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Review Article

Application of Radiology in Management of Incidental Lung Nodule

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Abstract

Incidental radiographic discoveries of pulmonary nodules are typical situations faced by pulmonologists and radiologists in daily clinical practice. Understanding the best management practices for these findings is of utmost importance as most of these nodules may be benign and require no treatment. On the other hand, others may indicate early-stage lung cancer requiring diagnosis and treatment. pulmonary nodule diagnosis includes relatively minimal invasive procedures such as biopsy, transthoracic aspiration or bronchoscopy, as well as more invasive procedures like thoracic surgical biopsies. Because these procedures are associated with financial cost and anxiety, it is necessary to set in place well-defined algorithms for the description of these nodules, as well as their management. There should be clear algorithms for the imaging protocols in lung cancer examinations. Of course, these algorithms are established in the United States and same should be done globally. This article highlights what we know about nodule definition, diagnosis, and management based on recent guidelines and current literature data.

Keywords: Pulmonary nodules; Low-dose computed tomography; Lung nodule management; Lung cancer

Introduction

Pulmonary nodules are a common clinical occurrence. Nodules with diameters as small as 1-2 mm have been routinely detected since the introduction of the multidetector row CT and the helical computed tomography (CT) in the late and early 1990s respectively. It is important to note that small lung nodules have been found in most smokers who undergo thin section computed tomography. Most of these lung nodules have a diameter that is less than 7 mm [1]. 39 percent of participants in the National Lung Screening Trial had a positive finding which was defined as a non-calcified pulmonary nodule whose size was above 4 nm [2]. The clinical significance of these small nodules differs substantially from the larger nodules found on chest radiographs. The vast majority of these small nodules are benign.

The accidental discovery of lung nodule(s) in asymptomatic persons is becoming increasingly common in daily clinical practice, and considered a clinical dilemma by radiologists and pulmonologists. The ability to identify and characterize malignant lung nodules accurately, and develop clear managerial algorithms, allowing the cure and complete resolution of early-stage lung cancer remains a challenge to medical professionals.

Several medical research societies, such as the British Thoracic Society (BTS), [3], the Fleischner Society, [4], the National Comprehensive Cancer Network, [5], and the American College of Chest Physicians (ACCP), [6], have recommended some algorithms for lung nodule management. While some minor discrepancies exist in these guidelines, all the approaches proposed have taken into consideration lung cancer risk factors, nodules imaging features, and past imaging studies to evaluate the probability of malignancy and effective management strategies. On the other hand, it is worth mentioning that most of these guidelines and recommendations are weak, do not have strong evidence, and current guidelines are adopted by just a few clinicians (40% approximately) [7]. What's more, the clinical management of incidental lung nodules rely heavily on the judgement of the clinician although there is evidence showing the need for a multidisciplinary approach and clear algorithms.

Management of nodules will become more paramount. Results from the National Lung Screening Trial indicates that screening of high-risk individuals with low-dose computed tomography may reduce risk of mortality from lung cancer through speedy identification of malignant nodules that corresponds to the early stage of the disease [2]. The aim of this paper is to give a comprehensive evaluation of the current knowledge of lung nodules as well as effective management strategies based on current guidelines and recommendations.

What is a pulmonary nodule?

A pulmonary nodule is a small, focal, rounded radiographic opacity that may be multiple or solitary. A solitary pulmonary nodule is a single, radiographic opacity with a diameter of up to 3cm. A solitary pulmonary nodule is completely surrounded by aerated lung [8]. Pleural effusion, hilar enlargement, and atelectasis are not associated with solitary pulmonary nodule. People who have solitary nodules are typically without symptoms. Focal pulmonary lesions with a diameter above 3 cm represent are identified as lung masses and presumed to be indicators of bronchogenic carcinoma until a more accurate diagnosis is given.

Based on how they are attenuated in CT imaging, lung nodules are typically placed into three categories:

- Solid nodules, typically the commonest type, whose primary feature is a homogenous soft-tissue attenuation.
- Ground-glass nodules, with a nonuniform appearance and a hazy increase in lung parenchyma attenuation without obscuring the vascular and bronchial structures.
- Part-solid nodules comprising ground-glass and solid attenuation components.

