Nonsolid and part-solid pulmonary nodules

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Summary

Introduction Non-solid and part-solid pulmonary nodules have recently been described on CT scans.

State of knowledge Nonsolid and part-solid pulmonary nodules account for 2.9 to 19% of all pulmonary nodules detected in high-risk patients included in CT screening series for lung cancer. Radiologic-pathologic correlations showed that the etiology could be of either benign origin (chronic pneumonia, atypical adenomatous hyperplasia, localized fibrosis) or of malignant origin (bronchioloalveolar carcinoma, adenocarcinoma, more rarely metastasis). Part-solid or nonsolid nodules are more likely to be malignant than solid ones. However, the doubling time of nonsolid nodules can be longer than part-solid ones and even longer than the doubling time of solid nodules. The prognosis of the patients is thus related to the percentage of subsolid component.

Prospects Management of these nodules requires prolonged surveillance of nodules less than 10mm in diameter and surgical excision of nodules greater than 10mm persisting on scans between 1 to 3 months after discovery and administration of anti-inflammatory and anti-infectious therapy.

Conclusion Nonsolid and part-solid pulmonary nodules at CT scanner warrant specific management.

Key-words: Lung cancer • Nonsolid nodule • Part-solid nodule • Adenocarcinoma • Bronchioalveolar carcinoma • Computed tomography.

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Introduction

An established management plan exists for solid pulmonary nodules greater than 10 mm in diameter, whether discovered incidentally, or when screening for lung cancer or for metastases [1-5]. In Europe, the discovery of a nonsolid or part-solid nodule has been rare and management has, until recently, been the subject of debate. The experience acquired from CT screening for lung cancer has transformed our knowledge of this type of nodule [6-10]. We now know that the discovery of a nonsolid or part-solid nodule suggests the possibility of lung cancer. Their management should allow for surgical resection of the most suspicious nodules while trying to avoid surgery for patients with benign lesions. The aetiology, prognosis, growth, CT scan morphologic criteria, and noninvasive investigations useful in diagnosing nonsolid or part-solid nodules are different from those of solid nodules and require specific description and explanation. The aim of this article is to review current knowledge of this rare type of pulmonary nodule.

Definition

Nonsolid nodules (also called pure ground-glass nodules), are spherical or oval pulmonary nodules less than 30 mm in diameter of lower density than the vascular pattern within them which is not modified (fig. 1) [11]. Part-solid nodules (also called mixed ground-glass nodules) have a nonsolid component containing tissue density components located centrally, peripherally or forming several islets (fig. 2) [12-14].

Detection

We have learnt from lung cancer screening campaigns that, even with the use of rapid acquisition volumetric scanning (<20s) with high-resolution slices (1mm thick, edge enhancement filter), many nodules are missed on image review. Thus, whatever the type of nodule (solid, nonsolid or part-solid) detection sensitivity if ≤5mm is 74% versus 82% if >5mm [15]. The detection of nonsolid or part-solid nodules is even more difficult because sensitivity is considerably decreased compared to solid nodules (65% versus 83%) [15]. This reduced sensitivity is mainly explained by difficulties in identifying these small nodules, particularly in the central regions of the lung, as they are frequently wrongly identified as vessels in section. Errors due to inattention could also be involved, considering the large number of images (300 to 400) to be analysed per patient. Sensitivity is increased when computer-aided detection is used for review as a second reader, but software is currently not capable of detecting subsolid nodules in routine practice [16]. MIP (maximum intensity projection) mode, which selects the most dense pixels in a stack of slices (nodules or vessels), provides more sensitive detection of solid nodules, and also those with a subsolid component, and should be systematically associated with review of axial slices (fig. 3) [17]. MinIP (minimum intensity projection) mode, which selects the least dense pixels in a stack of slices (air), could provide a useful alternative in the detection of these subsolid nodules as it increases the density differential between pulmonary air and the subsolid area. Identifying a nonsolid or part-solid nodule on a CT scan then finding it retrospectively on a previous CT is thus not rare. The spherical nature of a nonsolid or part-solid nodule can be verified with axial or sagittal reconstructions (fig. 3). Due to their low density, the vast majority of these nodules are missed on chest radiographs [6, 18].

