

Solitary Lung Nodule: The Impact of Computed Tomography on Pre-Test Probability of Malignancy, Lung Cancer Staging And Management

Aldo Pezzuto, Raffaele Ratta, Yuri Errante, Carlo Cosimo Quattrocchi, Anna Maria Frezza, Pierfilippo Crucitti, Giuseppe Tonini

Aldo Pezzuto, Department of Cardiopulmonary, Sant'Andrea Hospital, Sapienza University, Via di Grottarossa 1035, 00189, Rome, Italy

Raffaele Ratta, Department of Oncology, University Campus Bio-Medico, Via Alvaro del Portillo 200, 00128, Rome, Italy

Anna Maria Frezza, Giuseppe Tonini, Department of Oncology, University Campus Bio-Medico, Via Alvaro del Portillo 200, 00128, Rome, Italy

Yuri Errante, Carlo Cosimo Quattrocchi, Center for Integrated Research in Biomedicine and Bioengineering, Radiology, University Campus Bio-Medico, Via Alvaro del Portillo 200, 00128, Rome, Italy

Pierfilippo Crucitti, Department of Surgery, University Campus Bio-medico, Via Alvaro del Portillo 200, 00128, Rome, Italy

Correspondence to: Giuseppe Tonini, Department of Oncology, University Campus Bio-Medico, Via Alvaro del Portillo 200, 00128 Rome, Italy.

Email: g.tonini@unicampus.it

Telephone: +39-06-225411201

Fax: +39-06-225411933

Received: January 25, 2014

Revised: April 18, 2014

Accepted: April 23, 2014

Published online: May 18, 2014

ABSTRACT

Lung cancer still represents the leading cause of cancer death in both women and men with over a million deaths annually. It is often detected as a lung nodule, a frequent finding in both in smokers and non smokers. The early detection, accurate characterization, and appropriate management of pulmonary nodules require a multidisciplinary approach, involving radiologists, medical and radiation oncologists, pneumologists and thoracic surgeons. The purpose of our review is to summarize the main characteristics of lung nodules, their CT scan aspects (location, size, pattern and growth rate assessment) and the establishment of the pre-test CT probability of malignancy that is essential to guide management towards molecular non invasive tests and/or biopsy clinical management. When the malignant nature is defined, CT imaging allows lung cancer staging and guides the clinician for patient management.

Key words: Lung; Nodule; CT; Smoke; Carcinogenesis; Imaging; Biopsy; Patient management

Pezzuto A, Ratta R, Errante Y, Quattrocchi CC, Frezza AM, Crucitti P, Tonini G. Solitary Lung Nodule: The Impact of Computed Tomography on Pre-Test Probability of Malignancy, Lung Cancer Staging And Management. *Journal of Tumor* 2014; 2(5): 129-135 Available from: URL: <http://www.ghrnet.org/index.php/JT/article/view/678>

INTRODUCTION

Focal pulmonary opacities large up to 5 mm in diameter are routine finding in smokers. Most of them are benign, deriving from scars secondary to infectious diseases or inflammation.

Aim of this review is to discuss the origin, the clinical approach and the management of lung nodules in different types of subjects.

STATE OF THE ART

Definition and nature of lung nodules

According to the Nomenclature Committee of the Fleischner Society, a "solitary pulmonary nodule" is a roundish structured lesion less than 3 cm in diameter, completely surrounded by normal pulmonary parenchyma, while solitary lung lesions larger than 3 cm in diameter are defined masses and often malignant^[1]. Lung nodules are spherical, not coin-shaped and not associated with atelectasis, hilar enlargement or pleural effusion.

Nodular lesions recognise several possible etiologies, both benign or malignant (Table 1).

Infections are one of the leading cause of lung nodules. Infectious granulomas represent more than 80% of benign pulmonary lesions, most of the times due to mycobacterial and fungal organisms^[2].

A further possible aetiology is silicosis, either associated with tuberculosis or not^[3]. Silicosis, made of crystalline silica derived from occupational exposure, is a carcinogenic condition. According to retrospective studies, pulmonary malignancies in nodules of silicosis is established as 10% and the most frequent histological type is squamous cell carcinoma. Small opacities (12 point scale) and

Table 1 Causes of solitary pulmonary nodules (modified from Philip A *et al* Evaluation and Management of Indeterminate Pulmonary Nodules

Neoplastic, malignant	Primary lung malignancies (NSCLC, SCLC, carcinoid, lymphoma); solitary metastasis
Benign	Hamartoma; arteriovenous malformation; hematoma; pulmonary venous varix
Infectious	Granuloma; round pneumonia; abscess; septic embolus
Noninfectious	Amyloidoma; intrapulmonary lymphnode; rheumatoid (necrobiotic) nodule; Wegener granulomatosis; focal scar; infarct; sarcoid
Congenital	Sequestration; bronchogenic cyst; bronchial atresia with mucoid impaction

large opacities of different grade are the radiological findings useful to classify silicosis according to the ILO classification.

The scar lesions, resulting from a variety of infective, traumatic, environmental or occupational exposures, can also promote the development of lung cancer, possibly through mechanism of lymphatic drainage blockage and local pooling of carcinogens^[4].

