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Pulmonary Nodules—an Epidemic—Work Up and Management, Specific, and Unique Issues in the Elderly

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Abstract

Purpose of the Review Pulmonary nodules are increasingly encountered by physicians with the increasing use of, and easier access to computerised tomography for the investigation of a variety of conditions. With the wider introduction of lung cancer screening using low dose CT, it is likely that the number of patients with pulmonary nodules will significantly increase. The main challenge in pulmonary nodules investigations and management is the differentiation of benign from a malignant aetiology. There are also certain considerations in the elderly population.

Recent Findings A reliable assessment of the risk of lung cancer is required, and guidelines were devised based on a plethora of evidence to address this issue. Pulmonary nodules less than 5 mm in patients with no previous history of malignancy require no follow up. Larger nodules require either interval follow up imaging or proceeding to investigations such as positron emission tomography and image or bronchoscopy guided biopsy.

Summary Balancing the benefits of invasive investigations and associated anxiety against the risk of delayed treatment of an early lung cancer should be handled carefully through a multidisciplinary approach involving respiratory physicians, radiologists, surgeons, pathologists, and oncologists. The decision regarding appropriate management should be made following a detailed discussion with patients that considers level of fitness, comorbidities, quality of life, and personal preference.

Keywords Nodule · Lung cancer · Screening

Introduction

A lung nodule is a defined opacity that measures less than 3 cm [1]. Lung nodules are increasingly a frequent incidental finding on computerised tomography (CT), performed for unrelated reasons. In the USA one study estimated that over a 6-year period, 1.57 million Americans had a pulmonary nodule identified on a CT scan [2]. Such findings need to be assessed using structured pathways based on clinical evidence. A group of guidelines has been developed for this purpose including the British Thoracic Society and the Fleischner society guidelines [3, 4, 5••, 6••]. While lung nodules are more frequently non-malignant, the work up of patients with such abnormalities is focused at excluding malignancy. The approach taken in the guidelines is one of assessing risk of malignancy while minimising investigation-associated morbidity and patient anxiety.

The importance of lung nodules will likely increase as lung cancer screening is now more widely accepted as a standard of care and recent results from a large randomised study confirm the survival benefit associated with lung cancer screening that were previously shown [7]. This has been the case in the USA since 2013 when it was recommended by the US Preventative Services Taskforce [8]. In the UK, this has been commenced at a number of defined pilot sites [9]. The screening involves performing low dose CT for a population assessed as being high risk for developing lung cancer and is invariably associated with the detection of pulmonary nodules. In this article we aim at providing a review of the current evidence on the work up and management of pulmonary nodules and the practice guidelines that are widely used.

Causes

Pulmonary nodules can be caused by a variety of conditions. Broadly, these can be divided as inflammatory, infective, and

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malignant. Behaviour of lung nodules over time is a very important factor in differentiating the cause of a lung nodule. Table 1 provides a list of conditions that can be associated with pulmonary nodules.

Prediction of Risk of Malignancy

The core principle of managing lung nodules is identifying patients with lung cancer that can be treated early. Guidelines recommend assessing the risk of malignancy to guide investigations and treatment. Multiple risk factors have been assessed in large scale both prospective and retrospective studies.

Smoking

Cigarette smoking is the single most significant risk factor associated with lung cancer. Epidemiological studies have shown this significant association [10–12]. Results from the Framingham heart study also showed statistically significant higher incidence rates of lung cancer in current and former compared with never smokers (1.97, 1.61, and 0.26/1000 person-year, respectively) [13]. A large case–control study of 7181 patients with lung cancer also demonstrated that smoking cessation was associated with a significant reduction in the risk of lung cancer with patients who stopped for more than 10 years having half the risk of those who continued to smoke [14]. Passive smoking is also associated with increased risk of the development of lung cancer as shown in a metanalysis of 55 studies [15].