Prevalence

Estimates of the prevalence of nonsolid and part-solid nodules vary depending on the series. This can probably be attributed to acquisition techniques (slices from 1 to 10 mm) and image review modes (film, work-station, use of MIP mode). The results of the ELCAP study [19], presented in table I, indicate that nodules with a nonsolid component are more frequently malignant than solid nodules; the risk of malignancy is increased in the presence of a part-solid nodule. The results of the Chong study [20], summarized in table II, confirm the significantly increased risk of cancer when nodules include a nonsolid component (7/254 or 2.8%) compared with solid nodules (3783 or 0.37%) (p<0.01). Only 2.9% of nodules detected in an Irish screening campaign [21] included a nonsolid component.

Aetiology

Radiologic-pathologic correlations and surveillance over time have permitted the definition of aetiologies for
nonsolid and part-solid nodules which can be benign or malignant [11, 22, 23].

The most frequent benign aetiologies for both types are infections (fig. 4) and local inflammations. A nodule including a persistent nonsolid component can correspond to a localized focus of fibrosis or of desquamative interstitial pneumonitis [24].

Many studies have concentrated on the cancerous nature of these nodules. They were the subject of a recent review article [25]. Subsolid nodules can correspond to benign proliferation, atypical adenomatous hyperplasia (AAH), currently considered to be a dysplastic precancerous lesion of bronchioalveolar cancer and adenocarcinoma [26]. In this case, the subsolid nodule is small, the most often ≤5mm, but can exceed 10 mm (fig. 5) [27]. The same patient can present several associated nodules because of the diffuse action of carcinogens on the lung. Histology study shows localized proliferation of slightly or moderately atypical pneumocytes without any signs of invasion (fig. 6). AAH is identified the most often in patients presenting a cancer, and in particular lung cancer, with an incidence of 10% to 23% [28].

Malignant growths causing a nodular appearance with a nonsolid component include bronchioalveolar cancer, one of the 4 subtypes of adenocarcinoma [23], and more rarely metastases. Bronchioalveolar cancer is defined in the WHO classification [29] as lepidic growth (growth of neoplastic cells along pre-existing alveolar structures) without stromal, vascular or pleural invasion (fig. 7). Invasive adenocarcinomas are classified in the subtypes acinar, papillary, solid, or the most often mixed histology considering the coexistence of several cell components in the same tumor [29] (fig. 8). Some nodules associate atypical adenomatous hyperplasia, bronchioalveolar carcinoma and adenocarcinoma.

In 1995, Noguchi proposed an addition to the WHO classification [30] with a classification of small pulmonary adenocarcinomas in 6 categories (table III): 3 types of bronchioalveolar carcinomas and 3 types of non-bronchioalveolar adenocarcinomas. This classification of prognostic value recognizes the excellent prognosis of bronchioalveolar carcinomas showing purely lepidic growth and the less favourable prognosis in the presence of central fibrosis.

In their study, Yang et al. [12] showed that 94% of pure bronchioalveolar cancers without collapse of alveolar

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walls appeared as nonsolid nodules on CT scan, while 71% of bronchioloalveolar cancers with collapsed alveolar walls appeared as part-solid nodules on CT. They also showed that 50% of mixed histology adenocarcinomas (average size 14.5mm) with a bronchioloalveolar component appeared as solid nodules on CT scan while 29% appeared as part-solid nodules, and 21% were nonsolid. Finally, mixed adenocarcinomas without a bronchioloalveolar component appeared as homogeneous solid nodules. This study thus suggests a strong correlation between appearance on high-resolution CT, histologic type and prognosis. Correlations between data from the WHO classification of lung cancer, the Noguchi classification, and morphologic features on CT scan are shown in table IV.

The natural history of nonsolid and part-solid nodules measuring <30mm was explored in a prospective study which included 186 patients presenting 69 nonsolid nodules and 117 part-solid nodules of which 122 had undergone histologic verification or had disappeared spontaneously while 64 had remained stable and are still followed-up [31]. Mean survival was 8.6 months (extremes: 1-24). The proportion of
malignant nonsolid nodules reached 19.4% (7/36) versus 30.2% (26/86) for part-solid nodules, a smaller proportion than the previous surgical data [32] because the authors included transient nodules in their study. Of note was that 38% (26/69) of the nonsolid nodules disappeared on the follow-up CT scans while this proportion reached 48.7% (57/117) for part-solid nodules. Their disappearance was rapid as it was documented within 3 months of diagnosis for 88% of the nonsolid nodules and 98% of the part-solid nodules. The authors found a correlation between the disappearance of part-solid nodules and a high blood eosinophil count, suggesting an infectious or inflammatory origin.

