Diagnostic performance of ultra-low-dose computed tomography for detecting asbestos-related pleuropulmonary diseases: prospective study in a screening setting

Poster No.: B-0681
Congress: ECR 2015
Type: Scientific Paper
Authors: M. Schaal, F. Severac, A. Labani, M.-Y. Jeung, C. Roy, M. Ohana; Strasbourg/FR
Keywords: Thorax, Radioprotection / Radiation dose, CT, Screening, Dosimetry, Technology assessment, Occupational / Environmental hazards
DOI: 10.1594/ecr2015/B-0681

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Purpose

The monitoring of people who have been exposed to asbestos in their professional lives relies, in most European countries, on the detection of benign or malignant pleuropulmonary diseases by an unenhanced chest computed tomography (CT) every 5 to 10 years [1]. Like all screening tests, it is intended for asymptomatic people, and therefore must be the least deleterious possible. Minimizing the exposure to ionising radiation is consequently of paramount importance, and could be achieved through the use of an ultra-low dose (ULD) technique.

Thanks to technological development, and especially the implementation of iterative reconstruction techniques, it has become possible to obtain a chest CT at a radiation dose similar to that of a chest x-ray from a front and lateral view [2, 10]. If several recent studies dealing with the detection of pulmonary nodules by a ULD chest CT [2, 11, 12] have already shown very positive results, none have yet studied asbestosis screening.

The aim of this study is to justify the relevance of the ULD CT in the detection of pleuropulmonary diseases related to asbestos exposure.

The hypothesised theory is that the ULD CT is not inferior to the standard "full radiation dose" chest CT, with a non-inferiority threshold of 10%, in:

- the detection of global tomodensitometric abnormalities related to such an exposure (primary endpoint);
- the identification of specific pleuropulmonary abnormalities such as parietal pleural plaques, calcified pleural plaques, diffuse pleural thickening, interstitial abnormalities suggesting asbestosis or significant lung nodules (secondary endpoints).

Methods and materials

Our institutional review board approved this prospective study, and written consent was obtained from all participants.
**POPULATION**

For a period of 10 months (July 2013 to May 2014), all patients referred to our department for a chest CT to screen asbestos-related pleuropulmonary diseases were selected.

The inclusion criteria were an exposure to asbestos for a minimal period of 5 years and the absence of pulmonary symptoms or previous history of lung cancer or mesothelioma.

**CT EXAMINATIONS**

Each patient underwent an unenhanced chest CT with two successive helical acquisitions: one standard (120 kV, automated tube current modulation) used as the reference and one ULD (135 kV, 10 mA).

All examinations were carried out on the same 320-row scanner (*Aquillion One Vision Edition*, Toshiba, Japan). Patients were positioned prone with their arms above their heads [1], so as to avoid gravity dependent parenchymal abnormalities in the posterior regions [13, 14].

Acquisition parameters are summarized in *Table 1 on page 5*.

**CT INTERPRETATION**

CT images were analysed on a dedicated workstation (*Vitrea version 6.4*, Vital Images, Minneapolis, USA), with systematic multiplanar and Maximum Intensity Projection (MIP) reconstructions.

The analysis of the soft parts including the mediastinum, the intercostal space and the chest wall was made in a mediastinal window (width = 350 UH; center = 50 UH) reconstructed with a soft kernel. The analysis of the parenchyma was made in a lung window (width = 1500 UH; center = -700 UH) with a hard kernel. The contrast could be dynamically adapted by the reader.

Each examination was independently and anonymously interpreted by two chest radiologists, one senior (MO) with seven years' experience and one junior (MS) with four years' experience.
In the first instance, the readers interpreted all the ULD images in a random order. The reference acquisitions were secondarily interpreted three weeks later, in a different random order.

Based on consensus studies [1, 13], we followed a detailed reading protocol focusing on pleural abnormalities, pulmonary lesions and significant nodules (Table 3) [15, 16]. Each item within the categories was stated as present or absent, in an unequivocal "yes or no" fashion (secondary endpoints).

At the end of the reading, the radiologist concluded the presence or absence of asbestos-related global abnormalities, i.e. if the screening was positive or negative (primary endpoint), and gave their diagnostic confidence using a 5-level scale (Table 3 on page 6).

