgical treatment of lung cancer since the 1990s in Japan, because it is less invasive than the conventional open thoracotomy. The first report on VATS published by Japanese researchers, as indexed on PubMed, appeared in 1993 [1]. We started performing VATS in our department in 1992, and the first case report was published in 1993 [2]. We published a textbook on VATS written in Japanese, including preparation, instruments for VATS, techniques of basic procedures, and applications to various diseases, in 1997 [3].

Since the introduction of VATS, we have been responding to an increasing demand for resection of small intrapulmonary lesions to improve the postoperative survival of lung cancer. One of the challenges in treating small pulmonary lesions is confirming their location. During thoracotomy, surgeons can palpate the lung directly with their fingers

to readily find intrapulmonary nodules. However, manual palpation of intrapulmonary nodules cannot be done with VATS.

In the 1990s, some surgeons suggested that small pulmonary nodules might be resected through open thoracotomy rather than VATS. In a prospective study of VATS pulmonary metastasectomy followed by open thoracotomy, the majority of patients had additional nodules found during the open procedure [4].

However, parallel to the increasing use of VATS, high-resolution computed tomography (HRCT) has been widely applied to detect small pulmonary lesions suspected of being lung cancer. To date, it seems rare for intrapulmonary lesion not detected on HRCT to be found during surgery, even open thoracotomy. It has, therefore, become common practice to remove small intrapulmonary lesions, as detected on HRCT, through VATS.

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Indications for pulmonary resection of small nodules suspected of being early lung cancer

HRCT can detect very small pulmonary nodules suspected of being early lung cancer. In 1995, Noguchi et al. [5] found that a subgroup of small adenocarcinomas with a diameter of ≤ 2 cm had a very good prognosis after surgical resection. They identified an adenocarcinoma in this subgroup that shows lepidic growth along the alveoli without central fibrotic foci of the nodule. Pulmonary subsolid nodules showing ground-glass opacity were subsequently found to be identical to the adenocarcinoma showing benign features [6].

These subsolid pulmonary nodules are being found relatively frequently on health screenings in our country. Because whether or not these subsolid nodules are life-threatening is unclear, several guidelines for their assessment have been published. For example, the British Thoracic Society (BTS) guidelines (2015) recommend assessing the growth of nodules ≥ 80 mm³ or ≥ 6 mm maximum diameter by calculating the volume doubling-time based on repeat computed tomography (CT) at 3 months and 1 year [7]. The Fleischner Society guidelines (2017) recommend periodically following up subsolid nodules with a pure ground-glass opacity or partly solid nodules with a maximum dimension of ≥ 6 mm. These guidelines recommend that the second assessment be 6–12 months after the first, because these subsolid nodules are likely to disappear [8]. Finally, the Japanese Society of CT Screening (2013) recommends that subsolid nodules be biopsied and examined histologically if the maximum diameter of the entire nodule is ≥ 15 mm or if the maximum diameter of the solid component exceeds 5 mm on CT during follow-up [9].

Techniques of detection of small pulmonary nodules through VATS

VATS has the advantage of being less invasive than the conventional thoracotomy. However, it is generally more difficult to detect the location of pulmonary nodules with VATS than with thoracotomy, as the bimanual palpation of the intrapulmonary nodules cannot be done through VATS. As a result, many researchers have developed devices to identify intrapulmonary small nodules through small trocar access ports (Table 1). We have studied techniques for detecting intrapulmonary small lesions.

In 1995, we developed a tactile sensor to detect pulmonary nodules [10]. The principle of the tactile sensor was

Table 1 Techniques to detect small intrapulmonary nodules

Alternatives to finger palpation	
Tactile sensor	(1995 Ohtsuka) [10]
Ultrasound	(1999 Santanbrogio) [11]
Jet-air spray	(2006 Kawahara) [12]
Marking	
CT-guided hook wire placement	(1992 Mack) [13]
CT-guided coil placement	(1994 Asamura) [14]
CT-guided barium marking	(2001 Okumura) [15]
Virtual-assisted lung mapping	(2014 Sato) [16]

CT computed tomography

to detect differences in resonance frequency among materials according to their stiffness. The sensor was located at the tip of a probe. As we scanned the pulmonary surface with the sensor tip, any sudden change in the resonance frequency would be displayed on a monitor when the tip passed over the pulmonary surface where the nodule was buried. We determined the appropriate sensitivity with which to detect intrapulmonary nodules.

