Management strategy of pulmonary nodule in 2013

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Lung nodules are commonly found on computed tomography (CT) and need a standardized approach in order to avoid misdiagnosing lung cancer and delaying surgical excision whilst simultaneously avoiding unnecessary invasive procedures if the lesions prove to be benign. Great advances have been made in the last decade in various areas affecting the management of lung nodules: the understanding of the molecular mechanisms behind carcinogenesis, a new classification of lung adenocarcinoma, new data on lung cancer screening, widespread use of multi-detector row CT and development of volumetric analysis software for nodules. Recent decision-making algorithms are based on the size, density and follow-up of the nodule. The distinction between solid nodules, sub-solid nodules and pure ground glass nodules is fundamental, and has a strong correlation with the histologic spectrum of adenocarcinoma. In the absence of criteria suggesting benign disease, the radiologist’s report should offer one of the following two options: follow-up based on the recommendations if the nodule is equivocal, or multidisciplinary discussion to consider invasive management if the nodule is highly suspicious of malignancy. Recent data from this statement are reviewed and practical guidelines are offered based on international expert consensus opinion.

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Lung nodules are very commonly found on computer tomography (CT) which leads the doctor to question whether or not they are malignant. In his/her investigation report, the radiologist must rank the diagnostic possibilities and offer appropriate management based on the morphology of the nodule and its clinical context. This management may range
from no treatment, without follow-up, to surgical resection. It should always optimize the benefit-risk balance, i.e. not leave a potentially malignant nodule to progress, whilst at the same time limiting invasive investigations, patient anxiety and the radiation delivered by repeated CT scans. The selected strategy should follow recommendations incorporating recent findings from an extensive and rapidly changing literature. The imaging features of the nodule, and therefore the role of the radiologist, are essential for the definition of this management.

In 2002, a review of the management strategy recommendations for lung nodules was published in the Journal de Radiologie [1]. This strategy needs to be updated after a decade which has seen many advances in lung cancer understanding and imaging. The Journal de Radiologie Diagnostique et Interventionnelle is therefore offering its readers a new state of the art review. The first part of this article is a review of the different advances which impact on the management of a lung nodule. It then describes the diagnostic approach, based on recommendations published by expert consensus groups. It then offers the reader a summary table as a practical decision-support tool.

Definitions

A lung nodule is defined as a focal opacity whose largest diameter is between 3 mm and 3 cm in length [2]. The term micronodule is reserved for opacities under 3 mm in diameter and the term mass is used for opacities over 3 cm diameter. The accuracy of diameter measurement is fundamental as the size of a nodule correlates closely with its likelihood of malignancy. The percentage malignancy rate in the ELCAP screening study was 1% for nodules under 5 mm in size, 24% for those between 6 and 10 mm, 33% between 11 and 20 mm and 80% for nodules over 20 mm in size [3].

Diameters are measured in the parenchymal window on native transverse axial CT slices, which may be a source of errors if the nodule is asymmetrical and not spherical. If the nodule is small, then measurements must be taken after the image has been magnified. As a result of inaccuracies in manual measurements of diameter, semi-automated volumetric measurement techniques have been developed [4].

Alongside these geometrical measurements, densitometric analysis of the lung nodule has also become essential and has been made possible by row CT technology which allows continuous millimeter sections to be acquired. The terms solid nodule, sub-solid nodule and ground glass nodule were introduced by Claudia Henschke in 2002 [5]. A solid nodule has a homogeneous tissue density which obscures the vascular structures passing through it. A pure ground glass nodule has a lower density which does not obscure vascular and bronchial structures and a sub-solid or mixed nodule has both components, often in the form of a central solid nodule surrounded by a peripheral ground glass halo (Fig. 1).

This densitometric distinction is justified by their different behaviors in terms of malignancy. The malignancy rate for sub-solid nodules was 63% in the ELCAP study compared to 18% for pure ground glass nodules and 7% for solid nodules [5]. The lowest proportion of malignant nodules is therefore the solid ones, although, paradoxically, a lung cancer more often presents as a solid nodule than as a ground glass nodule [6,7]. Indeed, the vast majority of nodules in screening studies were solid but small and therefore benign. Note that the densitometric analysis of a nodule cannot be separated from its geometric analysis.

Advances in the understanding of molecular mechanisms in bronchial cancer

These advances mostly concern adenocarcinoma, the commonest but also most varied form of lung cancer, from a radiological, clinical, histological and molecular perspective. Adenocarcinomas diagnosed late (stages IIIb and IV) make up almost 80% of cases; the management of these has changed significantly in recent years. Several genes involved in oncogenesis ("oncogenic drivers") have been identified at the same time as biomarkers and targeted treatments have been developed.