When considering the results of this Korean study we need to take into account the different dietary habits of the patients compared to European subjects (consumption of raw meat, liver and fish) and their higher incidence of adenocarcinoma, particularly bronchioloalveolar cancer, compared to studies including Caucasian populations.

• Some nodules associate atypical adenomatous hyperplasia, bronchioloalveolar carcinoma and adenocarcinoma.
• There is a strong correlation between appearance on high-resolution CT, histologic type and prognosis.

CT scan morphologic criteria useful in diagnosis of benignity or malignancy.

In a study correlating high-resolution analysis of CT scan morphologic criteria for nodules between 3 and 20 mm (n=222) with histopathologic data, Li et al. [13] showed that nonsolid nodules spherical in shape were more frequently associated with malignant lesions (11/17, 65% of nodules) than with benign lesions (2/12, 17% of nodules); the presence of a central solid component was more frequently associated with malignant lesions (11/27, 41% of nodules) than with benign lesions (2/12, 17% of nodules) (fig. 2). However, size, margin spiculation, and the presence of an air bronchogram within the nodule, were not useful criteria in differentiating malignant nodules from benign nodules associated with malignant lesions (11/27, 41% of nodules).
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A polygonal (fig. 4) or flattened (fig. 3) shape however suggested a benign lesion [33].

- On CT, the features more suggestive of cancer are the spherical shape of the nodule, and the presence of a solid component within the nodule.
- Polygonal or flattened shapes are however suggestive of benign lesions.

Evolution of the nodules

Repeated CT scans have permitted study of the natural history of nonsolid and part-solid nodules. Takashima et al. [34] have shown that malignant nodules initially appear as nonsolid nodules; 75% increase in size and 17% progress to part-solid nodules. Kakinuma et al. [35] have identified three types of morphological evolution for malignant nonsolid nodules in a small series of 8 cases: increase in size of the nonsolid area (n=5); reduction in size of the nonsolid area associated with appearance of a solid component (n=2); stable size but progression to a part-solid nodule (n=1) (fig. 9). Reduction in nodule size in adenocarcinoma is thus proven by this study; these findings should be considered when interpreting follow-up CT scans of nonsolid nodules.

While the doubling time of malignant solid nodules is usually between 30 and 400 days, this time can be far longer with nonsolid and part-solid nodules. Based on a CT screening campaign for lung cancer, Hasegawa et al. [36] calculated a mean doubling time for nonsolid nodules of 813 days, against 457 for part-solid nodules, and only 189 days for solid nodules. Because of these doubling times prolonged surveillance of nonsolid and part-solid nodules is recommended; this goes against the concept of 2-year nodule stability implying that a nodule is benign [37].

• During follow-up, three types of morphological evolution have been identified for malignant nonsolid nodules: increase in size of the nonsolid area, reduction in size of the nonsolid area with appearance of a solid component, and stable size but progression to a part-solid nodule.
• The mean doubling time for nonsolid nodules is far longer than for part-solid nodules, and even longer again than for solid nodules.

Prognostic implications

The prognosis of patients presenting a nonsolid or part-solid nodule on CT has been studied in various series. Takashima et al. [38] showed that a nodule <15mm, whether nonsolid or part-solid, with a nonsolid component of >57% and with bronchioloalveolar cancer type histology presented excellent prognosis on univariate...
analysis. Using multivariate analysis, with the nonsolid proportion as the only independent prognostic criterion, small peripheral adenocarcinomas with a nonsolid component of over 50% on CT presented significantly less lymph node metastases or vascular invasion than those with a nonsolid component of less than 10% [39]. The nonsolid proportion also had an effect on patient survival as this was significantly superior in patients presenting a nodule with a nonsolid component of >50% compared to those with a nonsolid component of <50% [40]. These data have been confirmed by the Asamura study [40] of a series of 48 operated cancers ≤10mm, of which 19 were nonsolid nodules, 9 part-solid, and 20 solid. Three patients presented enlarged lymph nodes (2 N1, 1 N2), all related to a solid nodule. Follow-up showed bone metastases in one patient, and recurrence of enlarged lymph nodes in another patient operated for solid nodules. The presence of spiculation or peribronchovascular thickening around the nodule was associated with vascular invasion and lymph node involvement.