Other touch sensors using an ultrasound probe [11] and jet-air spray [12] have been described in the literature as alternatives to direct palpation for detecting small pulmonary nodules located deep in the lung parenchyma. However, it generally takes time to scan the entire surface of the lung with these probes. Moreover, we have often detected subsolid pulmonary nodules that are as soft as surrounding normal lung tissue.

Another major approach to detecting intrapulmonary nodules involves marking lung tissue. Fiducial markers placed via bronchoscopy or percutaneous puncture have been used worldwide [13–18]. CT-guided percutaneous hook wire placement at the lung surface near the lesion is the most common of these methods [13]. In our department, we have used this method for over 10 years. We have published our results of the hook wire placement elsewhere [18], with a 100% success rate in resecting the targeted pulmonary nodules (mean diameter 1.1 cm), and none of these cases required preoperative treatment for serious complications of the marking.

The rate of overall complications after hook wire placement was reported to be high, with the rate of pneumothorax being 32%, bleeding 14.9%, hemothorax 0.6%, and dislodgment 5% [19]. Furthermore, air embolism in the left heart, which was usually fatal, was mentioned in some reports [20, 21]. The incidence of air embolism was estimated to be 0.05–0.07% [22]. The mechanism underlying arterial air embolism may involve the co-penetration of the airway and pulmonary vein, with the air in the bronchi having the chance to migrate into the pulmonary vein, resulting in systemic arterial air embolism. Although the

incidence of air embolism is reportedly rare, we cannot overlook this serious complication. Bronchoscopic fiducial placement is a safer method for patients: a marking technique using barium sulfate observed through a fluoroscope [15] and that using indocyanine green observed with a near-infrared fluorescence thoracoscopy [16] were found to be most useful for detecting small pulmonary nodules, even if they were located deep in the lung parenchyma.

Virtual-assisted lung mapping

Virtual-assisted lung mapping (VAL-MAP) uses multiple dye markings of the lung surface made via bronchoscopy. VAL-MAP is a “mapping” technique showing a certain area to be resected rather than “marking” an approximate pleural surface to be resected. With the aid of three-dimensionally (3D) arranged CT images, multiple dye markings with indigo carmine are performed [17].

In brief, the steps in this procedure are as follows: (1) mapping is planned using virtual bronchoscopy, and 3D images are constructed from CT data; (2) bronchoscopic lung markings are made with indigo carmine under fluoroscopic observation; (3) the target bronchi are confirmed using virtual bronchoscopic guidance and a catheter preloaded with 1 ml of indigo carmine for each target; (4) the catheter is inserted into each target bronchus through the bronchoscopic working channel; (5) fluoroscopy is used to confirm the catheter direction and that the tip reaches the pleura; (6) the fluoroscopy is turned off, air gently injected, and the catheter removed. This procedure is repeated for all markings. We usually make three or more markings on the lung surface. After marking, CT is performed to reconfirm the placement of the markings.

The advantages of VAL-MAP are (1) having a precise plan of markings based on preoperative 3D CT and virtual bronchoscopy findings, (2) a low risk of bleeding or air embolism from dye injection through bronchoscopy, and (3) increased certainty of pleural marking with multiple dye injections.

The VAL-MAP technique provides an area including the pulmonary nodule surrounded by multiple markings that can be recognized easily as blue spots on the visceral pleural surface through thoracoscopy. This geometric information on the lung surface not only helps surgeons to identify small pulmonary nodules but also provides oncologically satisfactory resection lines, particularly in patients undergoing thoracoscopic sublobar anatomical lung resection. In addition, redundancy due to multiple markings helps to overcome the occasional marking failure.