These oncogenes may cause deregulations or point mutations which are acquired and only present in malignant tissue, and are not specific for lung adenocarcinoma as they are also found in colorectal and breast cancer, melanoma and blood malignancies, to give a few examples. The most widely studied mutations in lung oncology are those for the

Figure 1. Examples of solid (a), sub-solid (b) and pure ground glass (c) nodules.
gene coding for epidermal growth factor receptor (EGFR) which is a tyrosine kinase transmembrane protein. These mutations are responsible for overexpression of the EGFR protein which accelerates tumor cell proliferation. They are generally unrelated to smoking and are more common in women. They are found in approximately 10 to 15% of Caucasian patients and in more than 30% of patients of Asian origin [8–10]. Most people with these mutations respond to the tyrosine kinase inhibitors (TKI), which block overexpression of the EGFR protein. The first commercially available molecule was Gefitinib (Iressa®), which was shortly followed by Erlotinib (Tarceva®). Response rates in patients with the mutation are over 60%, with a median survival of approximately 2 years, whereas patients without the mutation have a response rate of between 0 and 5% and a median survival of only one year [11]. The EGFR-TKIs are now indicated for first-line treatment of patients with inoperable adenocarcinoma with the mutation [12], and according to the Institut National du Cancer (INCa) recommendations [13], patients with advanced adenocarcinoma should be tested routinely for the EGFR gene mutation.

Mutations other than those involving EGFR, which are often mutually exclusive, have also been found:
• the EML4-ALK rearrangement which is found in 5 to 7% of adenocarcinomas, often the mucinous form, which makes them sensitive to Crizotinib (Xalkori®) [14–18];
• the KRA5 gene mutation, which is more common in smokers, and which may reflect resistance to erlotinib and gefitinib [19,20];
• other more recently discovered mutations (BRAF, HER2, PIK3CA, AKT1, MEK1, CMET, ROS1) are currently routinely tested for [21,22];
• some oncogenic drivers have also been found in squamous cell carcinoma, the second leading cause of lung cancer, although the incidence of this is falling [23].

The development of these biomarkers and targeted treatments has therefore started a new “theranostic” era in the palliative care of non-small cell lung cancer. INCa has made this one of its priorities by starting a huge development program of molecular biology tests in 28 hospitals throughout France [13]. Only a minority of patients currently receive these new treatments and a substantial proportion of those patients finally become resistant to TKIs. However, new discoveries are made every week and many new areas of treatment are opening up [24]. Molecular phenotyping is also promising in refining tumor characteristics, as in the case of multiple nodules where it should be possible to distinguish between the metastases from the same clone and several synchronous primary lesions [25].

New histological classification of lung adenocarcinomas

Lung adenocarcinomas currently make up between 40 and 50% of primary lung cancers. This is a group of heterogeneous tumors with many subtypes, which have extremely different prognoses. The classification of adenocarcinomas was completely revised in 2011 to simplify and adapt it to advances in molecular biology [26]. The authors emphasize the multidisciplinary nature of this new classification, which must now create a common language for the different medical specialists who manage lung adenocarcinomas.

Pre-invasive lesions, which have a post-resection 5-year survival rate of almost 100%, have been redefined taking account of their size and level of cellular atypia (Boxed text 1). The new classification abolishes the use of the term “bronchioalveolar carcinoma” which was considered to be too inaccurate and could be used to describe several entities which have since been clearly defined as follows:
• atypical adenomatous hyperplasia: a proliferation of atypical pneumocytes along the alveolar walls, not exceeding 5 mm in diameter. This is considered to be a precursor of lung adenocarcinoma;
• adenocarcinoma in situ: a lesion under 3 cm in diameter, consisting exclusively of the lepidic subtype which is defined by a preserved alveolar architecture. This has a 5-year survival of 100% [27,28];
• minimally invasive adenocarcinoma: a lesion under 3 cm in diameter, consisting predominantly of the lepidic subtype, with an invasive component less than 5 mm in size with no necrosis or pleural, vascular or lymphatic invasion. This has a very good prognosis after resection, with a 5-year survival of nearly 100% [29,30];
• invasive adenocarcinoma with a predominant lepidic component: a lesion with an invasive component measuring more than 5 mm in diameter;
• invasive mucinous adenocarcinoma: the new name for multicentric bronchioalveolar carcinoma.

For surgically excised invasive lesions, it is recommended that the overly vague term “mixed type adenocarcinoma” no longer be used as the vast majority of invasive adenocarcinomas are made up of several histological subtypes. Each adenocarcinoma should now be classified according to

Boxed text 1 IASLC/ATS/ERS* classification of bronchial adenocarcinomas.

Pre-invasive lesions:
• atypical adenomatous hyperplasia;
• adenocarcinoma in situ (formerly: or bronchioalveolar carcinoma);
• minimally invasive adenocarcinoma.

