Clinically detected non-aggressive lung cancers: implications for overdiagnosis and overtreatment in lung cancer screening

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CT lung cancer screening is currently being implemented in clinical practice in the USA and pilot studies are ongoing in the UK.[1 2] Recently, an European Union statement recommended planning the potential implementation of lung cancer screening in Europe.[3] Overdiagnosis, the detection of a cancer through screening which would have never been diagnosed in the patient's lifetime if screening had not occurred, is a harm that inevitably occurs with the implementation of a screening programme. Therefore, more information on the occurrence of non-aggressive disease is essential to aid in successfully implementing a screening programme that minimises overdiagnosis and overtreatment.

Kale *et al* linked data from 1992 to 2010 of the Surveillance, Epidemiology, and End Results Database to Medicare claims in order to identify individuals with clinically detected, non-aggressive lung cancer in the USA.[4] The authors find low rates of non-aggressive lung cancers in clinical practice, but advise caution, as the rate of non-aggressiveness among screen-detected cancers is '…likely to be different as screening with CT may unveil small, slowly progressive cancers that are biologically dissimilar'. However, non-aggressive clinically detected lung cancer may share characteristics with those of non-aggressive lung cancers detected by screening. Thus, information derived from non-aggressive lung cancers in clinical practice may aid in reducing overdiagnosis and overtreatment in lung cancer screening.

For example, one of the concerns raised for implementing lung cancer screening has been the rate of false-positive results observed in the National Lung Screening Trial (NLST), mainly due to the detection of small pulmonary nodules.[5] Therefore, recent nodule management guidelines suggest applying higher nodule size thresholds for a positive screening result, which can considerably reduce the rate of false-positive results.[6–8] When Kale *et al* stratified their data by tumour size, they found a (non-statistically significant) decrease in the estimated rate of non-aggressive stage I cancers with increasing tumour size. This suggests that raising the nodule size threshold for a positive screening result may reduce the number of false-positive screens, and could aid in reducing the occurrence of overdiagnosis.

Nodule management guidelines commonly recommend to assess whether a nodule's size increases. However, some guidelines also suggest to evaluate the volume doubling time of the nodule, such as the British Thoracic Society (BTS) guidelines.[8] The BTS guidelines were based on an investigation of the Dutch-Belgian lung cancer screening trial (NELSON (a population-based randomised-controlled trial which evaluates whether CT lung cancer screening can reduce lung cancer mortality); ISRCTN63545820).[6 8] This study found that the size of the detected nodule, and its volume doubling time could be used to stratify an individual's probability of developing lung cancer. As non-aggressive lung cancers are by definition indolent or slow-growing, nodule management guidelines which incorporate recommendations based on nodule volume doubling time could reduce the detection of non-aggressive cancers. Thus, additional information on the characteristics of non-aggressive cancers may aid in further optimising nodule management guidelines.

Kale *et al*'s observation that the presence of chronic obstructive pulmonary disease (COPD) was associated with more aggressive cancers is in line with previous (subgroup) analyses of both the NLST and the Danish Lung Cancer Screening Trial.[9 10] However, it is important to consider that overdiagnosis is not limited to non-aggressive cancers alone. Thus, an aggressive stage III cancer that is detected by screening, but would not have been clinically detected before the person's death from other causes occurs, should also be considered as an overdiagnosed cancer. Therefore, when considering overdiagnosis, one should always take the life-expectancy of the population that is examined into account. For example, while the authors indicate the presence of COPD is associated with higher probability of tumour aggressiveness, COPD may also influence the occurrence of overdiagnosis due to its accompanying higher risk of all-cause mortality.[11] For example, more extensive smoking behaviour has been shown to increase the risk of developing lung cancer, and the risk of developing more aggressive types of lung cancer.[11–13] However, while focusing on individuals with more extensive smoking behaviour can improve the (cost-) effectiveness of lung cancer screening, this may also result in higher overdiagnosis rates due to their higher probability of dying from other causes.[11 14 15]

Still, this does not mean that acquiring information on tumour aggressiveness is limited to enhancing the screening phase of the screening programme. The recent European Union statement on lung cancer screening recommends using risk-stratification for future programmes.[3] Investigations on risk-stratification in lung cancer screening thus far have primarily focused on assessing an individual's risk for developing lung cancer.[6 16–18] If this risk can be supplemented with information on the individual's life expectancy and the potential for detecting a non-aggressive tumour, this could provide an assessment for this individual's risk for overdiagnosis. Incorporating this information in the risk-based selection of participants for lung cancer screening may allow identification of individuals for whom the risk of overdiagnosis outweigh the potential benefits of screening. Furthermore, such an assessment can further aid individuals in making an informed choice on whether or not to participate in screening.

