Hans-Ulrich Kauczor1,2,3, Claus Peter Heussel1,2,3 and Oyunbileg von Stackelberg1,2,3

Affiliations: 1Dept of Diagnostic and Interventional Radiology, University Medical Center Heidelberg, Heidelberg, Germany. 2Translational Lung Research Center (TLRC) Heidelberg, Member of the German Center for Lung Research (DZL), Heidelberg, Germany. 3Dept of Diagnostic and Interventional Radiology with Nuclear Medicine, Thoraxklinik, University Medical Center Heidelberg, Heidelberg, Germany.

Correspondence: Hans-Ulrich Kauczor, Dept of Diagnostic and Interventional Radiology, University Medical Center Heidelberg, Im Neuenheimer Feld 110, 69120 Heidelberg, Germany. E-mail: Hans-Ulrich.Kauczor@med.uni-heidelberg.de

Transforming lung cancer screening into a comprehensive programme to detect and treat smoking-related disease early

Cite this article as: Kauczor H-U, Heussel CP, von Stackelberg O. Time to take CT screening to the next level? Eur Respir J 2017; 49: 1700064 [https://doi.org/10.1183/13993003.00064-2017].

The paper by Pompe et al. [1] in this edition of the European Respiratory Journal investigated subjects from the National Lung Cancer Screening Trial (NLST), whose cause of death was recorded as being a respiratory illness other than lung cancer. The patients’ computed tomography (CT) scans were retrospectively reviewed and compared with the NLST participants of the CT arm who were still alive. Not surprisingly, significantly more lung diseases were detected in those who died from respiratory disease than in the matched control group.

We are all aware that the NLST has demonstrated a significant reduction in lung cancer mortality [2]. An additional finding of NLST showed that all-cause mortality was also significantly lower in participants screened with CT. When deaths from lung cancer were excluded from the comparison, the reduction in overall mortality with the use of low-dose CT dropped to 3.2% and was not significant anymore [2].

For their retrospective case–control study, the authors hypothesised that the pulmonary abnormalities in accordance with respiratory deaths should already be visible on the CT scans and that the NLST data provided a unique opportunity to investigate the importance of these CT diagnoses for survival [1]. Thus, the CT scans were visually assessed for the prevalence of emphysema (sub-classified as mild, moderate or severe/confluent and advanced destructive emphysema) [3], airway wall thickening and fibrotic lung disease. Pompe et al. [1] identified among the NLST participants 167 people who died from a respiratory disease other than lung cancer, most of them from chronic obstructive pulmonary disease (COPD). The authors double-checked the cause of death to put their results on stable ground. As might have been expected, these participants had significantly more pulmonary disease visible on the CT scan (severe emphysema, airway abnormalities and fibrotic lung disease) than the surviving matched-pair controls.

For their analysis, the authors relied on a very simple, visual, subjective approach. They had two radiologists with different levels of expertise reading the scans. They took simple binary decisions: presence or absence of severe emphysema, airway abnormalities or fibrosis. Obviously, this approach was very fast, and it took them less than a minute per scan. The results are sufficiently robust, with a high inter-reader agreement (weighted kappa 0.7–0.91). It is important to note that these results were achieved
using low-dose CT scans, which were not intended to serve for quantitative analysis. The disease
classification could be made with appropriate confidence despite higher image noise compared with
routine “diagnostic” CT scans.

However, the good results and the prompt visual assessment are just an intermediate step on the way to
software-based pre-reads and automated reproducible disease quantification, which should be
implemented in future imaging-based screening scenarios. The change from a visual binary categorisation
to contiguous quantitative data will make the output much more valuable [4]. Dedicated software tools
will also be capable of performing more complex analysis, such as feature extraction (radiomics) of
smoking-related diseases and co-morbidities (such as emphysema, bronchial-wall thickening, fibrosis,
arteriosclerosis, sarcopenia and osteopenia), and the results will be fully eligible for “big data” analysis
tools [5]. Such an approach will generate deeper phenotypic insights into unexpected associations.

At first glance, the results of this retrospective analysis seem rather trivial – at least for a radiologist
assessing chest CTs every day. Smokers who die from pulmonary disease have more abnormalities visible
on CT scan, and a higher number of abnormalities seen on the scan carries a higher risk for dying from
respiratory disease. This clearly emphasises that all CT-detectable abnormalities should be included when
screening a high-risk population, as severe COPD and fibrosis are associated with very limited life
expectancy even without development of synchronous lung cancer [6–8].

