Management of CT screen-detected lung nodule: the thoracic surgeon perspective

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Abstract: Implementation of lung cancer CT screening programs will increase the incidence of pulmonary nodules and require multidisciplinary efforts for devising appropriate treatment plans. The role of the thoracic surgeon is paramount in leading the discussion and shaping the treatment strategies. Management of CT screen-detected lung nodules differ from conventional lung cancer nodules given their smaller size, varied histologies and potentially indolent growth. Here we present a brief overview of the thoracic surgeon's perspective on the clinical evaluation, diagnostic tests and surgical approach to these nodules in the setting of a comprehensive lung cancer screening program.

Keywords: Thoracic surgery; lung cancer; cancer screening

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In the advent of lung cancer CT screening era, increased identification of small lesions warrants further assessment and referral to thoracic specialists for decision making plans. Thoracic surgeons are expected to play a pivotal role in the care and management of these patients, engaging in a leadership role within a multidisciplinary group encompassing primary care practitioners, medical oncologists, pulmonologists, pathologists, radiologists, in addition to thoracic surgeons. Unlike established protocols for management of lung cancer, CT screen-detected pulmonary nodules are often smaller, have variable solid component and may have indolent histologies that require reassessment of our approach. No guidelines currently exist for the evaluation of CT screen-detected lung nodules and management algorithms are still evolving. Here we provide a brief synthesis of the current evidence and present our approach to this problem. Understanding that every patient represents a unique case to be thoroughly assessed and evaluated, we aim to simplify the information offered to serve as a broad guideline to be implemented and adjusted according to personal experiences and institutional preferences. Our approach is centered on two guiding principles: (I) determine the risk of malignancy of the screen-detected lung nodule and (II) determine the medical fitness of the patient to undergo surgical intervention.

Determining the risk of malignancy

Many quantitative models have been proposed to determine the malignancy risk of a CT-screen detected lung nodule, all of which utilize a combination of clinical and radiographic data to generate a probability score. Accordingly, a nodule would fall into one of three categories: low, intermediate and high probability for malignancy. While no model claims superior predictive ability, most of them remain uncommonly used in clinical practice, and therefore we will avoid elaboration on their different attributes in this discussion. In the setting of a comprehensive lung cancer

CT screening program, multidisciplinary evaluation can comfortably replace these models and provide practical algorithms for further workup.

Initial evaluation

Every patient referred for a CT-screen detected lung nodule should undergo a thorough and systematic evaluation, assessing clinical findings, imaging characteristics and outcomes of diagnostic tests. The following factors are known to increase the risk of pulmonary nodule malignancy and should alert the thoracic specialist for potentially further evaluation.

- Age: increasing age is a documented risk factor for increased malignancy as well as increased incidence of malignant nodules (1,2);
- Smoking (current or past): tobacco smoking has a strong association with malignancy (3);
- Prior malignancy: a history of previous malignancy, particularly non-small cell lung cancer, increases the likelihood of malignancy in the screen-detected nodule (4);
- COPD: particularly emphysema (5);
- Family history (6).

Nodule characteristics on CT scan

In determining the malignant potential of the CT screen-detected lung nodule, the following characteristics are often assessed for their association with increased risk of malignancy: size, border, volume doubling time (VDT), density, and solid component.

- Size: increasing nodule size is an independent risk factor for malignancy, with around 20% increased risk for nodules 8–20 mm while nodules larger than 20 mm have more than 50% malignancy potential (7);
- Border: irregular nodules (e.g., scalloped, spiculated) are more likely to contain cancer cells than smooth spherical nodules (8);
- VDT of screen-identified lung nodules is becoming increasingly utilized to assess the risk of malignancy. Nodules with VDT <20 days tend to be associated with infectious and inflammatory conditions (9). Nodules with VDT >400 days are typically associated with slow/indolent lesions such as typical carcinoid and low grade tumors [adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and atypical adenomatous hyperplasia (AAH)] (10);
- Density: intranodular fat density is typically associated with hamartomas (11). Calcification patterns can distinguish between benign and malignant lesions. Asymmetric calcifications (eccentric, stippled) raise the suspicion for malignancy, while diffuse, central, laminated, and popcorn patterns are more likely to reflect benign etiologies;
- Solid component: while solid nodules are more common, there is a documented increase in the frequency of part-solid lesions thought to be due to a higher incidence of adenocarcinoma. AIS, MIA and AAH are the most common tumor histologies encountered in part-solid nodules. Compared to solid nodules, part-solid lesions are associated with a higher risk for malignancy (12-15). Subcentimeter lesions can be challenging and, depending on the clinical presentation, may require careful observation for potential of malignant transformation.