Tuberculosis often presents as nodules, especially in its miliary expression^[5]. The acute phase proteins produced during the early phase of tuberculous infection can result in a lung scar. Other granulomatous infections include histoplasmosis, aspergillosis, cryptococcosis, coccidioidomycosis. Infectious granulomas account for more than 40% of benign nodules and they most often have a well-defined smooth border. The coexistence of silicosis and tuberculosis in miners accelerates the development of lesions.

Hamartomas account for 15% of benign lesions^[5]. They usually show a chondroid pattern of calcification (central or diffuse) and may present a fat component in the context of the lesion with negative Hounsfield units values, which is a pathognomonic finding.

Previous radiation therapy and cigarette smoking increase the prevalence of scar lesions; smoke habit can lead to the development of malignant lesions, especially if smoke intake persists. Approximately 80% of lung cancers are associated to previous or concomitant smoking habit and several carcinogenic mechanism have been identified. Carcinogens contained in tobacco are a complex mixture of over 5,000 substances, including tobacco-specific N-nitrosamines, polycyclic aromatic hydrocarbons, aromatic amines, aldehydes, phenols, volatile hydrocarbons, nitro compounds, and other organic and inorganic compounds that can damage cell structures (DNA, lipids and proteins) in both direct and indirect ways^[5].

Inflammation seems to play a key role in the occurrence of lung cancers in smokers, being one of the first step leading to the release of cancer promoting factors such as the nuclear factor κ B (NF- κ B).

METHODS

Eligible articles included English language papers published in peer-reviewed journals reporting data on subjects with lung nodules. The choice included studies in vivo and in vitro, screening programs, guidelines. The inclusion criteria were the statement of smoking status, the age, risk of cancer. Papers referring to a possible therapy for nodule reduction were also considered. The MEDLINE, EMBASE, SCOPUS databases were systematically searched from inception to June 2013.

Clinico-radiological pre-test probability of malignancy

The early detection, accurate characterization, and appropriate management of pulmonary nodules require a multidisciplinary approach, involving radiologists, medical and radiation oncologists, pneumologists and thoracic surgeons.

From a clinical point of view, older age, smoking status, smoking cessation status and positive history for cancer have been recognized as independent predictors of malignancy in lung nodules.

Growth rate assessment is an important and cost-effective step in the evaluation of nodules, but it needs follow-up over time, multiple radiological examinations and it is not well accepted from the

patients' side. Thus, methods to establish the pre-test probability of malignancy have been developed, based either on Bayesian or on multivariate logistic regression analyses^[6]. However, none of these methods have been shown to be superior to the clinical judgment of an expert physician in predicting the probability of malignancy^[7]. With the application of these models that include clinical variables and gross nodule characteristics such as size and location, patients may be classified according to low, intermediate, high risk of lung cancer or to a probability estimated by means of equations developed considering the power of each variable in multiple regression models (Table 2).

Table 2 Risk of lung cancer associated with a solitary pulmonary nodule.

Variable	Risk of cancer		
	Low	Intermediate	High
Diameter of nodule (cm)	< 1.5	1.5-2.2	≥2.3
Age (years)	<45	45-60	>60
Smoking status	Never smoked	Current smoker (≤20 cigarettes/d)	Current smoker >20 cigarettes/d)
Smoking-cessation status	Quit ≥7 years ago or never smoked	Quit <7 years ago	Never quit
Characteristics of nodule margins	Smooth	Scalloped	Corona radiate or spiculated

From the radiological point of view, conventional chest radiographs are the diagnostic tool more often used. Unfortunately, despite the low radiation doses, chest X-ray (CXR) has low sensitivity for detection of nodules and a high false-positive rate due to the summation artifacts, both on standard postero-anterior and lateral projections^[8]. Muhm and colleagues reported that almost 90% of peripheral nodules and 75% of peri-hilar nodules identified during a lung cancer screening program conducted through chest computed tomography (CT) were detected after negative CXR performed within the previous three months^[9].

The failure to identify lung nodules can be due to either an incomplete visual survey by the evaluator^[10] or a nodule's low conspicuity when located in the upper lung, centrally^[11] or over other body structures such as the clavicle or hilar vessels.

Since its introduction in 1990s, the spiral (CT) became the standard for the detection of focal pulmonary opacities^[12].

The use of CT in chest imaging initially encountered some reluctance both because CXR was considered the best radiological technique for its high quality in imaging pulmonary nodules and also for the air contrast. However, in the late 1970s, CT scan of lung nodules was proven to be superior to chest radiography and linear tomography^[13].

CT nodule location, size and growth rate assessment

In the clinical nomograms, location and size of nodules contribute to the pre-test probability of malignancy.

Upper and middle lobe solitary pulmonary nodules have a likelihood ratio for malignancy of 1.2 to 1.6. The upper lobe location has been shown to be an independent predictor of malignancy^[14].

