Optimizing lung cancer screening: nodule size, volume doubling time, morphology and evaluation of other diseases

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Of all cancers, lung cancer causes the most deaths in the United States (US) (1). In fact, lung cancer causes more deaths than colon-, breast- and pancreatic cancer together. One of the reasons for this high mortality rate is that lung cancer often remains undetected until in a relatively advanced stage. At advanced stages curative treatment has low success rates or is not even an option. Given that lung cancer in the vast majority of cases is caused by tobacco smoking, subjects with high smoking exposure are at a higher risk of developing lung cancer. This leads to the rationale of lung cancer screening in heavily exposed current and former smokers. Already in 2011 the largest lung cancer screening trial with low-dose computed tomography (CT), the National Lung Screening Trial (NLST), showed a >20% reduction in lung cancer mortality as well as a 7% reduction in total mortality in high-risk subjects screened with CT, compared to those screened with chest radiographs (2).

One of the disadvantages of screening with CT is the high number of small pulmonary nodules that are found. It is currently not well known what the optimal management is for these nodules, although guidelines have been published for incidental solid and subsolid pulmonary nodules (3,4). Pulmonary nodules can lead to a large number of false positives or necessitate a general increase in the number of CT scans obtained in lung cancer screening subjects. Hence, the risks involved include increased radiation burden, costs, morbidity from invasive procedures for benign nodules and more anxiety in screening participants. Therefore, it is of great importance to develop an appropriate nodule management protocol, one that does not under-evaluate nor over-evaluate. Illustrated by the recent recommendation of the US Preventive Services Task Force to obtain CT in high-risk subjects yearly, appropriate nodule management will become increasingly relevant (5).

One of the key characteristics associated with lung cancer probability is nodule size. In this respect the recent study by Horeweg *et al.* in *Lancet Oncology* is of special interest (6). The authors report on the probability of developing lung cancer in participants from the Dutch-Belgian Lung Cancer Screening (NELSON) trial. The authors found that participants without pulmonary nodules had a very low risk (0.4%) of developing lung cancer during two years of follow-up. Interestingly, this risk was not significantly different in those with a nodule smaller than 5 mm (0.6%). Also, for those with nodules of 5-10 mm the risk remained below 1.3%. Due to this low risk of developing lung cancer in large subgroups of the screening population, it may well be that longer screening intervals are sufficient in a substantial proportion of subjects. Similarly to these findings, Yip *et al.* recently showed that raising the threshold of a positive screening result (i.e., ignoring the smallest nodules) is allowed at the cost of a maximal 9-month delay in lung cancer diagnosis in only few participants (7). Better management of pulmonary nodules and raising the bar of calling nodules positive carries high potential. The approach of Yip *et al.* would decrease the number of follow-up scans obtained in screening setting at least 34%, yielding great advantage in saving costs, radiation exposure and potential harmful additional tests at an acceptable trade-off. Smarter use of nodule presence and size can increase the cost-effectiveness of screening. Further analysis in ongoing trials and possible future trials will provide the data needed to optimize management of pulmonary nodules in screening setting.

A second key characteristic of nodules is their growth rate, as benign lesions tend to grow very fast or slow with primary lung cancers in between. In this regard Horeweg *et al.* expanded on previous publications and showed that volume doubling time is helpful in stratifying high-risk nodules from low-risk ones especially in intermediate-sized nodules (diameter between 5 and 10 mm or volume between 100 and 300 mm^3) (6,8). Subjects with slow growing intermediate-sized nodules (i.e., volume doubling times of 600 days or more) have the same cancer risk as subjects without pulmonary nodules. Contrarily, subjects with faster growing intermediate-sized nodules (i.e., volume doubling times of less than 600 days) are at increased risk of developing lung cancer. These findings complement earlier findings of the NELSON study showing that volume doubling times of more than 600 days had the highest true-negative rates for lung cancer after 2 years of follow-up (7). Previous work from the same group suggests that a cut-off at 600 days may even be lowered for solid nodules and that great care is needed with extrapolating doubling times of solid nodules to subsolid nodules (9,10). Unfortunately, volume measurements are not yet widely adopted. Instead the average diameter is dictated in the available guidelines and used in the I-ELCAP, while NLST used the single longest diameter in their analyses (3,4,11). This variation shows that it is important to pay close attention to size definition in interpreting and comparing studies. Also, given the resolution of CT, volume measurements are preferable for small nodules.

Is there anything beyond size and volume doubling time? Lung cancer screening trials elucidated some key morphology determinants that can gain a crucial role in making lung cancer screening more cost-effective. The first is the density of the nodule. Although it has been known for a long time that fully calcified nodules are benign, it is now also elucidated that subsolid nodules, presenting a lower density than solid nodules, are a special subgroup of pulmonary nodules with different clinical behavior regarding growth and malignancy rate (10,12). These nodules tend to grow slow, but also carry a high risk for adenocarcinoma or carcinoma in situ. Given the low prevalence of these nodules, much needs to be learned about their proper management. A second key morphologic feature is the typical shape and location of intrapulmonary lymph nodes. Intrapulmonary lymph nodes are common in humans and often can be accurately diagnoses with CT. These nodules were previously unrecognized, but are now known to be benign in the vast majority of cases (13). Of all small pulmonary nodules around 20% are typical intrapulmonary lymph nodes and these nodules should not be regarded as positive screen results or be followed. Follow-up of these nodules even caries a further risk of overtreatment as benign lymph nodes can grow at the same speed as lung cancer. Hence, proper use of morphological features can provide an alert for malignancy in case of subsolid nodules, but also prevent unneeded worries about possible lung cancer in typical intrapulmonary lymph nodes.