Diagnostic tests

Several diagnostic tests are available and widely used when evaluating suspicious lung nodules. Bronchoscopy, positron emission tomography (PET) scans, CT-guided biopsies, and surgical biopsies are the most commonly used. In many instances, when a thoracic surgeon examines a patient referred for assessment of a CT screen-detected lung nodule, one or more of these tests had been performed. We present these modalities in no specific order of preference; often one test or more are required to establish and confirm a diagnosis.

Functional imaging/positron emission tomography (PET)-scan

PET is used to determine the metabolic activity of a screen-detected lung nodule. PET is typically fully integrated with CT-scans providing super-imposed images of the identified nodule and the PET signal for improved nodule characterization. Owing to increased metabolic activity of cancer cells, enhanced uptake of fluorodeoxyglucose (FDG) is commonly an indicator for higher risk of malignancy. Standardized uptake value (SUV) is the reported unit of FDG-avidity, and while no cutoff particularly delineates malignant from benign nodules, higher values are more likely to be true cancer cells. In practice, SUV above 2.5 is a strong indicator for cancer (16), especially when combined with the clinical presentation and the imaging characteristics of the nodule. The sensitivity and specificity of PET are 87% and 83%, respectively (7,17). Inflammatory conditions like sarcoidosis and rheumatoid nodules, and infection like pneumonia or mycobacterial infection can cause false-positive PET findings (18). Smaller tumors less than 8 mm and part-solid nodules can cause false-negative PET findings (19). Furthermore, certain non-small cell lung cancer histologies (such as lepidic growth, AIS and MIA) and carcinoid tumors have lower metabolic activity and can also cause false-negative findings (20-22). Besides nodule characterization, PET-CT can identify positive lymph nodes that are otherwise non-suspicious based on size alone (23).

CT-guided fine-needle aspiration and biopsy

Trans-thoracic core needle biopsies and fine-needle aspirates (FNA) are performed to obtain tissue under CT guidance. In high-volume experienced centers, typical yield can exceed 90% for both malignant and benign lesions (24,25). Core biopsies are preferred to FNA because of their higher yield, but more importantly biopsies allow evaluation of tissue architecture, and provide sufficient material for immunohistochemistry and genetic analyses. The sensitivity of CT-guided biopsies can be excellent, exceeding 90% in high-volume centers with a pathologist/cytologist on-site to examine the specimens (26). CT-FNA is most suited for peripheral lesions in the vicinity of the chest wall or deeper lesions that do not require traversing a fissure. The most common complication is pneumothorax (10–60%), particularly when visceral pleura is traversed (27–29) with a 4–18% risk for chest tube placement (7). Hemorrhage may occur following CT-guided biopsy but is less common (1–10%) (29). Air embolism is an exceedingly rare yet another reported complication of FNA biopsy of the lung, which typically occurs when a pulmonary vein is traversed (30). Air embolism can be life-threatening and requires immediate attention such as administration of 100% O_2, patient placement in a Trendelenburg, left lateral decubitus position and occlusion of the needle to prevent further air entry. The following factors are thought to increase the risk of pneumothorax: deep parenchymal lesions, near fissures locations, traversing fissures to obtain biopsy, COPD and emphysema. Non-diagnostic CT-FNA and biopsies may require more invasive techniques such as a surgical biopsy, particularly when a diagnosis needs to be determined for further management.