As for size, the majority of smokers undergoing thin section CT are found to have small lung nodules and the detection of nodules

up to 4 mm in diameter is a routine finding in this population. The majority of lung nodules smaller than 5 mm are benign, deriving from scars caused by inflammatory processes, and the prevalence rate of malignancy in this group is 0-1%, with the exception of one small retrospective study^[15] that reported 2 nodules smaller than 5 mm in diameter as malignant^[16]. However, small size alone it is not enough to exclude lung cancer: in a study by Ginsberg and colleagues^[17], whose purpose was to determine the etiology of pulmonary nodules resected at video-assisted thoracoscopic surgery (VATS), 15% of malignant nodules were less than 1 cm in diameter and approximately 42% were less than 2 cm in diameter. Clinical context is also very important: a review by Mc Williams and colleagues^[18] on the risk of malignancy in small non-calcified nodules detected by CT reported a frequency of small pulmonary nodules of 5 to 60% and both a diameter greater than 10 mm or persisting growth in two surveys CT scan were identified as predictors of malignancy. In the same review, a smoking history of more than 30 pack-years was associated with an incidence of nodules of about 36-50 % on CT base, whereas a history of 10 pack-years was associated with nodule frequency of 23%.

According to Fleischner Society, the risk of malignancy is 0-1% for nodules <5 mm, 6-28% for nodules 5-10 mm, 33-60% for those >11-20 mm, 64-82% for those >20 mm. Therefore, in an approach solely based on size and clinical risk of cancer, follow-up CT scans to assess growth rate in incidentally detected nodules can be required (Table 2)^[19]. Since 15% of solid nodules smaller than 1 cm of diameter contain malignant areas, and this percentage becomes higher with the increase in diameter, a CT scan repeated after six weeks in order to evaluate the growth of nodules or its resolution after antibiotic therapy can be a valuable tool^[14,20].

The statement by Fleischner Society derives from different studies: in the Mayo Clinic lung cancer screening trial non-calcified pulmonary nodules were found in 69% of patients aged 50 years with a smoking history of 20 pack-years or more (high risk patients)^[21], in this trial 1.4% of nodules were lung cancers. A second retrospective review, referred as Benjamin trial, reported that 11% of examined nodules were malignant.

The measurement of the doubling time, defined as the time needed for a diameter increase of about 26%, is probably the most important method for the characterization of small lung nodules. Generally, a stability of nodule's size for two years is considered as a criterion of benignity, thus it doesn't require further evaluation^[22]. Doubling time of malignant nodules is usually between 20 and 300 days (most of them have a doubling time of less than 100 days)^[23,24], while benign nodules can have a doubling time significantly longer or very short (less than 30 days). A volume doubling time greater than 400 days is usually associated with benign lesions such as hamartomas and granulomas^[25]. These rules, although consistent, have been questioned in the case of malignant ground glass opacities that show longer volume doubling times than solid nodules. Nowadays a new method has been introduced for the lung nodule assessment and the early detection of lung cancer in individuals with solitary pulmonary nodules, this is the plasma microRNA biomarkers detection^[26]. A high sensitivity and specificity have been shown from this method.

CT nodule pattern

Lung masses associated with lymphadenopathy, synchronous parenchymal lesions or signs of mediastinal or chest wall infiltration are malignant until otherwise proven. When the lung nodule does not show definite benign characteristics such as pop-corn calcification, intranodular fat, a feeding artery or central vein (typical for arteriovenous malformations), CT morphologic aspects including

CT density, shape and margins, presence of calcifications or cavities must be taken into account to establish its probable nature and aetiology. The NELSON (Dutch Belgian Randomised Lung Cancer Screening) study retrospectively evaluated the doubling time in solid indeterminate non-calcified nodules, proving that the size growth was related to morphology, margins, location and size. The study population included subjects with nodules between 5 and 10 mm in diameter evaluated at 3 months and 1 year. The results revealed that smooth nodules with round shape and low CT attenuation did not become malignant, while a volume increase larger than 130 mm³ of the non-smooth unattached nodules was the predictor for malignancy^[27,28].

As for the density, dense lesions with a solid appearance are less frequently malignant than ground-glass opacities^[16,13]. About 34% of non-solid nodules represent carcinomas and the risk of malignancy increases together with the increase in size.

Small (≤ 10 mm) ground glass nodules usually represent adenocarcinoma in situ or atypical adenomatous hyperplasia while adenocarcinoma is rare. The frequency of invasive adenocarcinoma is greater for pure ground glass nodules measuring >10 mm, reported varying from 10% to 50%. A ground glass appearance has also been described for bronchoalveolar cell carcinoma. Nevertheless one small study reported the resolution of subsolid nodules at follow-up CT scans when they show larger sizes, a lobular border, a polygonal shape and partly solid attenuation^[29].

Nodule's margins can be smooth, lobulated, irregular or spiculated. Defined margins are often sign of benignity; however, Siegelman and colleagues^[30] reported that up to 21% of malignant nodular lesions are characterised by smooth and regular margins. Malignant nodules generally have irregular and spiculated margins or lobular border. In the Dutch-Belgian randomized lung cancer screening trial (Nederlands Leuvens Longkanker Screeningsonderzoek), it has been proved that nodules with lobular border have a higher likelihood for malignancy compared with smooth nodules, and that malignant lesions are usually intra-parenchymal, without attachment to vessels^[27,32]. Nodules surrounded by a ground-glass halo are nonspecific. The halo is often suggestive of infection (often fungal) or hemorrhage caused by vasculitis or metastatic disease.