Invasive adenocarcinomas:
• lepidic predominant adenocarcinoma (formerly: non-mucinous bronchioalveolar carcinoma);
• acinar predominant adenocarcinoma;
• papillary predominant adenocarcinoma;
• micropapillary predominant adenocarcinoma;
• solid predominant adenocarcinoma.

Invasive variants:
• invasive mucinous adenocarcinoma (formerly: mucinous bronchioalveolar carcinoma);
• colloid adenocarcinoma;
• well-differentiated fetal adenocarcinoma;
• enteric adenocarcinoma.

the predominant architectural subtype or component (lepidic, acinar, papillary, micropapillary or solid) (Boxed text 1, Fig. 2). The predominantly lepidic adenocarcinomas are less invasive and carry a better prognosis than the other subtypes. Predominantly acinar or papillary adenocarcinomas are intermediate grade, whereas the predominantly solid or micropapillary adenocarcinomas are high grade and carry the poorest prognosis. This histological classification has a significant prognostic impact, which is independent of TNM stage [31].

The lepidic subtype is defined by a proliferation of atypical cells (type II pneumocytes and Clara cells) along the alveolar walls, without invasion and therefore without alveolar collapse. Because of the persistent air spaces within the alveoli, this tissue has a relatively low CT density and there is a good correlation between the ground glass appearance within the tumor and the lepidic component [28,32]. Tissue or solid components on CT represent the invasive histological component [33]. The natural progression of pre-invasive lesions is slow, although the invasive component increases gradually in parallel with decreasing prognosis [34–37]. There is probably, therefore, a continuum between atypical adenomatous hyperplasia, adenocarcinoma in situ, minimally invasive adenocarcinoma and invasive disease [38]. Therefore, densitometric analysis of a nodule allows us to approach the diagnosis of these lesions (Fig. 3). Several studies have shown that the proportion of ground glass area within the tumor is a good prognostic indicator, independently of the dimensions of the adenocarcinoma [39–41].

The authors of the new classification propose that only the size of the invasive component should be used in determining T status, either from CT (c-TNM) or histological (p-TNM) findings. Several studies have suggested that the size of the invasive solid portion is a better prognostic indicator than the total size of the lesion [42–45]. Results of ongoing clinical studies, however, are needed before this proposal can be validated and possibly incorporated into the eighth version of the TNM classification. The new classification also provides recommendations for performing biopsies and cytology samples. In particular, they recommend that purely ground glass nodules should not be biopsied. On the other hand, for invasive lesions a sufficiently large amount of tissue should be obtained, particularly if they appear to be inoperable on CT, in order to allow histological examination, immunohistochemistry and molecular typing to be carried out.

**Screening for lung cancer**

The issue of lung nodules is becoming increasingly linked to the question of screening. Lung cancer has a number...
of features making it suitable for mass screening: its high disease-specific mortality, a defined at-risk population, its high prevalence in this population, the long clinical latent period, the fact that most of the diseases are inoperable when the diagnosis is made from symptoms, and the fact that early disease treated surgically carries a good prognosis, with a 10-year survival of almost 90% [46]. Screening for lung cancer with an annual chest radiograph has not been shown to be beneficial [47], nor has the use of serum markers, cytological sputum analysis or expired air. Since the 1990s, chest CT has been thought to be very promising for screening examinations as it has a ten-fold greater detection power than standard radiography for uncalcified nodules [48–50]. Published observational studies over the last decade [3,51–55] have shown that CT screening in an at-risk population diagnoses between 0.4 and 2.7% of people with cancers, mostly stage I. The effectiveness of screening, however, can only be demonstrated by showing a reduction in cancer-specific mortality which implies prospective randomized inclusion of a large number of patients. We had to wait, therefore, until 2011 and the results of the National Lung Screening Trial (NLST) for proof that CT scan screening was effective [56]. This study was conducted in 33 North American centers and included more than 53,000 smokers (55–74 years old, >30 pack-years) or former smokers who quit smoking within the previous 15 years. The subjects were randomized into two arms: annual CT scan for 3 years compared to annual chest radiograph for 3 years. After a median follow-up period of 6.5 years, lung cancer mortality was reduced to 20.3% in patients in the CT arm. An observational Japanese study reported similar results [57], although two other randomized studies have failed to confirm the results of the NLST [58,59]. These studies, however, did not have the statistical power of the NLST as they included a smaller number of patients (3000 to 4000 compared to 53,000 in the NLST).

