Review Article

The imaging of small pulmonary nodules

Zejun Zhou[1], Ping Zhan[1], Jiajia Jin[2], Yafang Liu[3], Qian Li[1], Chenhui Ma[1], Yingying Miao[1], Qingqing Zhu[1], Panwen Tian[4], Tangfeng Lv[1,2,3], Yong Song[1,2,3]

[1]Department of Respiratory Medicine, Jinling Hospital, Nanjing University School of Medicine, Nanjing 210002, China; [2]Department of Respiratory Medicine, Jinling Hospital, Southeast University School of Medicine, Nanjing 210002, China; [3]Department of Respiratory Medicine, Jinling Hospital, Southern Medical University, Nanjing 210002, China; [4]Department of Respiratory and Critical Care Medicine, Lung Cancer Treatment Center, West China Hospital, Sichuan University, Chengdu 610041, China

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Correspondence to: Tangfeng Lv; Yong Song. Department of Respiratory Medicine, Jinling Hospital, Nanjing 210002, China.
Email: bairoushui@163.com; yong_song6310@yahoo.com.

Abstract: Lung cancer is the leading cause of cancer death worldwide. The major goal in lung cancer research is the improvement of long-term survival. Pulmonary nodules have high clinical importance, they may not only prove to be an early manifestation of lung cancer, but decide to choose the right therapy. This review will introduce the development and current situation of several imaging examination methods: computed tomography (CT), positron emission tomography/computed tomography (PET/CT), endobronchial ultrasound (EBUS).

Keywords: Small lung nodule; computed tomography (CT); positron emission tomography (PET); endobronchial ultrasound (EBUS)

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Lung cancer is the leading cause of cancer death worldwide. Close to 70% of patients with lung cancer present with locally advanced or metastatic disease at the time of diagnosis (1). Screening of early lung cancer has been a continuing issue over the last 40 years.

Small lung nodule is a common problem in pulmonary practice. The definition of a classical solitary pulmonary nodule is a single, spherical, well-circumscribed, radiographic opacity less than or equal to 30 mm in diameter that is completely surrounded by aerated lung and is not associated with atelectasis, hilar enlargement, or pleural effusion (2). According to the density at thin-section computed tomography (CT), it is divided into nonsolid, ground-glass opacity (GGO), solid opacity (3). Possible causes of pulmonary nodules include many benign diseases, but the primary concern is bronchogenic carcinoma. Large tumor size and advanced stage are associated with worse prognosis. Rapidly identifying could not only avoid unnecessary surgery in patients with benign disease, but resect malignant lesions in a cost-effective manner. New developments in radiographic techniques as well as endobronchial ultrasound (EBUS) techniques have stimulated an increased interest in lung cancer screening. This review introduces the development of several imaging examination methods.

CT

In the 1970s, CT was invented by Hounsfield (4) and then applied to clinical. In 1989, spiral CT came out, since that it is playing a significant impact on the diagnosis of lung cancer. In 1990s, radiologists tried to diagnose the lung cancer based on clinical feature and CT-detected symptoms, and it had been recognized that there are some symptoms influencing the probability of cancer in a pulmonary nodule (5), including calcification (6),

size, change in size (7), number (8), density and so on. Short-term follow-up of pulmonary nodules with repeat volume measurements is believed to be the most reliable non-invasive method to distinguish between malignant and benign lesions (9). If a nodule doubles in volume in 1 month, its growth rate is uncharacteristic of lung cancer, a nodule grows at a rate consistent with cancer that doubles around 30 to 360 days (5).

Faced with a small pulmonary nodule, the radiologists must first assess the likelihood of lung cancer utilizing the parameters of age, nodule size, smoking history, spirometric findings, occupational history, the circumstances of the CT (baseline screen, interval 1-year screen, or study performed for other reasons), the number of nodules, the presence of radiographic or clinical signs of inflammatory lung disease, and the density of the nodule. According to the rule, if lung cancer is highly suspect, biopsy should be undertaken. If the nodule is judged to have an intermediate likelihood of being lung cancer, observation with a repeat CT in 6 to 12 weeks should be suggested. If resolution of the nodule occurs, no further evaluation is warranted. If a nodule fails to change over a 2-year period on CT, it is most likely benign; if it grows, biopsy should then be done. However, this necessary follow-up period is uncertain, and it may result in a delayed diagnosis of malignancy and consequently in delayed treatment. Besides, the accuracy of diagnosis by CT is not satisfied in 1990s, there are limitations. Many factors must be considered simultaneously. The images of the whole thorax is impractical which requires multiple breath-hold sets of contiguous spiral scans to cover the thorax completely with single-detector row CT (10). Respiratory motion is known to cause artifacts, which decrease tumor detectability, and alter quantification of localization in medical imaging (11-13). The radiologists' variable experience and perception capacity also greatly influence the accuracy of detection (14).