Finally, information on tumour aggressiveness may also be used to inform the treatment of screen-detected lung cancers. Kale *et al* showed that the majority of clinically diagnosed early stage lung cancers should be treated with curative intent. However, if the probability that a screen-detected cancer is non-aggressive can be accurately assessed, this may allow physicians to opt for less intensive treatment or even active surveillance of the tumour. Such an approach may help reduce overtreatment and prevent unnecessary harm to patients. In particular, some variants of adenocarcinoma in situ (AIS) and minimally invasive adenocarcinoma (MIA), previously classified as bronchioloalveolar carcinoma (BAC),

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have been shown to have good outcomes and to be associated with increased risk of overdiagnosis compared with other histologies.[14 19 20] This has led some to question the 'type and necessity of treatment' with regard to such tumours.[20] Unfortunately, Kale *et al* were not able to assess the rate of non-aggressiveness of these tumours, as the reclassification of BAC to AIS and MIA occurred after 2010. However, future research on MIA and AIS may identify characteristics that allow accurate assessment of the aggressiveness of these tumours.

Kale *et al*'s analyses provide an uncommon, valuable overview of the characteristics of non-aggressive lung cancers detected in clinical practice. These tumours may share characteristics with non-aggressive cancers detected by screening and could aid in assessing the aggressiveness of screen-detected cancers in the future. Such an assessment could enhance different phases of the screening process and aid in further optimising the balance between benefits and harms of lung cancer screening.

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REFERENCES

1 Jemal A, Fedewa SA. Lung cancer screening with low-dose computed tomography in the United States-2010 to 2015. *JAMA Oncol* 2017;3:1278–81.
2 Wise J. Mobile lung cancer testing in supermarket car parks is to be expanded. *BMJ* 2017;359:j5450.
3 Oudkerk M, Devaraj A, Vliegenthart R, *et al*. European position statement on lung cancer screening. *Lancet Oncol* 2017;18:e754–e766.
4 Kale MS, Sigel K, Mhango G, *et al*. Assessing the extent of non-aggressive cancer in clinically detected stage I non-small cell lung cancer. *Thorax* 2018;73:459–63.
5 Aberle DR, Adams AM, Berg CD, *et al*. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395–409.
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 Pinsky PF, Gierada DS, Black W, *et al*. Performance of lung-rads in the national lung screening trial: a retrospective assessment. *Ann Intern Med* 2015;162:485–91.
8 Callister ME, Baldwin DR, Akram AR, *et al*. British thoracic society guidelines for the investigation and management of pulmonary nodules. *Thorax* 2015;70(Suppl 2):ii1–ii54.
9 Wille MM, Dirksen A, Ashraf H, *et al*. Results of the randomized danish lung cancer screening trial with focus on high-risk profiling. *Am J Respir Crit Care Med* 2016;193:542–51.
10 Young RP, Duan F, Chiles C, *et al*. Airflow limitation and histology shift in the national lung screening trial. The NLST-ACRIN cohort substudy. *Am J Respir Crit Care Med* 2015;192:1060–7.
11 Thun MJ, Carter BD, Feskanich D, *et al*. 50-year trends in smoking-related mortality in the United States. *N Engl J Med* 2013;368:351–64.
12 Kenfield SA, Wei EK, Stampfer MJ, *et al*. Comparison of aspects of smoking among the four histological types of lung cancer. *Tob Control* 2008;17:198–204.
13 Haiman CA, Stram DO, Wilkens LR, *et al*. Ethnic and racial differences in the smoking-related risk of lung cancer. *N Engl J Med* 2006;354:333–42.
14 Han SS, Ten Haaf K, Hazelton WD, *et al*. The impact of overdiagnosis on the selection of efficient lung cancer screening strategies. *Int J Cancer* 2017;140:2436–43.
15 Ten Haaf K, Tammemägi MC, Bondy SJ, *et al*. Performance and cost-effectiveness of computed tomography lung cancer screening scenarios in a population-based setting: a microsimulation modeling analysis in Ontario, Canada. *PLoS Med* 2017;14:e1002225.
16 Tammemägi MC, Katki HA, Hocking WG, *et al*. Selection criteria for lung-cancer screening. *N Engl J Med* 2013;368:728–36.
17 Ten Haaf K, Jeon J, Tammemägi MC, *et al*. Risk prediction models for selection of lung cancer screening candidates: A retrospective validation study. *PLoS Med* 2017;14:e1002277.
18 Raji OY, Duffy SW, Agbaje OF, *et al*. Predictive accuracy of the liverpool lung project risk model for stratifying patients for computed tomography screening for lung cancer: a case-control and cohort validation study. *Ann Intern Med* 2012;157:242–50.
19 Travis WD, Brambilla E, Noguchi M, *et al*. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011;6:244–85.
20 Patz EF, Pinsky P, Gatsonis C, *et al*. Overdiagnosis in low-dose computed tomography screening for lung cancer. *JAMA Intern Med* 2014;174:269–74.