Subsolid pulmonary nodules: why not "watch and wait"?

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Subsolid pulmonary nodules include both pure ground-glass nodules (GGNs) and part-solid (mixed) nodules (PSNs). Incidence of subsolid pulmonary nodules has increased due to improved computed tomography (CT) technology, implementation of lung cancer screening programs with low-dose CT (LDCT), and expanded use of CT. We now know that the greater the solid component of a subsolid pulmonary nodule, the greater the risk of malignancy and metastatic potential (1,2), the latter being practically negligible in pure GGNs (3). This editorial aims to address specific aspects on diagnostic and therapeutic management of subsolid pulmonary nodules, recognizing that such management is controversial and depends on different variables.

PSNs are lesions with recognized aggressiveness and metastatic potential, especially when their solid component is larger than 5–6 mm (4). In general, these lesions are managed more aggressively, both from a diagnostic and therapeutic perspective (5). Initially, percutaneous CT-guided biopsy is not recommended since the vast majority are adenocarcinomas, there is a significant sampling error risk when attempting percutaneous biopsies (given the difficulty in targeting both solid/invasive and ground-glass/non-invasive components), and that certain pathologic diagnoses (such as adenocarcinoma *in situ*, minimally invasive adenocarcinoma…) cannot be made in small specimens obtained percutaneously (6-9). In light of this, many institutions prefer not to subject patients to the unnecessary risk of a preoperative percutaneous biopsy. Therefore, surgical biopsy (which can also serve as a therapeutic procedure) is preferred.

Management of pure GGNs and PSNs with a small solid component (less than 5–6 mm) is more variable and controversial (5). Although some clinicians prefer to use an aggressive/invasive strategy in this setting as well, a more thoughtful "watch and wait" approach (always considering different factors beforehand) may be feasible due to their indolent course and good prognosis (3,10-13). This latter approach is partly justified given the reported 5-year-survival rate of 100% in surgically resected clinical N0 non-small cell lung cancer (NSCLC) pure GGNs and of 97.6% in PSN subcentimeter NSCLC (14).

Some current pulmonary nodule management guidelines in lung cancer screening programs (such as the latest version of Lung-RADS®) (15) are recognizing that the persistence or even the slow growth of a pure GGN can be managed conservatively ("watch and wait") and categorized as "clinical-radiologically benign" lesions. Lung-RADS

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"Category 2" nodules correspond to "benign" findings (based on imaging features or indolent behaviour, not based on pathologic characteristics), despite the fact that they most likely represent malignant (adenocarcinoma *in situ* or minimally invasive adenocarcinoma) or premalignant (atypical adenomatous hyperplasia) lesions. This concept of "clinical-radiological benignity" in a lung cancer screening scenario is emerging, represents a paradigm shift regarding "malignancy/benignity" categorization of lung nodules, and is being increasingly taken into account by lung nodule management guidelines. If all Lung-RADS category 2 nodules are aggressively managed, there is a high risk of increasing the rate of overdiagnosis (i.e., resecting indolent tumours with no metastatic potential that would never lead to the death of the patient). We should bear in mind that both surgery (16) and nodule marking procedures [with wire-hooks (17), coils (18), dye (19), radioactive materials (20)…] are not without risk.

When deciding the diagnostic and therapeutic strategy of pure GGNs and PSNs, it is crucial to take into account the patient's age and comorbidities. One similar-looking GGN in two different individuals can be managed differently (i.e., surgically in one case and conservatively in the other case), being both approaches appropriate. In addition, the smoking history and the presence of multifocal GGNs are also factors that can influence their management, and may force physicians to be more cautious due to the likely probability of new pulmonary lesions appearing in subsequent CTs (thus requiring multiple lung resections). In any case, patients' preferences need to be considered and a consensual decision should be made after all risks and benefits of each strategy have been explained and discussed.

A tool that is currently available and is very helpful in assessing the size and growth of the solid component is volumetry (consisting of 3D volumetric measurements of lung nodules obtained with specific software). Nodule size and interval growth are more objectively and accurately assessed with volumetry than on 2D measurements (21). The evidence supporting clinical use of volumetry is expanding, being currently incorporated in lung cancer screening nodule management algorithms [recent versions Lung-RADS (15), British Thoracic Society guidelines (22)…].

However, future directions run toward artificial intelligence and radiomics. Several new tools are being developed in order to assess the lung cancer risk of patients with lung nodules on LDCT scans and even in patients without lung nodules. Ardila *et al.* developed a cancer detection algorithm that identifies pulmonary nodules, processes the region surrounding them using deep learning, and accurately predicts lung cancer within 1 and 2 years (23). More recently, another deep learning algorithm that predicts lung cancer risk up to 6 years from a single LDCT scan without demographic and clinical data and without requiring any radiologists to annotate areas of interest has been published (24). This algorithm reached area under the receiver operating characteristic curves (AUCs) of 0.90 in predicting cancer within 1 year, although results will require confirmation in prospective clinical trials. There is no doubt that these accurate tools will help clinicians assess the risk of screening-detected or incidental GGNs, decide whether follow-up or lung resection is optimal, minimize invasive procedures of nodules that are at low risk, and probably help determine optimal timing for surgery.

Just as the treatment of lung cancer has been diversified in the last decade (immune checkpoint inhibitors, targeted therapies, neoadjuvant treatment in early stages…), the management of subsolid nodules should not be rigid and should take into account several clinical and technical variables, as well as patients' preferences. These factors should certainly be discussed at a multidisciplinary tumour board. In large academic hospitals, with a high volume of lung nodules, and specially where lung cancer screening with LDCT is performed, the implementation of a specific board for pulmonary nodules (independent of the thoracic tumour board) should be recommended.

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