In 2000s, multi-detector row CT was used in screening programs, a CT exam can scan the entire thorax to acquire thin-section images in less than 10 seconds (15). Depending on the screening, the radiologists can get multiple spiral data during a single CT screening that helps them to generate clear CT images of different section thickness, even very small lung nodules. Computer-aided detection (CAD) methods to be applied to CT examinations are also formed to support radiologists to the large image data. Various CAD systems in chest radiography have been reported (16-18) and tested for the detection of lung nodules. CAD is designed to be used as a second reader; the diagnostic outcome is determined by both CAD analysis and the radiologists' diagnostic judgment. For example, De Boo *et al*. (14) conducted an observer study, they selected patients with CT and CXR within 6 weeks, and six readers of varying experience individually evaluated the CXR without or with CAD, then they calculated the sensitivity per lesion, figure of merit (FOM), and mean false positive per image (mFP). At last, they found the sensitivity increased for inexperienced readers (39% *vs*. 45%, P <0.05) with CAD and remained unchanged for experienced readers (50% *vs*. 51%). The mFP did not significantly increased for both inexperienced and experienced readers (0.27 *vs*. 0.34 and 0.16 *vs*. 0.21). All readers together dismissed 33% of true-positive CAD candidates. False-positive candidates by CAD provoked 40% of all false-positive marks made by the readers. This study showed that CAD could improve the sensitivity of inexperienced readers for the detection of small nodules and the diagnostic accuracy.

With the development of CAD, it come that CAD should be used as a first reader to reduce the radiologists' workload and reading time, and radiologists only inspect locations flagged suspicious by CAD, accept or reject the CAD marks. To fully utilize CAD as a first reader in lung CT screening, it is necessary that CAD reaches a high sensitivity for all screening nodules. In the past decade, efforts have been made to design generic CAD systems that detect all types of nodules. However, the published CAD systems still often missed important subgroups of suspicious nodules. For nodules larger than 5 mm, some kind of CAD systems achieved an average detection disappointing sensitivity. Although some modified CAD system could reach a high sensitivity of large nodules and the authors conclude that the proposed dedicated CAD system for large pulmonary nodules can identify the vast majority of highly suspicious lesions in thoracic CT scans with a small number of false positives (19), it still need more research.

As the developing of CT and the researches on pulmonary nodules, the details to describe pulmonary nodules are accurate and the existed guidelines on management of pulmonary nodules are changing. In 2015, the British Thoracic Society guideline based on a comprehensive and systematic review of the literature on pulmonary nodules published, which divided the persons into different group according to the size of the tumor and the rate of growth. People with nodule <5 mm diameter (or <80 mm^3) can be discharged. If the nodule is between 5 and 6 mm, it suggested people should have a CT scan 1 year later. If the nodule is >5 mm diameter (or ≥80 mm^3),

it suggested people should had a CT scan 3 months later. By evaluating the examination of the volume doubling time (VDT), doctors can made the proper management for the patients. This guideline showed the two malignancy prediction calculators to better characterize the risk of malignancy. The recommendations were a nodule size threshold for follow-up (≥5 mm or ≥80 mm^3) and a reduction of the follow-up period to 1 year for solid pulmonary nodules, which reduce the number of follow-up CT and improve cost-effectiveness and pressure on imaging services (20).

The maximum intensity projection (MIP) images are helpful for the diagnosis of small pulmonary nodules. It's invented by Jerold Wallis, MD, in1988. MIP is a volume rendering method for 3D data and is used for the detection of lung nodules in lung cancer screening programs which utilize CT scans, which enhances the 3D nature of these nodules, making them stand out from pulmonary bronchi and vasculature. A research about MIP reconstructions showed it remains a valuable adjunct to the interpretation of chest CT for increasing sensitivity and has the advantage of significantly lower false-positive rates (21).