Table 1 List of commonest causes of pulmonary nodules. NTM: nontuberculous mycobacteria; RB-ILD: respiratory bronchiolitis interstitial lung disease

Malignant
Lung cancer
Carcinoid tumour
Lymphoma
Metastasis commonly from breast, gastrointestinal and melanoma among other
Infection
Tuberculosis
Bacterial pneumonia
NTM
Aspergillosis
Septic emboli
Inflammatory
Vasculitis
Sarcoidosis
RB-ILD
Rheumatoid lung disease
Organising pneumonia
Other
Hamartoma
Amyloidosis
Intrapulmonary lymph node

Family History of Lung Cancer

A family history of lung cancer is associated with increased risk of early onset lung cancer. First degree relatives of lung cancer patients have been shown to have two-fold increase in their personal risk with a stronger association in women than men [16]. Apart from epidemiological studies, some genome-wide studies have shown multiple genetic polymorphisms associated with increased risk of lung cancer [17, 18]. One study identified increased risk with genetic polymorphism associated with nicotine dependence [19].

Age

Increasing age has been shown consistently in studies to be associated with increased risk of lung cancer [20, 21]. There is some variation in incidence of lung cancer across age group depending on gender; the highest incidence of lung cancer is in the age groups 85–89 compared with 75–79 years-old in men and women, respectively [22]. Over 90% of cases of lung cancer occurs in those older than 55 years [23].

Computerised Tomography Characteristics

Certain features on CT scan are associated with increased risk of malignancy. Also, there are some features that can help make a definite diagnosis of a benign lung condition.

Size

All nodule guidelines include nodule size as the first criterion to decide regarding likelihood of malignancy and the need for further investigations [5, 6]. This is based on a proportional increased risk of lung cancer with increased size, the poor resolution of positron emission tomography PET for small nodules, and the technical feasibility of a CT guided lung biopsy. A systemic review of eight lung cancer screening trials showed the prevalence of lung cancer to be 0–1% in nodules < 5 mm in diameter compared 64–82% in nodules measuring >20 mm [24]. The BTS guidelines recommend no follow up for nodules measuring < 5 mm in diameter or < 80 mm^3 in volume in the absence of history of previous malignancy [6].

Spiculation

The contour of nodules is routinely assessed by radiologists when examining CT scans. The presence of spiculation is associated with an increased risk of lung cancer. One study

showed spiculation to be present in 87% of malignant lung nodules [25]. However, the lack of spiculation does not exclude malignancy as some studies reported a smooth margin in 21–33% of malignant nodules [26].

Density

According to attenuation on CT scans nodules are divided into three groups with some significant pathological correlation: solid, part solid, and pure ground glass nodules. Solid nodules obscure the underlying parenchymal structure. Part solid and ground glass nodules can be due to infection or inflammation but if they persist on follow up then they should be considered suspicious for malignancy, most frequently minimally invasive adenocarcinoma (MIA) or adenocarcinoma in situ (AIS) as classified by the World Health Organisation (WHO) [27]. The recognition of this differentiation based on density on CT is pivotal as it has a significant impact on follow up, prognosis and management.

Features Suggestive of Benign Aetiology

Some characteristics on CT are suggestive of a benign entity. Intrapulmonary lymph nodes have specific features, and the guidelines recommend no further follow up if a radiologist is satisfied that certain findings are present such as a triangular shape and location with regard to the fissure [6••] (see Table 2). The presence of calcification is generally indicative of a benign nature, but some malignant nodules can develop dystrophic calcification which is more frequently eccentric as compared with central or diffuse solid calcification in nodules secondary to previous granulomatous infection [28]. The presence of fat within a nodule is also highly suggestive of a hamartoma [29].

CT Risk Prediction Models

Multiple malignancy risk prediction models for pulmonary nodules detected on CT have been proposed [21, 30, 31]. The main principle is using confirmed risk factors for malignancy to define a risk score that assists a shared decision-making process between patients and physicians.

Table 2 Radiographic features of intrapulmonary lymph nodes

Shape
Triangula, oval or round
Borders
Well defined
Location
Peri-fissural or subpleural

The BTS guidelines recommend using the Brock Model to assess the risk of malignancy in lung nodules > 8 mm in size; patients with > 10% risk should be referred for further investigations instead of a 3-month surveillance CT. The BTS, in collaboration with Cancer Research UK, has developed a mobile app that includes the guidelines and the recommended risk calculators. The Brock model was developed in a dataset from the Pan-Canadian Early Detection of Lung Cancer Study (Pancan) and validated in an independent dataset [20]. The information required by the Brock risk calculator is displayed in Table 3.