Either way, the position on screening is not definitive and several questions remain, such as the cost-effectiveness ratio, the radiation delivered by repeated CT scans, the large number of false positives on CT scans (98% in the NLST study), and the risk of over-diagnosis. One study published in 2009 estimated that 25% of lung cancers identified by screening would not in fact have been fatal because of the frequent smouldering nature of the disease and the comorbidities present in smokers [60]. In addition, the methodology of the NLST, which was an exclusively North American study, cannot necessarily be extrapolated to other healthcare systems. Scans were all read in expert centers, which is not necessarily possible in practice and could produce different results. Each country, therefore, needs to establish its own need for lung screening and the screening methods.

Joint work in France between the Intergroupe Franco- phone de Cancérologie Thoracique (IFIC: the Francophone Thoracic Cancerology Intergroup), the Groupe d’Oncologie thoracique de Langue Française (GOLF: the French Thoracic Oncology Group) and the Société d’Imagerie Thoracique (SIT: the Thoracic Imaging Society) has provided an answer to clinicians faced with a request for screening. The main points are summarized below, although we suggest readers refer to the original publication which appeared recently in Annals of Oncology [61]. Currently, screening only occurs on the basis of an individual patient making an active request. In view of the significant results of the NLST study, the authors felt that it should not be possible to refuse screening to a patient that has requested it and that it is reasonable to offer screening to at-risk patients. It should be noted that other European countries, such as Italy, feel that there are still too many uncertainties to extrapolate the results of the NLST to current clinical practice. The French expert group emphasizes the need for verbal and written patient information on the benefits and risks of lung cancer screening. In particular, people must be informed about the risk of false positive results and for any subsequent investigations. The rate of needless invasive procedures in the NLST study (surgery, bronchoscopy or needle-biopsy) was 2.6%, approximately 10% of which caused complications (0.24% of the whole screened population). The risks of radiation must also be explained. The same inclusion criteria are used as for the NLST study:

- age between 55 and 74 years old;
- smokers of more than 30 pack-years, either current or who have stopped within the last 15 years;
- no active cancer, respiratory or hepatic impairment, or unexplained weight loss in the last 12 months;
- no lung infection over the last 12 weeks.

Within current knowledge, screening should be annual and continued for at least 3 years. A study published in 2011 showed that stopping screening was associated with a significant increase in cancer deaths [62]. According to the French recommendations, screening does not require dual reading or a computer-aided detection (CAD) automated nodule detection system [61,63]. A recent publication from the NELSON group, however, suggests that CAD might be used, adjusting the sensitivity to reduce the number of false positives [64]. Signs of COPD should be mentioned on the final report [65]. Finally, it is important that the annual screening consultations are accompanied by strong and repeated encouragement to stop smoking.

**Lung nodule volumetry**

It is generally accepted that a solid nodule which remains stable in size for 2 years is benign [66–68]. The follow-up algorithms therefore recommend 2-year follow-up for equivocal solid nodules [1,69]. Tumor growth can be assessed from repeated CT during this period. Longitudinal comparisons of the diameter of small nodules, however, are imprecise [4,70] and a 5-mm nodule which has doubled in volume would only in fact have increased by 1.3 mm in diameter. This figure is below the intra-observer variability, which is between 1.3 and 1.7 mm. For this reason, only changes in diameter of at least 2 mm are deemed to be significant for manual measurements. Semi-automated volume measurement is more reliable, although at present it is not incorporated into the RECIST criteria, nor into the TNM stage, nor into the Fleischner Society recommendations.

A three-dimensional volume approach has been shown to be more precise and reproducible than single diameter measurement [71,72] and volumes measured at two different times can be used to estimate tumor growth [73] by calculating the volume doubling time (VDT) by the equation:
$VDT = \left( t \ln 2 \right) / \ln \left( \frac{Vf}{Vi} \right)$ where $Vi =$ the initial volume of the nodule, $Vf =$ final volume, $t =$ time between the two CT scans and $ln =$ Napier logarithm. The software packages which are currently available automatically measure the volume of a nodule at two different times and incorporate the time between the two CT scans to calculate a volume doubling time. Volume measurements have been validated for nodules between 5 and 10 mm in diameter, which represent a volume of approximately 50 to 500 mm$^3$ [74]. Changes in volume of at least 25% are deemed to be significant. The current cut-off for malignant versus benign nodules is a doubling time of 400 days, usually calculated from two CT scans performed 3 months apart [74,75]. This method therefore avoids the conventional 2-year follow-up, at least in straightforward situations. An earlier check at one and a half months has even been proposed [76]. Some people suggest reducing the cut-off of 400 days in order to reduce the number of false positives, although the risk in this situation is that adenocarcinomas with a lepidic predominant component, which grow more slowly, would be missed. Takashima found that the volume doubling time of a squamous cell carcinoma is 122 days, whereas the doubling time of an invasive adenocarcinoma, adenocarcinoma in situ and atypical adenomatous hyperplasia, were 384, 567 and 988 days respectively [77]. Hasegawa reported mean doubling times of 149 days for solid nodules, 457 days for mixed nodules and 813 days for ground glass nodules in a 3-year follow-up of 82 malignant nodules [78]. The concept of remaining stable over 2 years (doubling time > 730 days) therefore does not apply to pure or partial ground glass nodules which require longer follow-up. In addition, volumetry is not considered to be sufficiently reliable for ground glass nodules [74,79], despite some encouraging results [80]. A novel, promising approach for mixed nodules would involve measuring the nodule mass, by taking account of volume and density of the two components [81].

