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

Firdaus A. A. Mohamed Hoesein, Pim A. de Jong, Onno M. Mets

Department of Radiology, University Medical Center Utrecht, The Netherlands

Correspondence to: Pim A. de Jong, Department of Radiology, University Medical Center Utrecht, PO Box 85500, HP E01.132, 3508GA Utrecht, The Netherlands. Email: pimdejong@gmail.com.

Submitted Nov 17, 2014. Accepted for publication Nov 17, 2014.
doi: 10.3978/j.issn.2305-5839.2014.11.18

View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2014.11.18

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 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 mm³) (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 cutoff 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 carries 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 national 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.
Acknowledgements

Disclosure: The authors declare no conflict of interest.

References