Investigations

The differentiation of malignant nodules requires investigations that can be associated with harm to patients. The risk and anxiety that comes with these investigations need to be weighed against the potential risk of malignancy and patient suitability for any proposed treatment. The first decision to be made is whether to proceed with further investigations versus radiological surveillance to assess for growth. A patient must be eligible for treatment if investigations are to be undertaken—this becomes increasingly important in the elderly population. However, with increasing development of more minimal treatments such as limited resections, stereotactic, or endobronchial treatments this eligibility issue is likely to adapt over the next few years. Nodules that show significant growth on follow up surveillance can then be managed according to defined guidelines, but in general, options will be to pursue a histological confirmation or definitive treatment as a lung cancer based on the presence of serial growth. Investigations for suspicious lung nodules include positron emission tomography PET and image or bronchoscopy-guided biopsies. Other investigations such as pulmonary function tests, cardiopulmonary exercise testing, and echocardiogram are used to assess fitness for treatment.

Table 3 Characteristics used by Brock model to assess for risk of malignancy in pulmonary nodules

Age
Gender
Family history of lung cancer
Emphysema
Nodule diameter mm
Nodule count
Nodule type
Pure ground glass
Part solid
Solid
Nodule in upper lobe
Spiculation

PET

18F-fluorodeoxyglucose (FDG) positron emission tomography is a standard investigation for staging patients with suspected lung cancer and other malignancies. In the case of pulmonary nodules, PET is useful in predicting the risk of malignancy but also for staging if lung cancer is confirmed. One study looking at a lung cancer screening population showed that PET-CT had an overall sensitivity of 82% and a specificity of 92% with lower sensitivity for subsolid nodules [32]. Herder et al. developed a risk prediction model following PET-CT for pulmonary nodules in a study of 106 patients [30]. A validation study examined four models for predicting the risk of lung cancer in pulmonary nodules following PET-CT, and the Herder model was shown to be associated with the best accuracy [31]. The BTS guidelines recommend using the Herder model to decide on further investigations among patients with pulmonary nodules assessed with PET as part of the diagnostic algorithm [6••]. PET-CT has some limitations in the work up of pulmonary nodules. False positive findings can be seen with inflammatory and infective nodules. False negative findings can occur in the case of slowly growing lung cancers such as adenocarcinoma in situ AIS and minimally invasive adenocarcinoma MIA [33]. In addition, nodules < 9 mm are below the resolution of PET [34].

Sampling of Lung Nodules

Image-guided lung biopsy is a crucial investigation for the work up of patients with suspicious peripherally located lung nodules with no associated lymphadenopathy [35]. Fluoroscopy and ultrasound guidance can be used although much less frequently than CT. One metanalysis showed CT-guided lung biopsy to a have a diagnostic accuracy of 92.1%, sensitivity of 92.1%, and specificity of 100% for the detection of malignancy [36]. Bronchoscopic techniques such as radial probe endobronchial ultrasound and navigational bronchoscopy can also be utilised to sample suspicious lung nodules. The two main risks associated with image and bronchoscopy guided biopsies are pneumothorax and bleeding. A recent systemic review and meta-analysis looked at image guided versus bronchoscopy-guided nodule biopsies found a better diagnostic yield for the former versus less complications rate for the later [37]. Occasionally, a straight to surgery resection approach can be utilised for highly suspicious lung nodules, but this should only be done following a careful multidisciplinary team MDT discussion and following a detailed consultation with the patient.