Volumetry software packages are based on different mathematical algorithms (density threshold, shape analysis, combined mode). The variability between volume measurements using these algorithms may be as high as 25% [82] and it is therefore important to use the same software for the initial and repeat scans. The two scans also need to have the same acquisition parameters (level of inspiration, mAs, kV, collimation) and reconstruction (section thickness, filter) settings [83,84]. Overlapping millimeter sections are ideal, particularly for the smallest nodules [85]. A standard reconstruction filter is recommended [61]. Despite these precautions, volume measurements can be subject to some inter-examination variability which is estimated to be 13% by Goodman [86]. Inter-observer reproducibility on the same investigation is, however, excellent.

What type of CT acquisition?

Unenhanced scans are the only investigations required in the management strategy for lung nodules. Positron emission tomography (PET) has a marginal role in characterization and follow-up but is essential when excision surgery is considered, in order to confirm that no extrapulmonary lesions are present. CT acquisitions should combine a detailed investigation of the lung volume with high three-dimensional spatial resolution, at the lowest possible radiation dose. In follow-up of a known nodule, the acquisition may be restricted to the volume of interest [87]. Collimation should ideally be under one millimeter and the reconstructions performed using thin overlapping sections [79]. Ground glass nodules can only be correctly analyzed with sections of under 3 mm [88] and the Fleischner Society recommends 1 mm sections [89].

In terms of acquisition settings, the tube voltage is generally 100 kV although this should be adjusted in accordance with the patient’s body mass index. An intensity of 80 mAs is recommended for a person of average body morphology [90], although this may be reduced further (low dose mode) because of the very good natural contrast between lung tissue and nodules. The low dose mode is the standard for all of the major screening studies in which repeated CT scans are performed. There is, however, no precise definition of a low dose chest CT and in practice it would appear reasonable to obtain the acquisition at between 25 and 50 mAs [91,92], although some go down as far as 10 mAs [93]. Iterative reconstructions allow the dose to be reduced, at the same time maintaining reliable volumetric measurements [94], although their exact influence on volumetry is not yet sufficiently well known. In bronchial cancer screening, it is recommended that the dose length product should not exceed 150 mGy cm for an average 70 kg adult [61]. The mean effective dose per scan in the NLST study was 1.5 mSv and in the NELSON study a volume dose index was defined according to patient weight: 0.8 mGy if < 50 kg, 1.6 mGy if 50–80 kg and 3.2 mGy if > 80 kg [75]. Future screening studies will probably incorporate the risk of radiation-induced malignancy into the specific mortality rate calculation [95].

Management principles

By definition, a lung nodule (< 3 cm) is a potential T1 cancer, which therefore carries a high likelihood of survival after resection. All lung nodules must therefore be treated in a standardized way, with the aim of not delaying resection of a bronchial cancer. In the absence of formal criteria indicating a benign lesion, the radiologist should indicate the management strategy in his/her investigation report. This may involve:

• CT scan follow-up if the nodule is equivocal (and the specific details of this follow-up should also be stated);

• an invasive approach if criteria that strongly suggest malignancy are present, in which case the multidisciplinary team meeting (MDT) should decide on the most appropriate procedure.

The strategy proposed here is for a single nodule. When several nodules are present, in the absence of a clear cause such as infection, granulomatosis or metastatic disease, the management is dictated by the most suspicious nodule.

Criteria for benign disease

The first step is to examine for formal criteria of benign disease. Benign lung parenchymal lesions are relatively few. Some of these can be identified on the scan using well-known criteria:
- fatty plaque (−40 to −120 HU) within the nodule suggesting a hamartochondroma, this must be measured carefully with a low standard deviation of the density values;
- a completely calcified nodule or one containing central calcification, suggestive of a post-infectious granuloma. The central calcification feature should be confirmed on two orthogonal reconstructions (Fig. 4);
- a polygonal nodule under 10 mm in size, located less than 10 mm from the pleura or connected to a septum and beneath the carina, suggestive of an intrapulmonary lymph node (Fig. 5).