As for calcifications, Ko *et al*^[33] demonstrated that calcifications in malignant lesions are usually stippled and eccentric. Metastatic nodules often show multiple calcifications.

Both benign and malignant lung nodules can have cavitation and air bronchograms. Cavitation can be suggestive of infection, vasculitis, primary lung cancer, and metastatic disease. The cavity wall thickness can be regarded as a differential feature between benign and malignant nodules. A cavitation inside a nodule is found in lesions more than 3 cm in diameter or in lesions with a diameter ≤ 1 cm. A cavity wall thinner than 4 mm is suggestive of a benign lesions in 95% of cases, while a wall cavity ≤ 16 mm is usually associated to malignant lesions in a percentage between 84% and 95%^[34]. On CT, Honda *et al*^[35] reported that an irregular inner cavity wall was significantly more frequent in malignant compared with benign cavities (49% and 26%, respectively). A linear outer cavity wall was significantly more common in benign compared with malignant cavities (32% and 13%, respectively). A notch outer wall was identified more often in malignant than in benign cavities (54% and 29%, respectively).

A dilated bronchus leading into the nodule, the presence of a intranodular bronchiogram, and vascular convergence suggesting vascular and lymphatic invasion have been also associated to malignancy.

Clinical Management

Management strategies for a pulmonary nodule may be complex and final decision often takes into account multiple variables such as the availability of functional PET Imaging, local expertise in biopsy techniques, comorbidities, and patient preference.

Functional Imaging

The enhancement method in MDCT technique may be a valuable tool since the enhancement up to 15 Hounsfield units suggests a benign aetiology, with a sensitivity and specificity of 98% and 58% respectively^[36]. However, this technique does not differentiate malignant from infective/inflammatory lesions.

The positron emission tomography (PET) with 18F-fluorodeoxyglucose (FDG) has been proven to be accurate in differentiate benign from malignant lesions when used to evaluate a solitary nodule^[37]. According to different studies, PET sensitivity has been reported in the range of 80%-100%, with a specificity between 40%-100%. A retrospective analysis including 17 studies from Wahidi *et al*^[17] reported a sensitivity of 87% and a specificity of 83%. Abnormal 18F-FDG accumulation can be seen in case of infectious nodules due to fungi and mycobacteria, sarcoidosis, rheumatoid nodules, and other causes of inflammatory lung disease, causing false positive results.

Generally, lesions with low FDG uptake are considered benign, although these lesions should be followed radiologically because of the elevated number of false negative results^[38]. The diagnostic value of PET decreases considerably for lesions measuring less than 6 mm, while it is usually reserved for lesion measuring 10 mm or more. The assessment of nodules large 8 to 10 mm in diameter is often associated a large number of false negatives.

False negative results can also be due to the low metabolic activity of some tumors such as the lepidic-predominant adenocarcinomas when minimally invasive or in situ, mucinous adenocarcinomas and carcinoid tumors.

PET has lower specificity in distinguishing different forms of benign nodules. The differential diagnosis must be made among several possibilities including infections, congenital and neoplastic diseases. Integration with multidetector-tomography evaluating the shape and the wall thickness of the lesion is mandatory. Furthermore, this technique must be reserved for those lesions measuring 10 mm or more.

For ground glass opacities or partly solid nodules, PET Imaging is believed not to be reliable. A sensitivity between 80-100% and a specificity of 40-100% have been reported for a threshold uptake value of >1.2^[39].

The 99Technetium methoxyisobutylisonitrile (99TC-MIBI) scintigraphy was also used in one series to identify benign chest nodules and differentiate those from malign lesions. Lung cancer was diagnosed in 50% of patients with malignant lung nodule major than 2.6 cm. Among benign lesions, 76% were negative on 99TC-MIBI scan^[40].

Biopsy Techniques

Sampling is performed on nodules with high probability of malignancy, such as those with larger size or aggressive features. Sampling methods include transthoracic needle aspiration and biopsy (TTNAB), transbronchial needle aspiration and biopsy (TBNA), and minimally invasive video-assisted surgical methods.

The ideal nodules for a percutaneous sampling approach are those accessible without crossing major vascular structures^[41,42]. Sensitivity varies from 72% to 99%, but 90% is accepted as the average

yield. Unfortunately, the determination of benign disease is often challenging due to the small amount of tissue collected through this method. The most common complication associated with TTNAB is pneumothorax, which occurs in 20% to 30% of cases, followed by haemorrhage (about 1%). The risk factors for pneumothorax include age (between 60 and 69 years), smoking, chronic obstructive pulmonary disease, small size, deeper location, the need to traverse fissures^[43], the number of needle punctures^[44]. False negative results are in a range of 10-30%.