CT-guided percutaneous transthoracic needle biopsy (PTNB) is also established and matured. PTNB is advantageous in diagnosing peripheral lung lesions for high accuracy and safety (22), and complication rates are acceptable (23). Getting the tissue from the small lung nodule by PTNB is minimally invasive way to detect the mutation, which is not only useful for the diagnosis, but for the making therapeutic regimen.

Positron emission tomography/computed tomography (PET/CT)

Positron emission tomography (PET) is the most important advance in lung cancer imaging since the applying of CT scanning. When 18F-FDG is injected intravenously, it is taken up by tumor cells at a higher rate than in normal cells. Lung cancer cells have a particularly high avidity for FDG. The emergence of combined PET/CT imaging has greatly aided the investigation of lung cancer. In a retrospective study on identification of characteristics of solitary pulmonary nodule, the sensitivities of CT, PET and PET/CT were 93%, 69% and 97% while specifies were 31%, 85% and 85% (24). PET/CT has been shown to be invaluable for detecting distant metastasis, particularly in patients already known to have a primary tumor. In patients with confirmed non-small cell lung cancer (NSCLC), PET/CT has also repeatedly been shown to be more sensitive and specific than conventional noninvasive imaging methods for staging of the mediastinum (25). For these reasons, PET/CT has become widely used for staging of NSCLC is performed using the tumor, node, metastasis (TNM) classification system. The TNM staging system is presently the standard tool for staging lung cancer patients. The system is based on a combination of three basic aspects: the location and extent of the primary tumor (T); the presence or absence of changes in intrapulmonary, hilar, or mediastinal lymph nodes (N); and the presence or absence of other pulmonary nodules, pleural effusion, or extrathoracic (distant) metastases (M). The combination of the T, N and M scores is then used to place a given lesion in one of four disease stages (I–IV), stratifying individuals by prognosis and therapeutic prospects. PET has been used to assist in determining the presence of malignancy in SPNs, although, even in lesions over 1 cm in size, it has become clear that PET cannot be considered conclusive. High levels of FDG uptake correlate strongly with malignancy, as well as with prognosis in patients with known NSCLC (26).

It is currently estimated that approximately 75% of all NSCLC patients could benefit from radiotherapy at some point during their treatment (27,28). Preliminary evidence suggests that FDG-PET may has value in the planning of radical radiotherapy for NSCLC by ensuring that all gross primary tumor (29). Inadequate imaging with CT will limit the value of radiotherapy because of failure to include all gross tumors in the radiotherapy target volume, which will lead to inadequate dose of radiation. PET scans may be useful for assessing response to nonsurgical therapy for NSCLC by imaging changes in FDG uptake in tumor volume (30).

Although PET/CT has proven to be a particularly promising modality in NSCLC staging, several pitfalls must be taken into account when interpreting PET/CT findings. Neither usually specific nor sensitive is the limitations of PET, particularly for small pulmonary nodules, because low-grade malignant tumor such as bronchiole-alveolar carcinoma and carcinoid are frequently negative for FDG-PET due to their low glucose metabolism, while active infection, inflammation, or pulmonary infarction, sometimes showed positive due to their high glucose metabolism (31). Besides, prior study (32) showed that the malignant nodules less than 1 cm were hard to image. The spatial resolution of current generation of PET scanners is 7–8 mm, which can hardly image pulmonary nodules <1 cm.

EBUS

CT for evaluation of primary tumors and metastases was effective; however, the reliability in predicting metastatic involvement of mediastinal lymph nodes an airway infiltration was disappointing. Besides, it is difficult to differentiate two adjacent structures of soft tissue that there is no difference in the density of water (33). As different from CT, ultrasound imaging is based on signals generated by ultrasonic waves reflected from different anatomic layers, and it depends on the density of the tissues passed and on the energy of ultrasonic wave. Transthoracic ultrasound cannot image of the mediastinal structures because of the limited acoustic window resulting from the reflection of the ultrasonic wave by air contained in the lung tissue, so study was focused on developing devices for endoluminal applications. In 1990, Becker developed a flexible catheter with an ultrasound probe for application inside the central airways which provided a 360-degree view of the parabronchial and paratracheal structure (34). The endobronchial application of ultrasound for the diagnosis of lung cancer was first described in 1992 (35). Since then, major technological advances have occurred and much published research was reported on the indication and diagnostic accuracy of EBUS. Nowadays, EBUS has emerged as a highly effective and minimally invasive technique for sampling peribronchial, mediastinal, and lung masses for pathologic examination.