These criteria are very specific but are, however, less sensitive. Only 50% of hamartochondromas, for example, contain a visible fatty plaque on a CT scan [96]. It may provide reassurance to ensure that the nodule is stable with a repeat CT at 6 months, for example, if a small fatty plaque is present but difficult to measure.

Criteria for malignant disease

In the absence of criterion for benign disease, the second step involves identifying formal criteria for malignancy [7,97–100]: a solid or sub-solid nodule measuring more than 10 mm in diameter, with spiculated or lobulated outlines, an air bronchogram or pleural retraction (Fig. 6). The patient should be referred to a specialist consultation for invasive investigations to establish its histological type. Management options may be discussed in the MDT.

In most cases, however, the morphological features of benign and malignant disease are not present and the

Figure 4. Lung granuloma with central calcification. Native axial sections in the parenchymal window (a) and mediastinal window (b) showing a solid tissue nodule in the culmen measuring 22 mm in diameter, adhering to the scissure, with clearly demarcated outlines and containing a single, central, punctiform calcification. The coronal (c) and sagittal (d) reconstructions confirm that the calcification is central.

Figure 5. Typical appearance of an intrapulmonary lymph node. Triangular nodule (arrow), 4 mm in diameter, adhering to a septum and located beneath the carina.
nodule is still indeterminate. In that situation, size and density factors need to be considered, often adding the progression factor with CT scan monitoring. Following up a nodule over time has the advantage of being non-invasive but makes the management more complex as it necessitates volumetry software and decision-making algorithms. Whilst a nodule that is solid and stable over 2 years is considered benign, this concept is not valid for ground glass nodules which can have a long CT scan latent period before transforming into a more aggressive lesion. The question of how long these nodules need to be followed up has not yet been resolved. Some believe that this should be for at least 5 years, or even longer.

**Pure ground glass nodules**

A ground glass nodule may represent one of several different lesions [101,102]: local infection, local inflammation in an organized pneumonia, spot of fibrosis, atypical adenomatous hyperplasia or adenocarcinoma in situ. If the nodule is under 5 mm in size, the likelihood of malignancy is very low [103] and no monitoring is recommended [89] although some recommend a repeat CT at one year. If many small nodules are present, these are more likely to represent atypical adenomatous hyperplasia [104] and should then be followed up by an annual scan for 2 to 4 years [89]. If the nodule is over 5 mm in size, a scan at 3 months, possibly after antibiotic therapy, will distinguish between a transient nodule (infection, inflammation) and a persistent nodule adenocarcinoma in situ. An air bronchogram is suggestive of adenocarcinoma in situ [105]. However, the management of the nodule is dictated above all by its progression. Lesions which have increased in diameter (≥ 2 mm) or in which a solid component has developed, should be discussed in an MDT where excision surgery should be considered, depending on the clinical situation [61,89]. Long-term monitoring should be proposed for lesions which are stable at 3 months, through a minimum of one annual scan for 3 years [89], as 75% of these are adenocarcinomas in situ [102]. A very rapidly growing ground glass nodule should suggest infection, inflammation or metastasis [106]. There is no role for PET in monitoring pure ground glass nodules [89].

**Part-solid nodules**

A part-solid nodule is more suspicious than a pure ground glass nodule and needs more aggressive management if it persists [89,107]. This usually represents minimally invasive adenocarcinoma or lepidic predominant adenocarcinoma, although there may be overlaps with the other lesions from the adenocarcinoma spectrum (Fig. 3). A part-solid nodule can also be benign, infectious or inflammatory [108]. A repeat CT at 3 months, possibly after antibiotic therapy, is therefore recommended for all of these cases [61,89,90]. The total diameter of the lesion and the diameter of the solid central component should be measured as the size of the central component correlates with the likelihood of malignancy [29,35,109] although one study reported different results [100]. The nodule should be discussed in an MDT in order to consider surgical excision if the lesion increases in diameter (≥2 mm) and/or if the solid component increases [61]. If the lesion is stable at 3 months and has a solid component of over 5 mm, the likelihood of invasive cancer is still significant and it should also be discussed in an MDT [89]. This cut-off of 5 mm histologically reflects the distinction between a minimally invasive adenocarcinoma of very good prognosis and an invasive adenocarcinoma, which carries a significantly poorer prognosis. Annual follow-up for 3 to 5 years is recommended for nodules which are stable at 3 months and have a solid component of 5 mm or less.

PET CT is reported to be useful for nodules with a solid component of over 10 mm [110], although such a size alone is sufficiently suspicious to warrant immediate surgery. As a result, in reality, the PET CT is more part of the staging assessment than a diagnostic tool for the nodule. It should also be remembered that false positive PET CT results are not particularly uncommon (in infection or inflammation). Hypereosinophilia may help to characterize mixed nodules [100]. This is a very highly specific finding (97%) but unfortunately less sensitive (38%). This strategy, however, has not yet been demonstrated to be sufficiently useful.