TBNA enables biopsy of lesions centrally located and involving the airways. The sensitivity of this technique is widely variable, but has been reported to be 40% to 70% for nodules in the range of 2-3 cm. Recent advances in ultrathin bronchoscopy, electromagnetic navigation, and endobronchial ultrasound are promising technologies but are not yet widely available. The risk of pneumothorax has been reported in the range of 2-4%. False negative results are in a range of 30-70%.

Among surgical approaches, open surgery or video-assisted thoracoscopic surgery (VATS) are available. Tamura *et al*^[45] explore the role of thoracoscopy performed in FDG-PET negative nodules greater than 15 mm and with distance to pleura <10 mm. The surgical resection was undertaken after the lack of success of less invasive procedures such as transbronchial biopsy and CT-guided transthoracic needle aspiration biopsy.

In the trial of Rocco *et al*^[41], a single-access video-assisted thoracoscopic approach was used for peripheral pulmonary nodules in an ambulatory setting.

VATS is a safe alternative to thoracotomy. It is associated with fewer complications but is limited by the visual determination of the location of the nodule. If the nodule is not close to the pleural space, the nodule may not be accessible.

Drugs that affect lung nodule evolution

In a randomized double-blind trial, inhaled budesonide was used to evaluate whether the drug was able to reduce in number and size persistent CT-detected lung nodules in high risk asymptomatic subjects. Selected asymptomatic former smokers with lung nodules underwent treatment with budesonide 800 mg twice daily for 12 months^[46]. Budesonide was found to reduce the size of lung nodules in the longest diameter of 6% of cases while stable disease was observed in 84% of cases.

According to these results, we can assume that those nodules were probably of inflammatory origin caused by oxidants and reactive aldehydes. Moreover, recent evidence in literature suggest a possible anti-carcinogenic properties for molecules such as budesonide, isothiocyanate and N-acetylcysteine administered orally in an animal model^[47]. Animals previously exposed to cigarette smoke have been shown to present a higher incidence of both benign and malignant lung tumors. The administration of the above-mentioned agents, above all budesonide, was effective in protecting mice from carcinogenicity and preventing tumour progression.

In this line of evidence, some other drugs, such as fluticasone have been proved to be effective in nodule lung regression^[48]. In fact in a randomized trial from subjects recruited having bronchial dysplasia and heavy smoking habit, those with evidence of lung nodules undertook placebo or fluticasone. The fluticasone arm showed a decrease in lung nodules number.

DISCUSSION

The management of a patient with a single lung nodule starts from an

accurate evaluation of both clinical and radiological features. Border, shape, location and the pattern of calcification are essential features but patient age, smoking history and history of malignancies must be also taken into account. A close liaison between the radiologists, interventional radiologists, and clinicians is mandatory.

A “watch and wait” approach seems appropriate for those nodules stable over time. It has been suggested that a nodule stable for at least 2 years is a reliable indicator of benignity, as well as a 20 days volume doubling time. Nodules larger than 7 mm can be managed through non-invasive and invasive characterization. An early detection of lung nodules together with smoking cessation give the patient more probability to prevent lung cancer. A half of long-term smokers are estimated to die due to tobacco dependence, which is a disease specified in the 10th revision of International Classification of Diseases.

Lung cancer screening has largely improved after the introduction worldwide of CT scanners capable of imaging the entire chest within a single breath hold. Nodules greater than 7 mm and less than 3 cm are amenable to nodule enhancement study.

Lung nodules have to be monitored by CT scan and in some cases by PET, with a frequency depending on shape, density, size, presence or not of calcifications.

MRI has a limited role because of limited spatial resolution. PET has been proven to have a sensitivity of 96% and specificity of 88% for the diagnosis of nodule. However, the negative predictive value and sensitivity are lowered by its decreased spatial resolution.

Linear or sheet-like lung opacities are unlikely to represent lung neoplasms. However non-calcified solid pulmonary nodules have to be closely monitored until proved to be stable over a period of two years. Patients with at least 30 pack-year smoking histories have to be screened and followed up. The frequency of nodule detection increases proportionally with the narrowing of the slices.

Almost all nodules 4 mm or smaller are benign. Any calcification usually favours a benign cause. The upper lobe location increases the likelihood of malignancy. Comorbidities and smoking habit affect the malignant behaviour of small nodules.

One of these comorbidities is silicosis which is associated with lung cancer. Profusion of pneumoconiotic nodules is a risk factor for lung cancer development and likely to evolve in lung cancer varies in different series^[49]. The invasive approach is indicated for nodule larger than 8 mm in risk patients with higher probability of malignancy. The trans-thoracic needle aspiration is indicated for percutaneous sampling without crossing major vascular structures. TBNA enables biopsy of lesions centrally located with yields of 19% and 62% reported^[50,51]. The accuracy of CT guided biopsy is lower in nodules smaller than 10 mm in diameter. Some prevention therapies are considered potentially capable of reducing lung nodule in size. The glucocorticoids are effective in reducing lung nodule size and number, and in preventing lung tumor development; in fact the effectiveness of budesonide and fluticasone to reduce the size of the nodules suggests an inflammatory origin of these lesions.