Bronchoscopic evaluation and techniques

Conventional flexible bronchoscopy: the use of bronchoscopy in evaluating pulmonary nodules is most useful in the workup of central lesions. Biopsies and aspirates may be obtained through specific channels in the bronchoscope. Diagnostic accuracy is however low compared to CT-FNA (31); an even lower yield is associated with peripheral lesions (30). In the NELSON study, bronchoscopy had a sensitivity of 13.5% (32) and a negative predictive value of 47% (32). In the setting of a lung cancer screening program, bronchoscopy is of limited use, and should only be reserved where limited-availability or other reasons prevent obtaining CT-FNA of the lesion of interest.

Endobronchial ultrasound: EBUS utilizes radial ultrasound wave to obtain a 360° image of the airway and any masses surrounding the wall of the trachea and bronchi. Although EBUS gained wide popularity for staging mediastinal lymph nodes and has largely replaced mediastinoscopy in many centers, its use for evaluating CT-screen lung nodules remains marginal. Its sensitivity for accurately detecting malignant nodules is slightly >70% (33) and thus should not be advocated at the moment.

Electromagnetic navigational bronchoscopy (ENB) is a more recent technology that integrates a patient's CT scan with an electromagnetic field created around the chest to guide a sensor (in a GPS-like manner) mounted on the bronchoscope towards the lesion of interest. ENB can be used to obtain biopsies or to inject a dye for tumor localization prior to surgery.

Surgical biopsy

In the event non-surgical approaches fail to establish a definite diagnosis and clinical suspicion remains high for malignancy, a surgical excisional biopsy would provide the ultimate answer. It is highly specific and accurate and can be even used with non-malignant conditions such as mycobacterial infection where surgical resection can be therapeutic.

Surgical biopsy should be performed using minimally invasive techniques whenever possible. Video-assisted thoracic surgery (VATS) has largely replaced open thoracotomy in obtaining tissue for diagnostic purposes. It is safe, efficient, and provides expedient hospital course and return to normal function (34,35). In experienced hands, VATS wedge resection is associated with less than 5% morbidity and 1% mortality (36). VATS wedge resection is particularly useful in the workup of small (stage I) peripheral nodules where it can be both diagnostic and therapeutic. In older patients or those with lower pulmonary reserve, VATS wedge can also be used when benign parenchymal sparing is sought after.

There are no specific guidelines for the resection margin length when small peripheral tumors are excised. Some authorities recommend a minimum margin length larger than the tumor diameter (37,38). In a study by Mohiuddin *et al*., increasing margin length to 15 mm was shown to be associated with improved local control (39). Hence, when performing VATS wedge resection, visual inspection and digital palpation are crucial to delineate the boundaries for excision. In the CT screen-detected pulmonary nodules, there is higher frequency of non-solid or part-solid with predominant non-solid component which may render visualization and palpation challenging. In these cases, a variety of localization techniques can be used and are discussed further below.

Immediate availability and cooperation between the pathologist and the surgeon for frozen section (FS) analysis is highly recommended for intraoperative margin evaluation and establishing a diagnosis. However, the ultimate diagnosis requires standard formalin-fixed and paraffin-embedded (FFPE) histological analysis. FS has its limitations particularly when there is poor sampling of the tumor, tumor necrosis, freezing artifacts and architectural distortions. It is also less reliable with certain histologies (e.g., MIA, AIS, AAH, carcinoid), lower grade lesions or those smaller than 1 cm (40). Final pathology should always be obtained, and in many cases, the surgeon may need to re-operate to remove any residual disease.

Surgical management

Localization strategies

Most peripheral solid nodules can be localized by palpation or visualization during surgery. Nodules identified by CT screening are more likely to be challenging because of their smaller size and increased non-solid components. Many strategies have emerged to enhance identification of these nodules, the most popular of which are the following:

- Hook wire, coil: can be placed percutaneously (41,42) or using navigational bronchoscopy (41). Fiducial marker placement can be performed on the same day or on a different day. Intraoperative fluoroscopy is required to identify the coil's exact location and confirm removal;
- Radiotracer: a radioisotope tracer injection is performed percutaneously under CT guidance on the day of surgery. An intraoperative gamma radioprobe is utilized to localize the tracer (43);
- Methylene blue: tattooed into the lesion via navigational bronchoscopy immediately prior to surgery. The dye can be injected trans-thoracically or via navigational bronchoscopy. The latter reduces the diffusion of the dye allowing more precise and limited resections.