Thus, the part-solid nodules were more aggressive than the pure nonsolid nodules. Tumour aggressiveness increased with the proportion of solid component, resulting in a reduction in tumour volume doubling time, an increase in frequency of lymph node metastases and vascular invasion, and an increase in risk of recurrence [30, 26, 38, 39]. Nodule size correlates with histology grade and tumour aggressiveness (table IV). Thus, lymph node invasion is rare with small adenocarcinomas, occurring in approximately 10% of tumours less than 10mm and 20% of tumours between 10 and 20mm [41].

- The larger the nonsolid component, the better the prognosis.
- An increase in proportion of solid component reduces tumour doubling time, increases the frequency of lymph node metastases and vascular invasion, and increases the risk of recurrence.
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treatment implications

The majority of nonsolid nodules resected were in the early stage (T1N0M0) [42-44]. Considering the radiologic-histologic correlations and follow-up of patients after surgery, several authors have proposed modifications in surgical treatment of small nonsolid and part-solid peripheral nodules replacing lobectomy with atypical resection. Thus, in the study by Nakamura et al. [43], of 27 patients presenting nonsolid nodules who underwent resection in the period 1981-2002, no recurrence of metastases was documented. Over a period of 10 years (1991-2000), Asamura et al. [40] followed-up 48 operated lung cancers ≤10mm in diameter of which 19 were nonsolid nodules, 9 part-solid, and 20 solid. All the nonsolid and part-solid nodules (n=28) were bronchioloalveolar in type and there was no recurrence.

Some contradictory findings have been published, caution is thus required. Thus, Nakata et al. [44] have shown that nonsolid nodules are not always bronchioloalveolar cancers, as 7% of these nodules ≤10mm resected in this series were mixed invasive adenocarcinoma associated with a bronchioloalveolar component. The proportion of mixed invasive adenocarcinoma increased with nodule size reaching 38.5% in nodules between 10 and 20mm.

Further investigations

After CT scan assessment, as for all pulmonary nodules, they should be classified as benign, highly suspicious of malignancy, or indeterminate nodules [5]. Concerning nonsolid and part-solid nodules, the correlations of high-resolution CT scan findings with histopathologic appearance and patient follow-up have resulted in the following recommendations:

- nonsolid nodules ≥210mm in diameter and part-solid nodules, whatever their size, persisting on a check CT performed between 1 and 3 months after their discovery on CT are considered to be highly suspicious of malignancy.
- nonsolid nodules <10mm are considered to be indeterminate.

As a general rule, nodules highly suspicious of malignancy require histologic verification with biopsy or surgical resection, while indeterminate nodules should be explored with other techniques [5]. The specific histologic features of nonsolid and part-solid nodules have drastically changed the value of the investigations usually prescribed and have thus modified their management.

The study of enhancement within nodules [45], proposed for solid nodules ≥8mm, is not feasible because nodules with a nonsolid component are too low in density.

Positron emission tomography (PET), based on the study of 18-fluorodesoxyglucose (FDG) metabolism within nodules provides a sensitivity of 90% and a specificity of 83% for diagnosing the malignancy of pulmonary nodules according to a recent meta-analysis [46]. However, the rate of false negatives increased in the presence of bronchioloalveolar cancer or well-differentiated adenocarcinoma, the histologic types found in nonsolid or part-solid nodules, because of poor metabolism by the lesions. The study by Nomori et al. [47] included 136 pulmonary nodules explored with PET scan and resected. Of 10 nodules with a malignant nonsolid component, all corresponding to well-differentiated adenocarcinomas, 9 did not show uptake on PET scan (90% false negative) while of the 5 benign nodules corresponding to focal pneumonia, 4 were false positives (80% false positive). The sensitivity and specificity of PET for nodules with a nonsolid component was thus 10% and 20%, while for solid nodules they reached 90% and 71% respectively. The authors concluded that with nonsolid or part-solid nodules PET findings did not permit correct evaluation of the nature of the lesions [47].
Evaluation of modifications in size (growth, stability, decrease or disappearance) on repeated CT scans performed using identical technical criteria is recommended when studying small solid nodules ≤10mm [48, 49]. Dedicated software is currently used to perform segmentation, calculation of volume, and then determination of doubling times of nodules. However, nonsolid and part-solid nodules present three major obstacles to the use of this technique: (a) longer doubling times compared to solid nodules (between 813 and 457 days versus 189 days) requiring a longer period of surveillance; (b) the reduction in size observed in some malignant nodules, resulting in dangerous delays in management; (c) difficulties in segmenting these nodules using current software, resulting in reliance on transverse cross-sectional measures with their known imprecision [50].