Nevertheless, smoking cessation program is the most effective therapy in reducing cancer incidence and malignant transformation of nodules. In a review by Hecht and co-workers we can see that since we know that gas phase and particulate phase of cigarette smoke are co-carcinogens and inflammation is closely associated with tumor promotion, many antioxidants and anti-inflammatory agents have shown efficacy against lung carcinogenesis in animal models. For example anti COX2 agents may work in this direction, since this molecule is constitutively expressed as tumors progress. Therefore sulindac and aspirin are effective chemopreventive agents in tobacco

nitrosamines-treated mice^[52].

CONCLUSIONS

In the clinical approach to a lung nodule, the pretest probability of malignancy, which is related to patient risk and nodule characteristics can be used to guide management.

The possible nature of nodule should be investigated for a therapeutic approach. The patient’s occupational history should be assessed. Alternatives to CT follow-up include CT nodule enhancement, FDG-PET, transthoracic or bronchoscopic needle biopsy, and surgical resection.

Management requires collaboration of a range of specialists including the clinician, diagnostic and interventional radiologists, the bronchoscopist, surgeon, and pathologist.

The use of inhaled steroid drugs, along with the smoking cessation, could be useful to decrease the size of nodules of inflammatory origin.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

REFERENCES

- Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. *Radiology* 2008; **246**(3): 697-722
- Ost D, Fein AM, Feinsilver SH. Clinical practice: the solitary pulmonary nodule. *N Engl J Med* 2003; **348**: 2535-2542
- Arakawa H, Shida H, Saito Y, Johkoh T, Tomiyama N, Tsubamoto M, Honma K. Pulmonary malignancy in silicosis: factors associated with radiographic detection. *Europ J of Radiology* 2009; **69**: 80-86
- Bobba R, Holly SJ, Loy T, Perry MC. Scar Carcinoma of the lung: a historical perspective. *Clinical Lung cancer* 2011; **12**(3):148-54
- Robert J Mason, V Courtney Broaddus, Thomas Martin, Talmadge King Jr., Dean Schraufnagel, John F. Murray, Jay A. Nadel. Murray and Nadel’s Textbook of Respiratory Medicine. 5th edition published by Elsevier, 2010
- Charalambous S, Churhyard GJ, Murray J, De Cock KM, Corbett EL. Persistent radiological changes following military tuberculosis in miners exposed to silica dust. *Int J Tuberc Lung Dis* 2001; **5**(11): 1044-1050
- Jeremy J. Erasmus, H. Page McAdams, John E. Connolly. Solitary Pulmonary Nodules: Part II. Evaluation of the Indeterminate Nodule 1. Radiographics, 2000.
- Gould MK, Simkovich SM, Mestaz PJ, Mestaz, MS, Jamie Daniel, Gillian D. Sanders, Gerard Silvestri. Predicting the probability of malignancy in patients with pulmonary nodules: comparison of clinical judgment with two validated models. *Am J Respir Crit Care Med* 2012; **185**: A4425
- Austin JH, Romney BM, Goldsmith LS. Missed bronchogenic carcinoma: radiographic findings in 27 patients with a potentially resectable lesion evident in retrospect. *Radiology* 1992; **182**(1): 115-122
- Muhm JR, Miller WE, Fontana RS, Sanderson DR, Uhlenhopp MA. Lung cancer detected during a screening program using four-month chest radiographs. *Radiology* 1983; **148**(3): 609-615
- Samuel S, Kundel HL, Nodine CF, Toto LC. Mechanism of satisfaction of search: eye position recordings in the reading of chest radiographs. *Radiology* 1995; **194**(3): 895-902
- McWilliams A, Mayo J. Computed tomography-detected noncalcified pulmonary nodules: a review of evidence for