Surgical resection and mediastinal lymph node assessment

Lobectomy remains the current gold standard for lung cancer management in medically operable patients. Minimally invasive approaches such as video-assisted or robotic-assisted thoracic surgery (VATS, RATS) are now widely used and are preferred over open thoracotomy. In experienced centers, VATS resection is associated with safe and oncologically sound outcomes equivalent to open resection (35). VATS however is superior when factors such as need for blood transfusion, speed of recovery, post-operative pain management, and duration of hospital stay are considered (35).

Interest in parenchymal preserving lung cancer resection (sublobar resection) continues to gain grounds. Thoracic surgeons are seeing larger numbers of older and sicker patients, with lower cardiopulmonary reserve and multiple comorbidities. Therefore, preserving healthy pulmonary parenchyma is advocated by many, particularly with smaller (less than 20–30 mm) and peripherally located nodules. Although the incidence of such nodules is likely to increase considerably with the spread of screening programs, it will mostly occur in younger and healthier patients who enroll in such programs. The main concern with sublobar resection is local recurrence, which is particularly troublesome for younger patients who could have benefitted from a superior procedure.

Many retrospective studies from institutional and national database attempted to compare lobar *vs*. sublobar resection, and many report comparable overall and disease-specific survival, particularly early stage and elder populations (37,44). In a recent systematic review performed by our group comparing the outcomes of lobar *vs*. sublobar resection on 5-year survival rates in early stage lung cancer (45), we identified 23 distinct studies, with lobectomy performed in 4,564 patients and sublobar resection in 2,287 patients. Only four studies showed no difference in 5-year survival rates and 13 studies favored lobectomy. Although survival rates for lobar *vs.* sublobar resection were similar when adjustments for age, comorbidities and cardiopulmonary function were made, most of these studies were sufficiently heterogeneous to warrant traditional meta-analysis. Until the results of the Japan Clinical Oncology Group (JCOG 0802) and Cancer and Leukemia Group B (CALGB 140503) are known (both comparing lobar *vs.* sublobar resection in stage Ia NSCLC), it will remain unclear whether the two surgeries have comparable outcomes.

With extensive use of PET, the role of mediastinal lymph node dissection has been questioned. Most thoracic surgeons continue to believe that mediastinal lymph node assessment (in the forms of dissection or sampling) remains necessary for the two main purposes: (I) adequate staging and (II) improved survival for patients with node-positive disease who would benefit from adjuvant chemotherapy. In a subset analysis (N=97) of the Italian COSMOS study showed no positive nodes for stage Ia tumors less than 10 mm and PET negative (SUV_{max} <2.0) (46). Similarly, many groups do not favor MLN assessment for tumors smaller than 2 cm with a predominant non-solid component. We advocate a minimum of three mediastinal N2 stations (including subcarinal station 7) and about 10–15 nodes including N1 and N2 stations.

Take home lessons

- Screen-detected lung nodules incidence continues to rise with implementation of CT screening programs;
- Multidisciplinary deliberations are paramount;
- Minimally invasive approaches are recommended;
- Sublobar resection can be safely considered in peripheral tumors less than 2 cm in larger dimension and less than 50% non-solid component. Otherwise, lobar resection is preferred;
- Radiographic surveillance is appropriate in subcentimeter nodules with predominant nonsolid component which typically follow an indolent growth pattern;
- The results of the Japan Clinical Oncology Group (JCOG 0802) and Cancer and Leukemia Group B (CALGB 140503) will be impactful towards choosing lobar *vs.* sublobar resection;
- Mediastinal lymph node assessment (sampling or dissection) should be performed in all patients with predominantly solid component;
- Omitting mediastinal lymph node assessment in subcentimeter predominantly non-solid lesions can be considered, particularly with low suspicion index on CT scan or PET;
- Guidelines for managing these lesions continue to evolve.

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Footnote

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