We have established that lung nodules may be solitary or multiple. However, most individuals are usually diagnosed with multiple nodular lesions, mostly nonsolid nodules. In the 2017 NELSON trial, approximately 50 percent of the subjects screened had a solitary pulmonary nodule [9]. In other screening cohorts numbering two, the median nodule count was 5 and 7 respectively [10]. Following the NELSON trial management algorithm [11], it is generally proposed that multiple nodules be approached based on which nodule is larger or more suspicious [3,4]. Another recommendation is the separate evaluation of each nodule in the absence of a priori denying curative intent therapies [6] as several researches have shown that patients experiencing malignant dominant nodules present benign satellite lesions [12-14]. It is important to note that the size of a benign multiple nodules is not an indicator of its malignancy. A 2013 PanCan screening cohort showed that in approximately 20 percent of lung cancer patients, the malignant nodule was the fifth largest [10].

Measuring Primary Nodules

The evaluation of pulmonary nodules, especially small-sized pulmonary nodules that have a diameter of less than 8mm, requires the performance of a chest CT with thin sections less than or equal to 1.5 mm reconstructed with multiplanar reformations and maximum intensity projection using both pulmonary and soft tissue filter. Maximum intensity reformation projections are vital in small pulmonary nodule detection (Figure 1), making small nodules more sensitive while reducing their number, especially in the central lung [15,16]. The chances of malignancy in a pulmonary nodule are strongly correlated with both its growth rate and size, giving room for additional factors, like a history of extrathoracic malignancy or lung cancer [6].

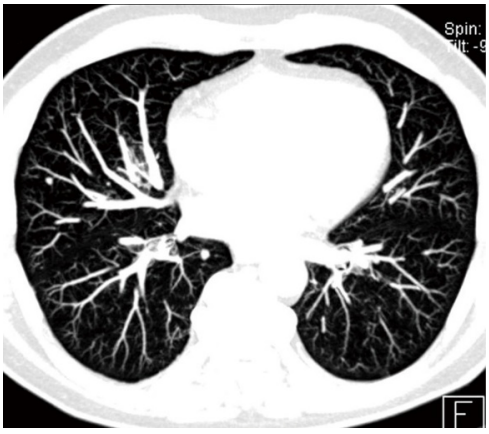

Figure 1: Multiple pulmonary nodules located in the right lung. The small nodules were detected using maximum intensity projection reformation that enhances the sensitivity of small nodule detection. Image credited: Sánchez et al. [17].

Size is vital to the prediction of malignancy in pulmonary nodules, as such accurate measurement is necessary. Measurement of primary nodule may require use of the largest diameter, the volume or the mean diameter. According to the Fleischner Society, risk estimation is best done with the mean diameter [18]. It is worth mentioning that the mean diameter is the average of the long axis diameter and the perpendicular short axis diameter in the same location, as measured in the axial plane. Risk estimation is best done using the mean diameter. Also, the mean diameter has a better correlation with tumor volume than a single measurement, especially in elongated nodules and in nodules whose short dimension is well-defined [19]. For determining the size of small pulmonary nodules, it is recommended to use lung window setting with a high spatial frequency filter [20]. Measurements taken have to be expressed to the nearest mm. Taking measurement with an electronic caliper has an intra and inter-reader variability. This explains why the Fleischner Society recommends reporting growth when there is at least a 2 mm change in diameter [18]. One can also take volumetric nodule measurements. The potential advantages of volumetric nodule measurements include the following:

- A primary nodule has a three-dimensional structure, and this structure may be better encapsulated by volume estimation.
- Volume estimation gives room for calculation of the volume doubling time (VDT). VDT is a more reliable parameter for defining nodule growth.
- It drastically reduces the inconsistency among and between observers measuring diameters [21].