- significance and management. *Proc Am Thorac Soc* 2008; **5**: 900-904
- 13 Schaner EG, Chang AE, Doppman JL, Conkle DM, Flye MW, Rosenberg SA. Comparison of computed and conventional whole lung tomography in detecting pulmonary nodules: a prospective radiologic-pathologic study. *AJR* 1978; **131**: 51-54
 - 14 Takashima S, Sone S, Li F, Maruyama Y, Hasegawa M, Matsushita T, Takayama F, Kadoya M. Small solitary pulmonary nodules (< or = 1 cm) detected at population-based CT screening for lung cancer: reliable high-resolution CT features of benign lesions. *Am J Roentgenol* 2003; **180**: 955-964
 - 15 Midtrun DE, Swensen SJ, Jett JR. Approach the solitary pulmonary nodule. *Mayo Clinic Proc* 1993; **68**: 378-85
 - 16 Suzuki K, Nagai K, Yoshida J, Ohmatsu H, Takahashi K, Nishimura M, Nishiwaki Y. Video-assisted thoracoscopic surgery for small indeterminate pulmonary nodules: indications for preoperative marking. *Chest* 1999; **115**(2): 563-568
 - 17 Wahidi MM, Govert JA, Goudar RK, Gould MK, McCrory DC; American College of Chest Physicians. Evidence for the treatment of patients with pulmonary nodules: when is it lung cancer? ACCP evidence based clinical practice guidelines (2nd edition). *Chest* 2007; **132**(Suppl 3): 94S-107S
 - 18 Ginsberg MS, Griff SK, Go BD, Yoo HH, Schwartz LH, Panicek DM. Pulmonary nodules resected at video-assisted thoracoscopic surgery: etiology in 426 patients. *Radiology* 1999; **213**(1): 277-282
 - 19 Mc Williams A, Mayo J. Computed tomography-detected noncalcified pulmonary nodules. *Proc Am Thorac Soc* 2008; **5**: 900-904
 - 20 MacMahon H, Austin JH, Gamsu G, Herold CJ, Jett JR, Naidich DP, Patz EF Jr, Swensen SJ; Fleischner Society. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from The Fleischner Society. *Radiology* 2005; **237**: 395-400
 - 21 Libby DM, Smith JP, Altorki NK, Pasmantier MW, Yankelevitz D, Henschke CI. Managing the small pulmonary nodule discovered by CT. *Chest* 2004; **125**: 1522-1529
 - 22 Swensen SJ, Silverstein MD, Ilstrup DM, Schleck CD, Edell ES. The probability of malignancy in solitary pulmonary nodules: application to small radiologically indeterminate nodules. *Arch Intern Med* 1997; **157**: 849-855
 - 23 Yankelevitz DF, Henschke CI. Does 2-year stability imply that pulmonary nodules are benign? *Am J Roentgenol* 1997; **168**: 325-328
 - 24 Weiss W. Tumor doubling time and survival of men with bronchogenic carcinoma. *Chest* 1974; **65**: 3-8
 - 25 Friberg S, Mattson S. On the growth rates of human malignant tumors: implications for medical decision making. *J Surg Oncol* 1997; **65**: 284-297
 - 26 Jun S, Ziling L, Nevins WT, Howard Z, Jipei L, Lei Y, Maria AG, Ruiyun L, Ling C, Min Z, Feng J. Diagnosis of lung cancer in individuals with solitary pulmonary nodules by plasma microRNA biomarkers. *BMC Cancer* 2011; **11**: 374
 - 27 Xu DM, van Klaveren RJ, de Bock GH, Leusveld A, Zhao Y, Wang Y, Vliegenthart R, de Koning HJ, Scholten ET, Verschakelen J, Prokop M, Oudkerk M. Limited value of shape, margin and CT density in the discrimination between benign and malignant screen detected solid pulmonary nodules of the NELSON trial. *Eur J Radiol* 2008; **68**: 347-352
 - 28 Esmaili A, Munden R, Mohammed TLH. Small Pulmonary nodule management. A survey of the members of the society of thoracic radiology with comparison to the Fleischner Society Guidelines. *J Thorac Imaging* 2011; **26**(1): 27-31
 - 29 Felix L, Serra-Tosio G, Lantuejoul S, Timsit JF, Moro-Sibilot D, Brambilla C, Ferretti GR. Timsit JF. CT characteristics of resolving ground-glass opacities in a lung cancer screening programme. *Eur J Radiol* 2011 Mar; **77**(3): 410-416
 - 30 Siegelman SS, Khouri NF, Leo FP, Fishman EK, Braverman RM, Zerhouni EA. Solitary pulmonary nodules: CT assessment. *Radiology* 1986; **160**: 307-312
 - 31 Shen J, Liu Z, Todd WN, Zhang H, Liao, JP, Yu L, Guarnera MA, Li RY, Cai L, Zhan M, Feng J. Diagnosis of lung cancer in individuals with solitary pulmonary nodules by plasma microRNA biomarkers. *BMC Cancer* 2011; **11**(374): 1-9
 - 32 Xu DM, van der Zaag-Loonen HJ, Oudkerk M, Wang Y, Vliegenthart R, Scholten ET, Verschakelen J, Prokop M, de Koning HJ, van Klaveren RJ. Smooth or attached solid indeterminate nodules detected at baseline CT screening in the NELSON study: cancer risk during 1 year of follow-up. *Radiology*. 2009; **250**: 264-272
 - 33 Ko JP, Naidich DP. Lung nodule detection and characterization with multislice CT. *Radiol Clin N Am* 2003; **41**: 575-597
 - 34 Woodring JH, Fried AM. Significance of wall thickness in solitary cavities of the lung: a follow-up study. *Am J Roentgenol* 1983; **140**: 473-474
 - 35 Honda O, Tsubamoto M, Inoue A, Johkoh T, Tomiyama N, Hamada S, Mihara N, Sumikawa H, Natsag J, Nakamura H. Pulmonary cavitary nodules on computed tomography: differentiation of malignancy and benignancy. *J Comput Assist Tomogr*. 2007; **31**: 943-949
 - 36 Henschke CI, Yankelevitz D, Westcott J, Davis SD, Fleischon H, Gefer WB, McLoud TC, Pugatch RD, Sostman HD, Tocino I, White CS, Bode FR, Swensen SJ. Work-up of the solitary pulmonary nodule. American College of Radiology. ACR Appropriateness Criteria. *Radiology* 2000 Jun; **215** Suppl: 607-609
 - 37 Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodule and mass lesions: a meta-analysis. *JAMA* 2001; **285**: 914-924
 - 38 Erasmus JJ, McAdams HP, Patz EF Jr, Coleman RE, Ahuja V, Goodman PC. Evaluation of primary pulmonary carcinoid tumors using FDG PET. *AJR Am J Roentgenol* 1998; **170**(5): 1369-1373
 - 39 Chun EJ, Lee HJ, Kang WJ, Kim KG, Goo JM, Park CM, Lee CH. Differentiation between malignancy and inflammation in pulmonary ground-glass nodules: The feasibility of integrated (18)F-FDG PET/CT. *Lung Cancer*. 2009 Aug; **65**(2): 180-186
 - 40 Nikoletic K, Lucic S, Peter A, Kolarov V, Zeravica R, Srbovan D. Lung 99m TC-MIBI scintigraphy: impact on diagnosis of solitary pulmonary nodule. *Bosnian J of Basic Medic Sciences* 2011; **11**(3): 174-179
 - 41 Rocco G, Romano V, Accardo R, Tempesta A, La Manna C, La Rocca A, Martucci N, D' Aiuto M, Polimeno E. Awake single access video-assisted thoracoscopic surgery for peripheral pulmonary nodules in a complete ambulatory setting. *Ann Thorac Surg* 2010; **89**: 1625-1628
 - 42 Yankelevitz DF, Vazquez M, Henschke CI. Special techniques in transthoracic needle biopsy of pulmonary nodules. *Radiol Clin North Am* 2000; **38**: 267-279
 - 43 Rizzo S, Preda L, Raimondi S, Meroni S, Belmonte M, Monfardini L, Veronesi G, Bellomi M. Risk factors for complications of CT-guided lung biopsies. *Radiol Med* 2011 Jun; **116**(4): 548-563
 - 44 Ayyappan AP1, Souza CA, Seely J, Peterson R, Dennie C, Matzinger F. Ultrathin fine-needle aspiration biopsy of the lung with transfissural approach: does it increase the risk of pneumothorax? *AJR Am J Roentgenol* 2008 Dec; **191**(6): 1725-1729
 - 45 Tamura M, Oda M, Fujimori H, et al. Institutional report-Thoracic Oncologic. *Interactive Cardiovasc and Thoracic Surg*

