Visual assessment of first and last CT scans of the Danish Lung Cancer Screening Trial: observer agreement and time-trend

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Aims and objectives

Aim of the study was to evaluate interobserver agreement and time-trend in chest CT analyses of emphysema, airways and interstitial abnormalities in large lung cancer screening cohort.

Visual assessment of computed tomography (CT) scans of the lung is an important tool in the routine clinical workup of patients with pulmonary diseases[1,2]. However, visual evaluation is subjective, and the conclusion is dependent on the observer[3,4]. For longitudinal studies of lung diseases such as emphysema, an accurate and reliable visual assessment is necessary if disease progression is to be detected[5]; as early intervention is of great importance[6]. Reliability of visual assessment depends upon a good intra- and interobserver agreement in assessing the presence and the severity of disease. Interobserver agreement in visual assessment of CT of the lung has previously been shown to be varying; emphysema[2,7] being easier to agree upon than interstitial abnormalities[8-10]. Previous conclusions on interobserver variation in visual assessment of airways disease are highly variable; some show reasonable levels of agreement and others show considerable interobserver variability[11,12].

Studies on visual assessment of progression of disease are lacking; the ability of the trained human eye to detect a change in the severity of emphysema over time is, for instance, unknown.

In the Danish Lung Cancer Screening Trial (DLCST) the participants in the screening arm of the study were followed with annual CT scans for five years. This is a reasonable time span, during which significant change in lung function[13] and lung density[14] has been detected in this population. It was, therefore, plausible to test whether the progression of emphysema, airways diseases and interstitial abnormalities can be detected visually within this time frame.
Methods and materials

A lung cancer screening cohort consisting of relatively healthy heavy smokers (n=1990) scanned annually for 5 years comprised the study population. Visual assessments of first and last scan of each participant were performed by two observers, and results were standardised by means of an electronic score sheet; and kappa and time-trend analyses were performed.

DLCST is a 5-year prospective randomised controlled trial comprising 4,104 participants randomised to either screening (with annual low-dose CT, n=2,052) or no screening (control group, n=2,052)[15]. Inclusion criteria comprise smoking history of at least 20 pack years, age 50-70 years, and FEV\textsubscript{1} of at least 30\% of predicted. Only participants with at least two scans were included (n=1990).

The first and the last available scans from each participant were selected, and two sets with scans in random order were produced. Each set was evaluated by two observers. Thus, the two observers were blinded to participants' id, clinical data, and scan date. The visual evaluations were performed individually.

Participants in the screening group were scanned annually during a period of 5 years, using a multi-slice CT scanner (16 rows Philips Mx 8000, Philips Medical Systems). Scans were performed in supine position at full inspiration with a low dose technique (120 kV and 40 mAs) with following specifications: Section collimation 16 x 0.75 mm, pitch 1.5, and rotation time 0.5 second. Images were reconstructed with 1 mm slice thicknesses using hard reconstruction algorithm (kernel D).

Visual assessment was performed using a window width of 1500 Hounsfield Units (HU) and a level of -500 HU.

Each lung was divided into three regions; upper zone above carina, middle zone between carina and inferior pulmonary vein, and lower zone below inferior pulmonary vein. Each region was assigned an emphysema grade: 0\%, 1-5\%, 6-25\%, 26-50\%, 51-75\% or 76-100\%[10]. Airway wall thickening and airway dilation were registered.

The occurrence of ground glass attenuation, reticulation, centrilobular noduli and/or honeycombing was registered; and a conclusion regarding suspicion of interstitial lung disease (ILD) was stated.

Statistics
Interobserver agreement was based on baseline scans and tabulated for each question on the score sheet as kappa. Kappa agreement levels were 0-0.2: poor, 0.21-0.4: fair, 0.41-0.6: moderate, 0.61-0.80: substantial, 0.81-1.0: almost perfect. The p-values for kappa were based on the exact binomial test.

Progression of disease severity was investigated by comparing the first and last scan for each participant, and a trend was calculated. The p-values for trends were based on sign test.