Giving antibiotics with a repeat scan at 3 months is relatively empirical. Between 37 and 70% of nodules containing ground glass appearances in the screening studies have been shown to be transient [100,108], although antibiotic therapy as a test to abolish these has not been shown to be beneficial. The only study on this subject was retrospective and showed no difference between groups which were and which were not given antibiotic therapy [111]. Expert opinions are split between those who recommend it [3,61,112] and those who are opposed to it [69,89,113]. Other questions remain, such as the difficulty of distinguishing a pure ground glass nodule from a sub-solid nodule for lesions under 5 mm in size. Some adenocarcinomas may also transiently decrease slightly in size because of fibrosis or atelectasis [38,60,114], although these changes are often associated with a concomitant increase in tumor attenuation.

**Solid nodules**

Solid nodules are the most common, although only 2 to 7% are malignant [5,115], explaining the very large number...
of false positives in the screening studies. It is essential, therefore, to try to limit the number of non-contributory investigations. Volumetry techniques should help to reduce the number of follow-up scans and patient radiation.

Three situations exist depending on the size of the nodule. Nodules over 10 mm in diameter are very suspicious of malignancy and should be discussed in an MDT with a view to surgical resection [61]. Nodules under 5 mm in size are very rarely malignant and require annual follow-up only if they are over 3 mm in size and have developed in a patient with risk factors (age > 40 years old, smoking > 30 pack-years, exposure to asbestos, past history of neoplasia) [69]. Nodules between 5 and 10 mm in diameter should be checked at 3 months with volume measurements at D0 and D90 to calculate the volume doubling time. If the doubling time is under 400 days, which generally represents an increase in volume of over 25%, the nodule is deemed to be very likely malignant and should be discussed in an MDT [61]. If not, a follow-up scan at 1 year is recommended. If software is not available or volumetry cannot be performed, as, for example, with vascular or chest wall contact, the diameter must be measured carefully by displaying the two investigations simultaneously and zooming onto the nodule in question. An increase in diameter of more than 2 mm is deemed to be positive.

Examination for enhancement of under 15 HU after injection to confirm that a lesion is benign [116] is complex in practice, involves considerable radiation (4 successive spiral acquisitions 1, 2, 3 and 4 minutes after injection) and is only really reliable for nodules over 8 mm in diameter. This method should no longer, therefore, be used [87]. Similarly, the performance of PET is limited for lesions under a centimeter in size [117]. The advantage of volumetry lies in the fact that it is non-invasive, as it does not require injection, and it involves only low doses of radiation as the acquisition volume can be reduced to the region of interest.

Summary table

The sheer variety of cases occurring make an analytical approach difficult, and a decision-support guide summarizing the most appropriate strategy for each situation is therefore necessary. Within the summary table, we propose a tabulated summary which is sufficiently exhaustive to cover all of the cases, but which is also simple to use (Fig. 7). Some specific clinical presentations, however, may fall outside of this general approach and require specific discussion in an MDT. This particularly applies to elderly or “borderline” surgical patients. Management may also differ slightly depending on whether or not the finding comes from screening. It is reassuring, for example, to know that a patient with a 4 mm ground glass lesion who is a smoker will anyway benefit from follow-up as part of the screening.

This table does not provide information about the invasive strategy to be used (biopsy or surgery, and type of surgery) as this decision should be taken on a joint basis by all of those present in the MDT.

The MDT. When to perform a biopsy?

The Cancer plan launched in 2003 made MDT’s obligatory for all patients suffering from cancer, which might be held before starting initial treatment or before any significant change in treatment [118]. The MDT is based on good practice recommendations in order to offer standardized

<table>
<thead>
<tr>
<th>Diameter (mm)</th>
<th>Follow-up CT at 3 months (± after antibiotic therapy):</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5</td>
<td>No follow-up</td>
</tr>
<tr>
<td>5-10</td>
<td>Follow-up CT at 3 months</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>Follow-up CT at 3 months</td>
</tr>
<tr>
<td>Pure ground glass</td>
<td>- if stable at 3 months: 1 CT/year for 2-4 years</td>
</tr>
<tr>
<td>Part-solid (measure the diameter of the solid component)</td>
<td>- if stable at 3 months and solid component ≤ 5 mm: 1 CT/year for 3-5 years</td>
</tr>
<tr>
<td>Solid (with no feature of benign disease)</td>
<td>- if size &lt; 3 mm or no RF: no follow-up</td>
</tr>
<tr>
<td></td>
<td>- if size = 3-5 mm and RF: CT at 1 year</td>
</tr>
</tbody>
</table>

MDT

*RF*: Risk factor; D0: Volume doubling time; D90: Volume doubling time; D1: Volume doubling time; D2: Volume doubling time. Table produced from the expert consensus recommendations [61,69,89,90].
management to each patient. A recent study has shown that MDTs have a significant impact on patient management, particularly by increasing access to treatments such as radiotherapy and chemotherapy, although this does not appear to affect survival [119]. As in other specialties, the radiologist plays an essential role in the MDT in thoracic oncology and is involved in all phases of management.

