Editorial

Management of subsolid pulmonary nodules in CT lung cancer screening

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Abstract: The distinct appearance and behavior of subsolid pulmonary nodules (SSNs) has resulted in separate recommendations for the management of solitary SSNs, both for incidentally detected as well as for screen detected nodules. However, these guidelines have been based primarily on expert opinion. Recently two studies were published regarding SSNs detected in low-dose computed tomography (LDCT) lung cancer screening, including management advices.

Keywords: Subsolid pulmonary nodule (SSN); computed topography; lung cancer; screening

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Introduction

In view of the prospective results of the National Lung Screening Trial (NLST), and baseline results of other trials, interest in low-dose computed tomography (LDCT) for lung cancer screening in high-risk individuals is increasing. In 2011, the U.S. NLST demonstrated that screening using LDCT reduces lung cancer mortality by 20% compared to screening by chest radiography (1). This result was translated by several U.S. medical associations, including the U.S. Preventive Services Task Force, into a recommendation to screen subjects at high-risk for developing lung cancer by LDCT (2-6). Recently, the American College of Radiology released Lung-RADS, a classification system for LDCT lung cancer screening (7).

In these guidelines, a distinction is made between solid and subsolid nodules. Solid lung nodules are by far the most common type of nodules found at lung cancer screening (8,9). In a small number of participants, a subsolid pulmonary nodule (SSN), defined as a circumscribed area of increased lung attenuation with preservation of the bronchial and vascular margins (10), is detected. An SSN can be classified as a nonsolid, purely ground-glass attenuation (GGN), or as part-solid lesion, containing both solid and ground-glass components. Usually, a SSN is due to inflammation, infection, or fibrosis, but it can also represent adenocarcinoma, most likely non-aggressive adenocarcinoma *in situ* (11-13).

Although usually not lethal, SSN malignancy rates ranging from 19.7-75% have been published (14,15). Development or increase of a solid component in a SSN greatly increases lung cancer risk. Other important predictors of malignancy include increase in mass, larger nodule size and a larger relative percentage of the solid portion of a part-solid nodule, and the presence of a lobulated border (16-19). Very slow growth rates, with volume-doubling times as long as 813 days, are reported for SSNs (20). The major challenge in the management of SSNs in LDCT lung cancer screening is to timely identify increase in cancer stage, but to avoid overdiagnosis and overtreatment of non-aggressive, indolent lung cancers (21).

The distinct appearance and behavior of SSNs has resulted in separate recommendations for the management of solitary SSNs at initial detection, both for incidentally detected (10) as well as for screen detected nodules (7,22,23), as shown in *Table 1*. Since these guidelines have been based primarily on consensus/expert opinion, recently two studies were published regarding SSNs detected in LDCT lung

Table 1 Management of clinical and screen-detected SSNs, at initial detection

Management protocol	Referral for work-up*	3-month follow-up	6-month follow-up	1-year follow-up	No follow-up required
Fleischner (10)	Part-solid >10 mm	GGN >5 mm Part-solid ≤10 mm			GGN ≤5 mm
NCCN (22)	Part-solid ≥8 mm	GGN >10 mm Part-solid 6 -<8 mm	GGN 5-10 mm	GGN <5 mm Part-solid <6 mm	
ACCP (23)	Part-solid >15 mm	Part-solid ≤15 mm		GGN >5 mm	GGN ≤5 mm
LungRADS® (7)	Part-solid; SC ≥8 mm	Part-solid ≥6 mm; SC ≥6 -<8 mm	GGO ≥20 mm Part-solid ≥6 mm; SC <6 mm	GGN <20 mm Part-solid <6 mm	

ACCP, American College of Chest Physicians; GGN, ground-glass nodule, nonsolid nodule; NCCN, National Comprehensive Cancer Network; SC, solid component. *, chest CT with or without contrast, PET/CT and/or tissue sampling depending on the probability of malignancy and comorbidities.

cancer screening, including management advices (24,25).

Results of the studies

Yankelevitz *et al.* reported the results of nonsolid nodules in the International Early Lung Cancer Action Program (I-ELCAP). In that study, a nonsolid nodule was identified in 2,392 of 57,496 (4.2%) baseline screenings and a new nonsolid nodule in 485 of 64,677 incident screenings (0.7%) (25). Of the 2,877 nonsolid nodules, one third resolved or decreased during follow-up. This happened more frequently in annual repeat rounds than in baseline rounds. Lung cancer diagnosis of a nonsolid nodule was made in 84 participants (73 at baseline), all stage IA adenocarcinoma. All cancer diagnoses were made in growing nodules, and in 22 of 84 cancer cases (26.2%), a solid component appeared in a previously nonsolid nodule. After a median follow-up period since diagnosis of 78 months, the lung cancer survival rate was found to be 100%.

In the different guidelines regarding screen-detected nonsolid nodules, nodule management is based on the diameter of largest nodule, with recommendation of repeat imaging within one year for large nonsolid nodules (7,22,23). However, in the study of Yankelevitz *et al.*, it was found that survival rate did not differ between nodules of different size categories (25). This resulted in the conclusion that screen-detected nonsolid nodules of any size can be safely followed with LDCT at 12-month intervals.

The second study reporting the clinical course of patients with SSNs, by Scholten *et al.*, was published in the *European Respiratory Journal*. In the Dutch-Belgian randomized lung cancer screening (NELSON) trial, at least one SSN (non-solid or part-solid) was detected in 234 of 7,135 subjects (3.3%) (24). One hundred forty-seven SSNs in 126 participants resolved during follow-up. In total, 69 persistent purely non-solid lesions were detected, of which 20 developed a solid component in follow-up. Median follow-up of all SSNs was 95 months (range, 20-110 months).

In total, 33/126 SSNs (11 nonsolid and 22 part-solid) were resected, including 28 cases of (pre) invasive disease. Of the 11 resected pure nonsolid lesions; six were pre-invasive adenocarcinoma *in situ*, and four were invasive adenocarcinomas. The remaining nonsolid nodule turned out to be benign. Seven of 20 (35%) nonsolid lesions in which a solid component appeared during follow-up were diagnosed as lung cancer; two adenocarcinoma *in situ* and five invasive adenocarcinomas. Stage I disease was found for all but one invasive adenocarcinoma (stage IV, due to delayed resection because of a competing malignancy). During follow-up, none of the non-resected SSNs progressed into a clinical relevant malignancy. Scholten *et al.* (24) concluded that long-term follow-up with CT to monitor changes in persistent SSNs instead of resection may be a safe option in the management of SSNs. They suggest to resect only SSNs that show more than 30% growth or a new appearing or growing solid component.

Most important limitation of both studies was that no histological diagnosis was made for all stable or growing nonsolid nodules. The actual cancer rate, therefore, might be higher. However, after a follow-up time comparable to follow-up of lung cancers, no aggressive lung cancers derived from these nodules.

Conclusions

What are we to conclude from these studies? SSNs are a specific subtype of pulmonary nodules, which, because of their non-aggressive behavior, should be dealt with differently compared to solid nodules. Despite the relatively high risk of malignancy in these nodules, especially in part-solid nodules, progression to cancer stage beyond stage I is very rare. Thus immediate resection of these nodules may mostly be not desirable, and close follow-up of SSNs by annual LDCT usually is sufficient. Implementation of the results of Yankelevitz *et al.* (25) and Scholten *et al.* (24) contributes to the optimization of management of screen-detected SSNs, in terms of reduction of overdiagnosis and overtreatment. Future research should point out if biannual follow-up of screen-detected SSNs does not increase overall mortality and morbidity rates.

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Footnote

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