To carry out a qualitative volumetric assessment, it is necessary to maintain reconstruction and acquisition consistency (mostly the reconstruction algorithm and section thickness). It is also of utmost importance to carry out sequential nodule evaluations with identical type and version of software [18,21]. Evaluation of subsolid nodules and nodules linked to vessels or pleura are especially difficult due to their segmentation [21]. Adding nodule volume to existing malignancy prediction models gives rise to more correctly classified nodules [22]. Volumetric assessment is recommended by all current guidelines. The British Thoracic Society (BTS) added volume doubling time and initial volume time calculations to the diameter, while the Fleischner Society included volume to diameter in its most recent guidelines [3,4]. To verify volume growth in a nodule it has to exceed 25 percent, owing to the fact that volume changes less than 25 percent may be caused by interscan variability [11,23]. Volumetric assessment helps detect growth earlier and better compared to diameter. Minor changes in diameter may represent very important volumetric changes. A 25 percent increases in the diameter of spherical masses corresponds to an increase in overall volume [24]. There is also need to perform a follow-up CT with low-dose technique above 3 mGy. The aim in follow-CT is evaluation of nodule persistence and growth rate.

How often does the radiologist encounter lung nodules?

Previous reports have shown that approximately 150,000 nodule detections were recorded per year in the United States [25,26]. This figure was a rough estimate based on historical data obtained from chest x-ray studies aimed at nodule detection. The data showed that a solitary lung nodule was discovered in 0.09% - 0.20% of all chest x-rays performed at the time [27,28]. There has been an astronomic increase in the incidence of lung nodules since the advent of chest CT imaging in clinical practice. A 2015 retrospective study reported an increase in nodule detection by chest CT from 3.9 to 6.6 per 1000 person-years in the United States. This increase occurred between 2006 and 2012 [29]. It is interesting to note that this drastic increase in nodule identification was not paralleled by the rate of lung cancer cases (63,000 new diagnosis). An epidemiological study undertaken between 2002 and 2005 in the French population reported a lower incidence (12.6 per 100,000 person-years) [30].

Pretest probability of malignancy assessment

Assessing the pretest probability of malignancy is key in the evaluation of patients with newly detected lung nodule. Of course, this depends on the absence or presence of risk factors in the patient's history. These risk factors include:

History of tobacco smoking (current or past)

Tobacco smoking is the deadliest risk factor for lung cancer. Studies have shown that tobacco smoking is implicated in at least 85% of cancer-related deaths [31]. The link between lung cancer risk and smoking has long been proven to be dose dependent [32,33]. The risk increases proportionately to the amount of tobacco smoked daily, and the duration of smoking also contributes to the risk [34]. But it is worth mentioning that there is no safety margin or threshold for tobacco. It not harmless in any way. Smoking cessation reduces the risk for lung cancer [35-37]. Nevertheless, the likelihood of lung cancer development in former smokers remains higher when compared to non-smokers. Although a large percentage of epidemiological data emphasizes active cigarette smoking as a key risk factor, there is evidence showing a link between cancer development and other related products such as cigars and pipes [38,39], and even second-hand smoking. The smoking landscape has changed owing to the introduction of electronic cigarettes. Potential health conditions associated with electronic cigarettes, such as carcinogenicity remain unexplored, and epidemiologic studies that tackle these issues with be unavailable in the short term. Of course, there are experimental data that suggest that use of electronic cigarette exposes the body to lung carcinogens [40] and may cause in vivo and in vitro DNA damage [40,41].

Occupational exposure to carcinogens

This is one of the most overlooked lung cancer risk factors. The clinician must take a detailed history of the patient's past and present occupation which will them be used as an integral part of evaluation of patients with lung nodules. Different kinds of fumes, metals, and dusts have been linked with lung cancer [42-44]. Exposure to cigarette smoke acts in synergy, further augmenting the risk of cancer [45-47]. For example, non-smokers who are exposed to asbestos have almost twice the risk for lung cancer development as in healthy or nonexposed individuals. The risk is nine times higher in smokers [48].