Follow up

Less suspicious pulmonary nodules should be followed up to assess for serial growth. Different guidelines recommend different size cut off and follow up schedules. Overall smaller nodules require longer interval for follow up to assess for growth and decision regarding follow up includes some form of risk assessment. In our institution we follow the BTS guidelines that recommend volume measurement of nodules to assess volume doubling time as used in the NELSON screening trial [38]. In addition, part solid and pure ground glass nodules require at least 4 years of follow up considering the risk of slowly growing lung adenocarcinoma, while 1–2 years of follow up is the recommendation for solid pulmonary nodules. In our practice, follow up for most patients with pulmonary nodules is done through a virtual clinic with an option for face-to-face consultation according to patient's preference. Potentially, these patients might be eligible for further CT imaging as part of lung cancer screening can potentially continue within a virtual follow up clinic.

Management of Growing Lung Nodules

In the case of significant growth at follow up a discussion by the MDT is strongly recommended to decide on the available and appropriate treatment options including stereotactic body radiotherapy SBRT, surgical resection, or a biopsy procedure depending on patient's preference and fitness. A significant growth in the BTS guidelines is defined based on volume doubling time VDT < 400 days with separate recommendations for nodules with VDT 400–600 days [6••].

Nodules in the Context of Lung Cancer Screening

The national lung cancer screening trial NLST showed screening with low dose CT in patients at high risk for lung cancer had a 20% relative reduction in mortality when compared with chest radiograph follow up although it was associated with a 36% false positive finding rate, mostly benign lung nodules [39]. This led to the recommendation by the US Preventive Services Task Force (US PSTF) for annual screening in adults aged 55 to 80 years with a significant smoking history [40]. The Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON), which is the largest lung cancer screening trial ran from 2004 to 2019 and showed a significant survival benefit from CT screening [41••]. In the prevalence subset of the NELSON trial baseline CT was performed in 2052 patients considered high risk and pulmonary nodules were detected in 594 (29%). The total number of nodules detected was 897 of which 708 (78.9%) nodules did not require further follow up or investigations according to protocol and the false positive findings rate was 7.9% [42]. In addition to the USPSTF recommendation, the EU position statement on lung cancer screening was published in Dec 2017 recommending that planning for implementation of low-dose CT screening should start in Europe [43]. While lung cancer screening presents an opportunity for early detection and treatment of lung cancer, the current evidence suggests it is associated with a significant

number of false positive findings, mostly benign pulmonary nodules, that need to be managed carefully through a structured approach to minimise harm and anxiety to patients. Also, as follow up CT scans are increasingly performed, physicians need to be aware that new nodules detected at follow up behave differently and should be managed considering a higher risk of malignancy [44].

Nodules in Elderly Patients

Pulmonary nodules are frequently detected in older patients, and understandably, guidelines have no specific recommendation for management in this group of patients. More elderly patients are having CT scans for variable indications, and one study from the USA showed the detection rate of pulmonary nodules among patients older than 65 years to have nearly doubled from 2008 to 2014 [45]. In this retrospective study, age was not a factor in decisions regarding follow up or further investigations, while both comorbidities index and estimated life expectancy were. The USPSTF recommends lung cancer screening in patients aged 55–80 years [40], while the NELSON trial included patients aged 50–75 years [38]. The introduction of SBRT has been shown to reduce the rate of untreated stage 1 non-small lung cancer elderly patients and a modest increase in overall survival [46]. In elderly patients a careful evaluation of comorbidities, fitness, and life expectancy should be considered taking patient priorities into account regarding quality of life and independence. There is scarce literature regarding the management of pulmonary nodules in the elderly and the role of geriatrics assessment. Further research in this area is required to support making recommendations that are evidence based. Prospective studies looking at the older population within lung cancer screening eligible group would provide a valuable opportunity to assess this further.

Conclusion

A reliable assessment of the risk of lung cancer is required and guidelines were devised based on a plethora of evidence to address this issue. Pulmonary nodules less than 5 mm in patients with no previous history of malignancy require no follow up. Larger nodules require either interval follow up imaging or proceeding to investigations such as positron emission tomography and image or bronchoscopy-guided biopsy. Balancing the benefits of invasive investigations and associated anxiety against the risk of delayed treatment of an early lung cancer should be handled carefully through a multidisciplinary approach involving respiratory physicians, radiologists, surgeons, pathologists, and oncologists. The decision regarding appropriate management should be made following a detailed discussion with patients that considers level of fitness, comorbidities, quality of life, and personal preference.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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