- 2010, **11**: 590-593
- 46 Veronesi G, Szabo E, Decensi A, Guerrieri-Gonzaga A, Bellomi M, Radice D, Ferretti S, Pelosi G, Lazzeroni M, Serrano D, Lippman SM, Spaggiari L, Nardi-Pantoli A, Harari S, Varricchio C, Bonanni B. Randomized phase II trial of inhaled budesonide versus placebo in high-risk individuals with CT screen-detected lung nodules. *Cancer Prev Res* 2011; **4** (1): 34-42
- 47 Balansky R1, Ganchev G, Iltcheva M, Steele VE, De Flora S. Prevention of cigarette smoke-induced lung tumors in mice by budesonide, phenethyl isothiocyanate, and N-acetylcysteine. *Int J Cancer* 2010; **126**: 1047-1054
- 48 van den Berg RM1, Teertstra HJ, van Zandwijk N, van Tinteren H, Visser C, Pasic A, Sutedja TG, Baas P, Golding RP, Postmus PE, Smit EF. CT detected indeterminate pulmonary nodules in a chemoprevention trial of fluticasone. *Lung Cancer* 2008; **60**: 57-61
- 49 Arakawa H1, Shida H, Saito Y, Johkoh T, Tomiyama N, Tsubamoto M, Honma K. Pulmonary malignancy in silicosis: factors associated with radiographic detection. *Eur J Radiol* 2009; **69**: 80-86
- 50 Makris D1, Scherpereel A, Leroy S, Bouchindhomme B, Faivre JB, Remy J, Ramon P, Marquette CH. Electromagnetic navigation diagnostic bronchoscopy for small peripheral lung lesions. *Eur Respir J* 2007; **29**: 1187-1192
- 51 Gould MK, Donington J, Lynch WR, Mazzone PJ, Midthun DE, Naidich DP, Wiener RS. Evaluation of individuals with pulmonary nodules: when is it lung cancer? *Chest* 2013; **143**(5) **suppl**: e93S-e120S
- 52 Hecht S, Kassie F, Hatsukami D. Chemoprevention of lung carcinogenesis in addicted smokers and ex-smokers. *Nature Rev Cancer* 2009; **9**: 476-487
- Peer reviewers:** Nobuhiro Kanaji, MD, PhD, Department of Internal Medicine, Division of Endocrinology and Metabolism, Hematology, Rheumatology and Respiratory Medicine, Faculty of Medicine, Kagawa University, 1750-1, Ikenobe, Miki-cho, Kitagun, Kagawa 761-0793, Japan; Chun-Ru Chien, Department of Radiation Oncology, China Medical University, 2nd Yuh-Der Rd, North District, 40402, Taiwan.