History of previous lung conditions

Survivors of lung cancer have an extremely high risk for a recurrence [49-52]. In a study involving patients with stage 1 non-small cell lung cancer who underwent surgical resection, researchers discovered that the incidence of a recurrence was seven times higher than that of the first lung cancer incidence in the first year following resection and remained four times higher at a decade [51]. Patients suffering a head-and-neck squamous cell carcinoma [53,54] or other malignant neoplasms due to smoking, such as pancreatic or bladder cancer [55,56] also have a high risk for a metachronous or synchronous primary lung cancer. It is also important to note that lung cancer is the second most prevalent solid tumor that presents in survivors of Hodgkin disease [57,588]. It also presents in survivors of non-Hodgkin lymphoma [59]. Chemotherapy and radiotherapy with alkylating agents for index lymphoma treatment have been implicated in development of lung cancer, both additively and independently [58,59].

Aging

Old age consistently correlates with a high probability of malignancy in individuals with lung nodules and is incorporated in composite prediction models set up for risk assessment in these patients [1,10,60,61]. Over 50% of all cancers develop in people over the age of 70 [62,63].

Chronic lung disease

Many studies [64-67] propose a solid and independent relationship between lung cancer and chronic obstructive pulmonary disease. According to these studies, this relationship extends beyond the smoking etiology [68-70]. In the National Lung Screening Trial, COPD patients had a two-fold increase in lung cancer risk compared to individuals with healthy lungs [71]. It is also worth mentioning that the emphysema found in chest CT scans correlates independently with increased risk of lung cancer, adjustment of airflow limitation notwithstanding [64]. Lung cancer is an established comorbidity of idiopathic pulmonary fibrosis, with a 10% prevalence in this group of patients [72]. While smoking may be a common risk factor for both groups, researchers have hypothesized that carcinogenesis could be promoted by pulmonary fibrosis through seemingly vague mechanisms [72,73]. Comorbid lung conditions and consequent physiological compromise present challenges in the management of lung nodule and should be assessed carefully during the decision-making stage.

Pulmonary nodules and cancer risk

Many parameters may be used to assess the probability of malignancy in a primary nodule. Such parameters include clinical predictors and radiological predictors. Size is the first radiological predictor of malignancy. The risk of cancer in nodules below 100 mm3 (6 mm) in high-risk patients is less than one percent. Nodules that measure 250 mm3 (6 – 8mm) have a 0.5 – 2.0% risk of malignancy [10]. The risk of cancer is lower in low-risk patients. The risk of cancer increases astronomically in patients whose pulmonary nodules are larger than 8 mm. Upper lobe location, pleural indentation, nodule growth, and spiculation are also examples of radiological nodule features [3]. Assessment of specific radiological features is more difficult in small nodules; the morphology of nodules become more distinct as the nodule increases in size. It is strongly advised that management be determined by nodule appearance as well, and not by size alone [4]. In the evaluation of subsolid nodules (SSNs), malignancy rate is increased substantially when radiological criteria such as presence of bullae, internal structure, borders, solid core characteristics, or surrounding tissue is included [74]. According to the NELSON study, the probability of malignancy is higher in new solid nodules even at a small size and should be followed up aggressively compared to nodules detected at baseline or already established nodules [75]. Growth rate is vital in the prediction of malignancy. Volume try and volume doubling time (VDT) are used for better estimation of growth rate. Pulmonary nodule VDT above 500 days calculated by software has a negative predictive value of 98% for the diagnosis of malignant pulmonary nodules; while VDTs between 20 – 400 days are known to result in malignant solid nodules [76]. Smoking and old age are major clinical risk factors for lung cancer development [77]. There is a clear association between age and the risk of cancer. The prevalence of lung cancer is lower among individuals younger than 35 years and rarely occurs before 40 years of age. The likelihood of malignancy doubles for every 10-year increase in age [60]. Cigarette smoking is a well-known risk factor for lung cancer a fact that has been established since the 1960s; former or current smokers are 8 times more likely to develop malignant nodules compared to never-smokers [60]. A smoking history of 30-pack years and quitting within the past decade and half has been used by the NLST screening program as the qualifying tobacco exposure threshold, and should serve as indicators of high-risk status in patients with solid nodules [2]. Other factors that may constitute a risk include idiopathic

pulmonary fibrosis, emphysema, and established pulmonary or extrapulmonary malignancy. These are useful risk factors that have greater application in solid pulmonary nodules compared to SSNs.