Although there are no clear recommendations in this field, we feel that any biopsy of a nodular lesion should ideally be discussed in an MDT so that the decision on the biopsy can be made in view of the planned treatment strategies. Biopsy under CT guidance is a relatively simple technique, although it is not without morbidity. The correct indication for biopsy is one in which the results will influence subsequent management and benefit the patient. An inoperable nodule, because of metastatic spread, or a patient who is inoperable for clinical safety reasons are generally correct indications for a biopsy. Conversely, if the CT scan is highly suggestive of a primary lung lesion with no significant lymph node or distant localization, a preoperative biopsy may be questionable. Some groups organize first-line surgical excision with ex temporeanous histological examination. Others perform a biopsy whenever possible, which occasionally reveals alternative diagnoses and may help the surgeon to plan video-assisted lobectomy. If a nodule is associated with hypermetabolic mediastinal adenopathy, endobronchial ultrasound or mediastinoscopy are probably more appropriate, as this will provide tumor histology together with "N staging" and could be followed by thoracotomy for lung resection. It is important also to remember that the absence of malignant cells in a biopsy never guarantees that the mass is benign. The distinction between a primary bronchial carcinoma and a single metastasis remains a correct indication for biopsy.

When biopsy is indicated, a few simple rules should be followed. There is no advantage in carrying out a biopsy on a ground glass lesion, which usually represents a lepidic component. The solid portion of a mixed nodule should therefore be targeted. For large tissue nodules, it is essential to target the contrast-enhanced or hypermetabolic PET areas if previous investigations are available. The aim of this is to avoid necrotic regions which cannot be interpreted histologically. The purpose of a nodule biopsy in inoperable patients is to obtain sufficient material for molecular typing of a possible adenocarcinoma and particularly to test for the EGFR gene mutation. An alternative to biopsy is fine-needle aspiration, which usually allows EGFR subtyping to be performed after including the centrifugation deposit obtained in paraffin [120]. Some people recommend repeating the biopsies in patients who do not respond to first-line treatment, because of the histological molecular heterogeneity of the tumors.

Which treatment for which nodule?

The different treatment options (surgery, radiotherapy, chemotherapy, radiofrequency ablation, etc.) are decided jointly in an MDT. The clinical situations vary greatly and make it difficult to construct decision-support algorithms. Also, there are not very many recommendations that are based on high levels of evidence. Each indication must therefore be considered on a case-by-case basis, depending on the appearance of the lesions, the patient’s age and general health, and the techniques and skills available in each centre.

In proven malignancy, the reference treatment is still lobectomy and mediastinal lymph node dissection. Lung sparing surgery is recommended for ground glass nodules [89], ideally under video-assisted thoracoscopy which has a lower morbidity than conventional thoracotomy [121—123]. This may involve atypical ("wedge") resection, segmentectomy or sub-segmental resection. Lymph node curettage is recommended, particularly if the nodule has a solid invasive component. The surgeon must be able to identify the nodule on palpation, which may be more or less difficult depending on its size, density and whether it is central or peripheral. Prior identification with a harpoon, coil or methylene blue can be carried out, particularly for the smallest and most central lesions [124—126]. These identifications, however, may be difficult (there is a risk of the coil or harpoon moving and surgery needs to be scheduled immediately after the scan). Above all, surgeons want a detailed analysis of the segmental location of the nodule. In the case of multiple nodules, the choice of surgical procedure may be complex. Multiple ground glass nodules are more likely to be synchronous primary tumors than metastatic nodules [28,127]. Finally, the role of radiofrequency ablation has not yet been sufficiently examined but remains restricted, as does stereotactic radiotherapy, to inoperable patients.

Conclusion

A considerable amount of new knowledge has emerged in recent years, which has significantly changed the management of the lung nodule. Defining the non-invasive nature of a nodule is still almost exclusively the role of CT. This now also involves measurements of diameter, volume and density. Densitometric analysis appears to correlate particularly well with the disease spectrum of adenocarcinomas. In view of the high detection capacity of CT, the prevalence of lung nodules found upon CT scanning is high and continues to increase with the lung cancer screening, which is currently developing. It is important, therefore, that radiologists are familiar with these new concepts and can recommend optimal management.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Management strategy of pulmonary nodule in 2013