EBUS plays a role in the staging of NSCLC and the diagnostic evaluation of endobronchial lesions, peripheral pulmonary nodules (PPNs), and mediastinal abnormalities. Chavez *et al.* (36) conducted a retrospective trial about the diagnostic performance of transbronchial biopsy (TBB) with EBUS-GS, they collected 212 patients with PPNs (≤30 mm), and found that the overall diagnostic accuracy of EBUS for PPNs and central parenchymal nodules is about 71% and 77%, which can be maximized for PPNs that are away from the pleura and when the EBUS probe can be placed within the lesion. Radial-endobronchial ultrasound (r-EBUS) is used to identify peripheral pulmonary lesions and sampling sites that provide a 360° radial image of the surrounding structures. Herth and coworkers (37) demonstrated that r-EBUS-guided transbronchial lung biopsy had a diagnostic yield of 80%. These researches showed r-EBUS is an acceptable diagnostic method for small pulmonary nodules. The 2013 ACCP guidelines on lung cancer diagnosis recommend radial EBUS when the appropriate instruments and a skilled operator are available (38).

Mediastinal lymph node staging is divided into noninvasive and invasive staging. Noninvasive techniques include CT, magnetic resonance imaging (MRI), PET, and PET/CT. The sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastasis is 51% (95% CI, 47–54%) and 85% (95% CI, 84–88%), the sensitivity and specificity of PET scanning for identifying mediastinal metastasis is 74% (95% CI, 69–79%) and 85% (95% CI, 82–88%), respectively (39). These data demonstrate that while PET is more accurate than CT, the technology is still fallible. Some studies (40-42) using EBUS for mediastinal staging showed strong sensitivity and specificity. In 2006, Herth and colleagues (42) evaluated EBUS-TBNA in patients with lung cancer and a radiographically normal mediastinum; this study showed an unexpected detection rate of mediastinal metastases of 17% in 119 lymph nodes 5 to 10 mm in size. Endoscopic ultrasound-fine needle aspiration (EUS-FNA) and EBUS-TBNA are sometimes combined because EUS has better access to the posterior and inferior mediastinum, and EBUS to the anterior and superior mediastinal lymph nodes. Wallace and coworkers (43) compared the diagnostic accuracy of transbronchial needle aspiration, EBUS-TBNA, EUS-FNA, and their combinations. They reported a sensitivity of 93% (95% CI, 81–99%), and a negative predicted value of 97% (95% CI, 91–99%) for the combination of EUS-FNA and EBUS-TBNA in a population with a prevalence of mediastinal metastases of 30%. In addition, they reported that the combination of EUS-FNA and EBUS-TBNA was better than either alone, even when evaluating scenarios that favored one technology over the other. Both technologies far outperformed blind TBNA in assessing mediastinal lymph nodes.

Virtual bronchoscopic navigation (VBN) is a method to guide a bronchoscope to a peripheral lesion under direct vision using virtual bronchoscopic images of the bronchial route. Virtual images can be prepared using commercial general-purpose image preparation software. Electromagnetic navigation (EMN) is a relatively new navigation method that utilizes electromagnetism. An electromagnetic field is prepared around the patient's chest, and biopsy instruments are guided to a pulmonary lesion based on the positional information of the electromagnetic micro-center and CT information acquired beforehand (44). Ultrathin bronchoscopy with a working channel applicable for biopsy has recently been used not only for bronchoscopy in children but also in diagnosing peripheral pulmonary lesions in adults (45). Each technique has advantages and disadvantages, and it is necessary to understand these and investigate

appropriate combinations corresponding to individual cases.

In conclusion, there have been great advances in image processing allowing for both characterization and detection of small pulmonary nodules, but the early diagnosis of lung cancer is still very hard. Crucial breakthrough is still needed. Mixing with several detection methods may lead to technological improvement. The new idea to diagnose and evaluate lung cancer is also looking forward.

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Footnote

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