Evaluation and management of pulmonary nodule on CT and MRI

Dynamic computed tomography and magnetic resonance imaging

Because asymptomatic pulmonary nodule is a common finding on chest CT and radiographs, it is of utmost importance to separate malignant nodules from benign nodules using the least invasive means and to make as accurate and specific a characterization as possible. Medical researchers and investigators have used MR imaging, CT, and PET/CT or FDG-PET to evaluate radiological features, water molecule diffusion, MR relaxation time, metabolism of pulmonary nodules, and dynamic contrast enhancement-based assessment of blood supply to differentiate benign nodules from malignant nodules with promising results.

Lung nodule evaluation with dynamic perfusion CT involves administration of iodine contrast media followed by the capturing of iodine bolus transit through the lung nodule using CT scan acquisitions. Perfusion CT is a technique that aids the in-vivo quantification of blood flow properties within a lung nodule, while also presenting the opportunity to contribute dynamic features (permeability, blood volume, mean transit time, blood flow, peak enhancement and time to peak enhancement) to those supplied by volumetric CT. Several studies have successfully correlated histological markers of tumor angiogenesis to diagnosis and prognosis [78-80] of lung cancer nodules. Recent studies have emphasized on validation of perfusion CT outputs against corresponding histological markers thus evaluating the diagnostic assets of this modality [81,82]. Results from previous studies show that non-contrast-enhanced MR imaging has limited potentials for characterizing peripheral lung masses and nodules and identifying the benign nature of pulmonary nodules due to minimal intrinsic signal intensity of the lung parenchyma, patient-related motion artifacts, and poor spatial resolution [83-85]. Generally, many pulmonary nodules, such as pulmonary metastases, lung cancers and low-grade malignancies such as lymphomas and carcinoids are indicated as intermediate or low signal intensities in T1 images. On T2-weighted images, they are demonstrated as slightly high intensities [83-85]. Nevertheless, it is possible to characterize some histological forms of pulmonary nodules, such as tuberculoma, bronchocele, hamartoma, mucinous bronchioalveolar carcinoma and aspergilloma on pre- or post-contrast enhanced T1 and T2-weighted images according to their MR findings [86-88]. Diffusion-weighted imaging (DWI) has recently been suggested as a new technique for detection of nodules as well as for evaluation of pulmonary adenocarcinoma [89-91]. This technique is suggested due to its capability to assess water molecule diffusion within tissues through apparent diffusion coefficient measurements or signal intensity ratio between the spinal cord and lesion ratio. While there may be no direct comparisons between DWI and PET/CT or PET were resent, these researches may indicate the primary significance of DWI for non-contrast-enhanced MR assessment of pulmonary nodule in the future. Although there are variations in enhancement levels due to underlying microscopically-determined pathological conditions such as tumor interstitial spaces, tumor angiogenesis, the absence or presence of fibrosis, and necrosis and scarring within the tumor, malignant pulmonary nodules indicate homogenous enhancement but at various levels on T1-weighted images after contrast media administration [92,93]. Consequently, clinicians encounter a diagnostic dilemma in differentiating malignant pulmonary nodules from benign pulmonary nodules when using pre-contrast and post-contrast conventional T1 and T2-weighted images [83-85]. As such, it has been suggested that blood supply or enhancement patterns evaluated with dynamic contrast-enhanced MR imaging may play a vital role in the diagnosis and management of pulmonary nodules [94-96].

Conclusions

Efficient management of asymptomatic individuals with pulmonary lung nodules discovered incidentally should balance between the need for early diagnosis of malignant nodules and potential harm – due to irrelevant invasive procedures (usually in the case of benign nodules). Technically, this is not always feasible or simple. All management algorithms take into consideration lung nodule CT features and the clinical probability of lung cancer. The compliance rates with these recommendations are low, however, clearly indicating complexity. Patient preferences should be considered during management decisions. Cardinal importance should be applied to multidisciplinary tumor boards. Future research should be targeted at the development of simpler nodule evaluation algorithms, taking into consideration novel diagnostic modalities, including liquid biopsies, biomarkers, and molecular signatures.

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