The evaluation of VAL-MAP

We conducted a multi-institutional prospective study of VAL-MAP to verify its safety and reproducibility and to identify those who benefit most from this procedure [23]. From 1781 markings in 500 patients at 18 participating hospitals, complications associated with VAL-MAP necessitating an additional therapy occurred in four patients (0.8%). Minor complications included pneumothorax (3.6%), pneumomediastinum (1.2%), and alveolar hemorrhaging (1.2%). Similar incidences were noted between the primary center and other centers. Markings were identifiable during surgery in approximately 90% of cases, and the successful resection rate was 99% due to multiple redundant markings. Surgeons felt that VAL-MAP was very helpful in resecting subsolid nodules and small tumors (diameter ≤ 5 mm). Imaginary auxiliary lines and anatomical landmarks denoted using multiple marks were useful for successful resection of newly found nodules during surgery [24].

VAL-MAP has successfully indicated the pulmonary surface areas to be resected. However, to secure a clear surgical margin, especially if the tumor is located deep in the lung parenchyma, we must consider how to secure the deepest margin from the resected line. In cases of wedge resection, in particular, we must consider the depth of the tumor.

In general, the distance between the resection surface and the proximal surface of the lung cancer is a crucial factor determining the probability of postoperative tumor recurrence, as with other malignant neoplasms. Mohiuddin et al. [25] retrospectively analyzed patients undergoing wedge resection for small lung cancer (diameter ≤ 2 cm) without lymph-node metastases and found that a larger margin was significantly related to a reduced risk of local recurrence. The authors, thus, concluded they should secure a surgical margin of ≥ 15 mm when performing pulmonary wedge resection for the early lung cancer.

Wolf et al. reviewed patients with small malignant lung tumors (≤ 2 cm) who had undergone pulmonary wedge resection. They also found that a larger margin was an independent factor associated with a reduced risk of recurrence [26]. We are now studying the second version of VAL-MAP (VAL-MAP 2.0), which includes fiducial marker placement through bronchoscopy at the same time as dye injection to localize the deepest resection point.

Electromagnetic navigation bronchoscopy

Electromagnetic navigation bronchoscopy (ENB) is an image-guided approach that uses 3D-reconstructed CT scans and sensor location technology to guide a steerable

endoscopic probe to peripheral lung lesions that may be beyond the reach of conventional bronchoscopes [27–30].

ENB enables the guidance of bronchoscopic instruments to target areas within the lung parenchyma that often are too far from the view of a standard fiberoptic bronchoscope. Once directed to radiographic abnormalities, the standard bronchoscopic forceps and cytological brushes can be used to obtain tissue specimens. The ENB system available at present (superDimension; Medtronic Co., Minneapolis, Minnesota, USA) consists of four essential components [27]:

1. A computer software program that creates a 3D virtual bronchoscopic reconstruction from CT images; the initial planning phase involves the incorporation of CT scan data by the superDimension software program into the standard digital imaging and communications in Digital Imaging and Communications in Medicine (DICOM) format.
2. An electromagnetic location board that emits a low-dose electromagnetic field.
3. A sensor probe that has an eight-way steering mechanism and is locatable within the electromagnetic field. After registration, the system can display the real-time location of the sensor probe within the patients' thorax in relation to virtual endoscopic and CT images in sagittal, coronal, and axial views.
4. An extended working channel that, when secured, enables the placement of the bronchoscopic tools in relation to the lung periphery.

To improve the rate of successful resection of pulmonary nodules, we plan to couple VAL-MAP and ENB. We recently used this ENB system and fluoroscopy to perform VAL-MAP in the operating room, followed by VATS. Before surgery, 3D CT and virtual bronchoscopy were performed using high-resolution CT, and the sites of dye injections for VAL-MAP were planned. In the operating room, ENB was performed under tracheal intubation and general anesthesia, and the target sites were entered into the ENB software program. Guided by the virtual bronchoscopy map and ENB navigation, the probe tip was advanced to the targeted spot. After reconfirming the tip location with fluoroscopy, indigo carmine was injected. After ENB was finished, the patients were reintubated with a double-lumen tracheal tube and placed in a recumbent position in the preparation for VATS.

Conclusion

Multiple techniques, summarized here, have been developed to detect pulmonary nodules when planning VATS. With the early detection of lung cancer, the size of target lesions and the surgical routes to these lesions have become smaller;

therefore, more precise methods of tumor localization are needed to safely improve surgical outcomes.

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Compliance with ethical standards

Conflict of interest Jun Nakajima has no conflicts of interest.

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