However, the results of this study go beyond this simple assumption and confirm the value of the high
sensitivity of CT for the detection of respiratory diseases, especially COPD. CT was also shown to have
a clear impact on the outcome of the participants or patients, which is a core requirement in value-based
medicine, which is also applicable to radiology. If done properly, either sticking to the algorithms of the
NLST or even using matured algorithms, CT screening of lung cancer will reduce lung cancer mortality in
high-risk smokers. Because of the evidence generated by the NLST, lung cancer screening with annual
low-dose CT has been introduced in the US in adults aged 55–80 years who have a 30 pack-year smoking
history and currently smoke or have quit within the past 15 years [9], with cancer incidence in lung cancer
screening dropping dramatically after the first round [10]. Longer screening intervals result in lower
cumulative radiation dose, but intervals as long as 2.5 years are not recommended because there is a
higher interval cancer rate and a higher proportion of advanced-stage disease [11].

Recommendations for the potential implementation in Europe were published jointly by the European
Respiratory Society and the European Society of Radiology in 2015 [12, 13]. Several calculations and
simulations demonstrate that CT screening for lung cancer can be cost-effective [14, 15]. Surprisingly, a
comprehensive approach towards the early detection of the “Big Three” killers associated with cigarette
smoking (lung cancer, COPD and cardiovascular disease) is still missing, despite the fact that all of them
are more or less visible on a single non-gated, non-enhanced, low-dose CT scan. POMPE et al. [1] nicely
demonstrated the outcome-based value of the CT diagnosis of emphysema, airway remodelling and COPD
within lung cancer screening programmes. They confirmed and enriched the results from other studies,
showing the value of reporting abnormalities related to “COPD”, especially emphysema and other
interstitial abnormalities. It is known that patients with emphysema have a higher risk of developing lung
cancer, and the greater the emphysema, the higher the risk [16].

The value of diagnosing fibrotic lung disease in smokers has been evaluated only in a single site of NLST,
and showed a prevalence of almost 10% and a progression of 37% at 2-year follow-up [17]. In addition,
the combination of COPD and fibrosis as a smoking-related lung disease has received increasing interest
recently, and a new term, “combined pulmonary fibrosis and emphysema” (CPFE), has been coined [18, 19].

To take CT screening of the lung to the next level, the risk for cardiovascular events has to be assessed as
well. Image-wise, smoking-associated cardiovascular disease is best represented by the extent of vascular
calcifications. The non-gated, non-enhanced, low-dose scans obtained in lung cancer screening cohorts are
well suited to diagnose cardiovascular calcifications [20], which are a well-established risk factor for
cardiovascular events and death [21–23]. The findings have been grouped into coronary artery calcification
(CAC) and extracoronary calcification (ECC), and can be established accurately by visual and/or
quantitative analysis. There is a strong association between ECC load and established cardiovascular risk
factors such as smoking history, hypertension, diabetes and hypercholesterolaemia [21]. Using a simple
visual assessment of CAC on a low-dose CT scan, a risk assessment of coronary heart disease death and
all-cause mortality can be generated, which is comparable to the Agatston score and strongly associated
with outcome [24]. But again, a visual binary assessment will do as a first step, while a software-based
assessment will provide a more extensive basis for further risk calculations.

There are even debates about extending the scanning field of low-dose chest CT to the neck. This would
allow for assessment of vascular calcifications as well as the lipid core of the plaques in the carotid vessel
in the same examination. The impact of these findings on the risk profile of smokers still has to be determined, however [25].

In order to obtain comprehensive data on the “Big Three” from a single low-dose screening CT, a dedicated software tool is required, which will depict and measure lung nodules, low-attenuation areas (emphysema), airway wall and lumen, “fibrosis”, and coronary and extracoronary arterial calcification load. Furthermore, such a software tool should be capable both of obtaining radiomics data by feature analysis (e.g. malignancy potential of a nodule, lipid core of a plaque), and of measuring changes in the subsequent screening rounds or follow-ups. The image-based “phenotypic” biomarkers of risk should be complemented by minimally invasive biomarkers from blood, serum, plasma (“liquid biopsy”) [26, 27] or exhaled breath [28, 29] in the future, either to increase pre-test probability or to reduce the number of false-positive results.

Such comprehensive results of a screening programme must not be used as an excuse for patients to continue smoking but rather to increase the individual success rate of smoking cessation. Confronting the participants with convincing visual findings from their scans will increase the awareness of the vulnerability of their own body and increase the motivation to stop smoking, e.g. evidence of nodules increases the success of smoking cessation from 5% to 40% [30].

In conclusion, it is time to reshape our conception of lung cancer screening and take CT screening to the next more holistic level. We have to fight the reduced life expectancy of heavy (i.e. high-risk) smokers, which is about 10–12 years lower than in never-smokers. To be successful, two strategies have to be merged: (1) to stop smoking and (2) to detect and treat survival-limiting, smoking-related disease early. This should be done by a comprehensive screening programme for heavy smokers, offering a smoking cessation programme together with a risk-model based CT screen and biomarker analysis of the “Big Three” smoking-related killer diseases: lung cancer, COPD and cardiovascular disease.

References


https://doi.org/10.1183/13993003.00064-2017