We have learned much about CT based lung cancer screening in the past decade, but we would like to emphasize that there may be even more promise with using chest CT for screening subjects who have an increased risk for lung cancer. Utilizing the chest CT scans for additional evaluation of other diseases than lung cancer is likely another way to increase the cost-effectiveness of lung cancer screening (14). Highly-exposed current and former smokers are also at risk for two other smoking related diseases with a major burden of disease: chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD). The pathological processes underlying COPD can be quantitatively analyzed in chest CT, and are related to lung function decline and to the risk of developing COPD in lung cancer screening participants (15). Interestingly, it has been shown that quantitatively assessed emphysema, air trapping and airway wall thickness can be used to automatically identify subjects with COPD in a lung cancer screening setting (16). Also participants with a high burden of coronary and aortic calcium can be identified even on low-dose ungated CT scans. It has been shown that these ungated calcium scores can be used to predict the risk of cardiovascular events in male lung cancer screening participants (17). Further, assessing bone density and vertebral fractures might further increase the yield of lung cancer screening given the independent association with mortality (18,19). Further trials will be needed to investigate the gain in cost-effectiveness of multi-disease screening when compared to lung cancer screening.

In conclusion, costs-benefit balance of CT lung cancer screening is an important issue. A recent study estimated that annual lung cancer screening for the next 5-year will cost Medicare alone 9.3 billion US dollar (20). Costs of 81,000 US dollar per quality-adjusted life-years (QALYs) have been estimated (21). Smarter screening with improved strategies based on nodule size, volume doubling time, morphology and a more multi-disease approach may bring a bright future for chest CT screening.

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References

1. U.S. Cancer Statistics Working Group. United States Cancer Statistics: 1999-2007 Incidence and Mortality Web-Based Report. Atlanta: Centers for Disease Control and Prevention; 2010. Available online: http://apps.nccd.cdc.gov/uscs, accessed December 2014.
2. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
3. MacMahon H, Austin JH, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. Radiology 2005;237:395-400.
4. Naidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. Radiology 2013;266:304-17.
5. Humphrey L, Deffebach M, Pappas M, et al. Screening for Lung Cancer: Systematic Review to Update the U.S. Preventive Services Task Force Recommendation. Evidence Synthesis No. 105. AHRQ Publication No. 13-05188-EF-1. Rockville, MD: Agency for Healthcare Research and Quality; 2013.
6. Horeweg N, van Rosmalen J, Heuvelmans MA, et al. Lung cancer probability in patients with CT-detected pulmonary nodules: a prespecified analysis of data from the NELSON trial of low-dose CT screening. Lancet Oncol 2014;15:1332-41.
7. Yip R, Henschke CI, Yankelevitz DF, et al. CT Screening for Lung Cancer: Alternative Definitions of Positive Test Result Based on the National Lung Screening Trial and International Early Lung Cancer Action Program Databases. Radiology 2014;273:591-6.
8. van Klaveren RJ, Oudkerk M, Prokop M, et al. Management of lung nodules detected by volume CT scanning. N Engl J Med 2009;361:2221-9.
9. Heuvelmans MA, Oudkerk M, de Bock GH, et al. Optimisation of volume-doubling time cutoff for fast-growing lung nodules in CT lung cancer screening reduces false-positive referrals. Eur Radiol 2013;23:1836-45.
10. Scholten ET, Jacobs C, van Ginneken B, et al. Detection and quantification of the solid component in pulmonary subsolid nodules by semiautomatic segmentation. Eur Radiol 2015;25:488-96.
11. Henschke CI, Yankelevitz DF, Yip R, et al. Lung cancers diagnosed at annual CT screening: volume doubling times. Radiology 2012;263:578-83.
12. Henschke CI, Yankelevitz DF, Mirtcheva R, et al. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol 2002;178:1053-7.
13. de Hoop B, van Ginneken B, Gietema H, et al. Pulmonary perifissural nodules on CT scans: rapid growth is not a predictor of malignancy. Radiology 2012;265:611-6.
14. Mets OM, de Jong PA, Prokop M. Computed tomographic screening for lung cancer: an opportunity to evaluate other diseases. JAMA 2012;308:1433-4.
15. Mohamed Hoesein FA, de Hoop B, Zanen P, et al. CT-quantified emphysema in male heavy smokers: association with lung function decline. Thorax 2011;66:782-7.
16. Mets OM, Buckens CF, Zanen P, et al. Identification of chronic obstructive pulmonary disease in lung cancer screening computed tomographic scans. JAMA 2011;306:1775-81.
17. Mets OM, Schmidt M, Buckens CF, et al. Diagnosis of chronic obstructive pulmonary disease in lung cancer screening Computed Tomography scans: independent contribution of emphysema, air trapping and bronchial wall thickening. Respir Res 2013;14:59.
18. Buckens CF, van der Graaf Y, Verkooijen HM, et al. Osteoporosis markers on low-dose lung cancer screening chest computed tomography scans predict all-cause mortality. Eur Radiol 2015;25:132-9.
19. de Jong WU, de Jong PA, Vliegenthart R, et al. Association of chronic obstructive pulmonary disease and smoking status with bone density and vertebral fractures in male lung cancer screening participants. J Bone Miner Res 2014;29:2224-9.
20. Roth JA, Sullivan SD, Ravelo A, et al. Low-dose computed tomography lung cancer screening in the Medicare program: Projected clinical, resource, and budget impact. J Clin Oncol 2014;32:5s.
21. Black WC, Gareen IF, Soneji SS, et al. Cost-effectiveness of CT screening in the National Lung Screening Trial. N Engl J Med 2014;371:1793-802.

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