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EDITORIAL

# The Vexing Problem of Small Pulmonary Nodules

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In this issue, Tang et al. [1] from Taiwan report on an increasingly important issue in thoracic medicine and surgery, the natural history of small, asymptomatic lung nodules. The widespread use, over the last couple of decades, of increasingly sensitive computed tomography (CT) scans with reducing radiation dose has resulted in the recognition of a significant population of otherwise healthy patients who have a lung nodule of undefined nature. In most cases, this lung nodule has been detected at the time of a CT scan for a completely different issue—atypical chest pain, back pain, shoulder pain, and often for investigation of abdominal symptoms where the CT scan picks up a lesion in the lower zone of the lung. This has implications as to which nodules need follow-up, how long the follow-up should be performed, the effect of radiation from repeated CT scans, and has important resource/cost implications since some hospitals have set up ''lung nodule clinics'' and many extra CT scans will be performed in the follow-up of these lesions.

The major reason for continued surveillance of a lung nodule is to detect a lung carcinoma. The development of a lung cancer, particularly adenocarcinoma, can be quite slow in some patients. At a biologic level, there are at least three stages in the process of immune surveillance and cancer development–elimination, equilibrium, and escape [2]. Most cells with a DNA mutation and at risk of forming a cancer are recognised and removed by the immune system. A small number of cells escape removal and survive, while remaining in check by the immune system, effectively static in size or ''dormant''. Eventually, further cancer cell mutations occur or a change in immune response takes place which allows the cancer cells to escape control and to proliferate without restriction [3]. In the case of lung cancer, the switch from in situ carcinoma to invasive growth represents a crucial stage in the evolution of a cancer, and is correlated with an increase in expression of Ki67 protein and P53 positivity, both markers of malignancy [4,5]. The period of equilibrium or dormancy can last up to years, as often seen with the late development of metastatic lesions many years after treatment for the primary cancer.

Pulmonary nodules have been classified into three main groups–solid, part-solid (PSN) and pure ground-glass nodule (GGN or ground-glass opacities, GGO). The latter two are grouped together as sub-solid nodules (SSN). These GGO and PSN lesions are often of the lung adenocarcinoma spectrum, and occur more frequently in women, non-smokers, and Asians, suggesting different aetiology compared to non-small cell lung cancer (NSCLC) in general [6–8]. Previous studies have suggested that the solid component is an important prognostic factor [9–11].

Tang et al. followed the course of a pulmonary nodule (all being sub-solid in nature) in 128 patients. The initial mean nodule size was almost 10 mm in the longest diameter, with initial mean solid part of 2.7 mm in size. Most of the nodules (73%) were pure GGO lesions, and the other 27% were PSN lesions. They assessed the presence of any growth in the nodule more than 2 mm, and in particular the occurrence of ''Substantial SSN growth'' which was defined as an increase of $\geq$5 mm in SSNs, or an increase in the solid portion of more than 5 mm. The nodules were also classified by the Lung-RADS system, a quality assurance system developed by the American College of Radiology, which grades nodules from Category 1 to 4 on the basis of the degree of suspicion of malignancy [12].

During follow-up of the 128 nodules, 62 were surgically resected for lung cancer, with 48 patients having invasive adenocarcinoma, and the others having minimally invasive adenocarcinoma (MIA) or adenocarcinoma in situ (AIS). In terms of substantial growth (more than 5 mm in total size or for the solid portion), the 5-year progression rate was 67% for PSN patients and 10.6% for GGO. The median time to substantial progression was 3 years (mean of 4 years) for PSN and 9 years for GGO. The risk factors for prediction of substantial SSN growth were a part-solid nodule (odds

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ratio = 5.4), older age, and of course the length of follow-up. The initial nodule size did not correlate with progression. The pathologic invasiveness correlated with substantial SSN growth than with other parameters.

The study does have some limitations. Coming from a thoracic surgical program, there may have been a bias towards a higher proportion of surgically important lesions, and secondly, not all patients underwent resection (ultimately 62 of 128 patients) so that, on the other hand, there may be a failure to recognise some cancers or underdiagnosis of lung cancer (partial verification bias or false negatives).

There are several issues of relevance to clinicians. Firstly, there are substantial inter-individual variations in disease progression, so that guidelines are indeed only a guide, and need to be considered and applied within the context of the patient's findings.

Secondly, the study re-confirms the importance of the presence of a solid component within a ground glass nodule as a diagnostic and prognostic factor in lung adenocarcinoma.

Thirdly, the time to substantial progression is slow, being a mean of 4 years (median of 3 years) for partly-solid nodules and up to 9 years for GGO. Previous studies have reported the relatively indolent nature and course for GGO [13–15]. This has implications for the length of follow-up. Recently, the Fleischner Society 2017 guidelines recommended less frequent but a longer follow-up, up to 5 years for sub-solid nodules [16], and this would appear to be the minimum time required, and for GGO lesions the follow-up should probably be longer.

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