Transsthoracic biopsy, which has been proposed for nodules over 7mm in diameter, depending on the expertise of the radiologist, has not been studied in the specific context of nodules with a nonsolid component.

**Thoracotomy**

The resection of nonsolid or part-solid nodules persisting on 2 CT scans at an interval of 1 to 3 months has shown a high proportion of lung cancer, reaching 88% in the Yoon series [51] which included 94 patients operated with video-assisted thoracic surgery for a peripheral pulmonary nodule. Several other authors recommend resection of nonsolid and part-solid nodules >10mm persisting on a check CT scan performed between 1 and 3 months after discovery of the nodule and after trial antibiotic or anti-inflammatory treatment [7].

**Management**

The specific management of nonsolid and part-solid nodules is different from that recommended for solid nodules [5]. Their management requires consideration of the likelihood of malignancy. The main factors to be taken into account are a history of neoplasia, age, smoking, nodule size, internal features and evolution. The additional factors to be considered are ethnic (Caucasian or Asian) and genetic (Asian women who are non-smokers develop peripheral pulmonary adenocarcinoma more frequently than...
Caucasian women), as well as local dietary habits, responsible for eosinophilic inflammatory reactions.

The recently issued Fleischner Society recommendations [5] propose a well-considered approach on the incidental discovery of small pulmonary nodules on CT, with the aim of limiting repeated check CT scans, which are detrimental because of the exposure to radiation and anxiety caused, while ensuring rapid diagnosis of lung cancers. These recommendations mainly apply to solid nodules but can be adapted to nonsolid or part-solid nodules. Under these conditions, we propose the following management plan for nonsolid or part-solid nodules (fig. 9).

**Conclusion**

Nonsolid and part-solid nodules have only recently been described because their identification has resulted from research using CT in screening for lung cancer. Their aetiology can be benign or malignant and requires specific management as there is a far higher likelihood of malignancy than with solid nodules of the same size. However, the aggressiveness of an adenocarcinoma presenting as a nodule containing a nonsolid component is inversely proportional to the surface of the nonsolid component. Prognosis after resection is better for cancers purely nonsolid in appearance on CT than for part-solid or solid cancers. For this reason, some authors advise atypical resection in the presence of a pure nonsolid nodule.

**KEY POINTS**

- An entirely nonsolid nodule or a part-solid nodule suggests the possibility of lung cancer.
- Assessment of these subsolid nodules is different from that of solid nodules.
- Entirely nonsolid nodules are spherical or oval pulmonary lesions measuring less than 30 mm in diameter without modification in their vascular pattern.
- L’étude de l’ARN ribosomal et de l’ADN mitochondrial.
- Part-solid nodules have a nonsolid component containing a tissue density component.
- The best screening tool is thoracic CT scan.
- Nodules containing a subsolid component are more frequently malignant than solid nodules.
- Subsolid nodules can be benign (infection, inflammation) or malignant (bronchioloalveolar cancer, adenocarcinoma) in aetiology.

- Many subsolid nodules disappear spontaneously in the 3 months following diagnosis.
- The features indicating the possible malignant nature of a nodule are its spherical shape and the presence of a solid component.
- The doubling time for nonsolid and part-solid nodules is far longer than for solid malignant nodules.
- Small peripheral adenocarcinomas with a nonsolid component of over 50% have a better prognosis than those with a nonsolid component of less than 10%.
- Part-solid nodules are more aggressive than pure nonsolid nodules.
- Nodules highly suspicious of malignancy require histologic verification with biopsy or surgical resection.

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