Level of significance was set at $p < 0.05$. 
**Fig. 1:** Centrilobular emphysema in right and left upper lung zones.

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Fig. 2: Paraseptal emphysema predominance.

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Results

Results of analyses are shown in table 1. There was substantial interobserver agreement (kappa=0.74) in early emphysema diagnosis and highly significant (p <0.001) time-trend in both emphysema presence and grading (higher prevalence and grade of emphysema in late scans). Agreement on centrilobular emphysema subtype was substantial and agreement on paraseptal subtype moderate; while agreement was only fair on panlobular and mixed subtypes. Interobserver agreement was fair regarding airway analysis, and interstitial abnormalities were infrequent in the cohort and agreement on these fair to moderate. A highly significant time-trend was found regarding interstitial abnormalities, which were more frequent in late scans.

Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Kappa</th>
<th>p</th>
<th>Time-trend</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emphysema present</td>
<td>539</td>
<td>0.74</td>
<td>&lt;0.001</td>
<td>0.032</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emphysema grading</td>
<td>1990</td>
<td>0.57</td>
<td>&lt;0.001</td>
<td>0.036</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Emphysema predominant subtype: paraseptal</td>
<td>231.5</td>
<td>0.52</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Emphysema predominant subtype: centrilobular</td>
<td>254.5</td>
<td>0.65</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Emphysema predominant subtype: panlobular</td>
<td>2.5</td>
<td>0.40</td>
<td>0.003</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Emphysema predominant subtype: mixed</td>
<td>50.5</td>
<td>0.26</td>
<td>&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Airway wall thickening</td>
<td>49.5</td>
<td>0.37</td>
<td>&lt;0.001</td>
<td>0.005</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>p-Value 1</td>
<td>p-Value 2</td>
</tr>
<tr>
<td>----------------------</td>
<td>-----</td>
<td>------</td>
<td>------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Airway dilation</td>
<td>128.5</td>
<td>0.43</td>
<td>&lt;0.001</td>
<td>0.016</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Interstitial findings</td>
<td>346</td>
<td>0.60</td>
<td>&lt;0.001</td>
<td>0.018</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ground glass attenuation</td>
<td>104.5</td>
<td>0.55</td>
<td>&lt;0.001</td>
<td>0.010</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Honeycombing</td>
<td>10</td>
<td>0.40</td>
<td>0.089</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reticulation</td>
<td>168.5</td>
<td>0.63</td>
<td>&lt;0.001</td>
<td>0.015</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural nodules</td>
<td>85.5</td>
<td>0.53</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Centrilobular nodules</td>
<td>47</td>
<td>0.41</td>
<td>&lt;0.001</td>
<td>0.000</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Subpleural/paraseptal nodules</td>
<td>36</td>
<td>0.24</td>
<td>0.045</td>
<td>-0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mosaic attenuation</td>
<td>11</td>
<td>0.42</td>
<td>0.081</td>
<td>-0.003</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Consolidation</td>
<td>9.5</td>
<td>0.42</td>
<td>0.081</td>
<td>-0.002</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No ILD</td>
<td>1752.5</td>
<td>0.63</td>
<td>&lt;0.001</td>
<td>0.017</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Equivocal for ILD</td>
<td>210.5</td>
<td>0.55</td>
<td>&lt;0.001</td>
<td>0.016</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ILD suspicion/centrilobular</td>
<td>10</td>
<td>0.40</td>
<td>0.089</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>ILD suspicion/ subpleural/mixed (incl. UIP pattern)</td>
<td>15(1)</td>
<td>0.56</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.883</td>
</tr>
</tbody>
</table>

Definitions of abbreviations: ILD: interstitial lung disease, UIP: Usual Interstitial Pneumonia

* N: mean number of participants where variable was present at baseline
Fig. 3: Per cent of lung regions by severity of emphysema in early and late scans.

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Conclusion

Visual scoring of chest CT, using a systematic approach, could characterise presence, pattern, and progression of early emphysema.

Visual assessment of early airways disease was ambiguous.

Further studies are needed on reliability in visual assessment of incidence and development of interstitial lung disease.