Image quality was independently evaluated by both readers, both quantitatively (HU standard deviation measured in an intra-luminal tracheal ROI on the lung kernel images) and qualitatively, using a 5-level scale (Table 4 on page 7).

All discrepant cases were reviewed by an experienced chest radiologist (MYJ, with 32 years' experience).

The final interpretation of the full dose CT that was obtained was considered the "gold standard", to which the ULD was compared.

All the results were recorded in an anonymous spreadsheet (Excel 2010, Microsoft, Seattle, USA).

RADIATION DOSE

The dose-length product (DLP) expressed in milligray.cm (mGy.cm) was recorded for both acquisitions.

The effective dose given to the patient was estimated using the following formula: Effective dose = DLP x 0.017 [17].

STATISTICAL ANALYSIS
The diagnostic performance of the ULD CT for primary and secondary endpoints was compared to the gold standard, obtained by the final reading of the full dose chest CT. The sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), accuracy and error rate were calculated using a confidence interval of 95%, according to the exact method of Pearson.

The agreement between the readers was analysed using the Cohen's Kappa test. The confidence intervals for Cohen's Kappa coefficients were calculated using the Bootstrap method.

The Gaussian nature of the quantitative variables was assessed using the Shapiro-Wilk test. The radiation exposure, image quality, noise and diagnostic confidence were compared with a Student's *t*-test when the parametric conditions were met, and otherwise with a Wilcoxon test. A *p* less than 0.05 was considered significant.

Images for this section:

<table>
<thead>
<tr>
<th>Table 1: Acquisition parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>ULD Acquisition</strong></td>
</tr>
<tr>
<td>Collimation</td>
</tr>
<tr>
<td>Scanning time</td>
</tr>
<tr>
<td>Pitch</td>
</tr>
<tr>
<td>Voltage</td>
</tr>
<tr>
<td>Tube current</td>
</tr>
<tr>
<td>Slice thickness</td>
</tr>
<tr>
<td>Reconstruction of the mediastinum volume</td>
</tr>
<tr>
<td>Reconstruction of the lung volume</td>
</tr>
</tbody>
</table>

Table 1: CT acquisition parameters
### Table 2: Pleural and parenchymal abnormalities related to asbestos

<table>
<thead>
<tr>
<th>Pleural abnormalities</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural plaques (Thickening of parietal pleura)</td>
<td>Circumscribed quadrangular pleural elevations, or multiple bilateral non quadrangular elevations with sharp borders and tissue density</td>
</tr>
<tr>
<td>Calcified pleural plaques</td>
<td>Circumscribed quadrangular pleural elevations with calcified tissue density, or multiple bilateral and calcified non quadrangular elevations with sharp borders</td>
</tr>
<tr>
<td>Thickening of the parietal pleura which appears malignant suggesting mesothelioma</td>
<td>Unilateral sheet-like or lobulated pleural thickening encasing the entire lung, and/or radical pleural thickening with invasion of the chest wall, pericardium, mediastinum, or diaphragm and/or subdiaphragmatic extension (liver, peritoneal or retroperitoneal damage)</td>
</tr>
<tr>
<td>Diffuse pleural thickening (Thickening of visceral pleura)</td>
<td>Significant pleural thickening of tissue density, more or less calcified, with parenchymal bands (linear opacities extending through the lung when in contact with the pleural surface) and/or crow's feet images or rounded atelectasis. Crow's feet images were linear opacities measuring 2 cm or more, radially extending throughout the lung when in contact with the pleural thickening. Round atelectasis, that was defined as a mass near an area of pleural thickening, with a parietal interposition of lung parenchyma between the pleura and the mass. There was a visible «comet tail» of vessels and bronchi sweeping into the lateral aspect of the mass.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parenchymal abnormalities</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subpleural and centrilobular micronodules and subpleural opacities</td>
<td></td>
</tr>
<tr>
<td>Intralobular lines</td>
<td>Linear images with a smaller dimension than that of the interlobular septas appeared as Y-shaped branching structures.</td>
</tr>
<tr>
<td>Septal lines</td>
<td>Short, discrete nonbranching lines, perpendicular to the pleura</td>
</tr>
<tr>
<td>Curvilinear subpleural lines</td>
<td>Linear areas of opacity within 1 cm of the pleura and parallel to the inner chest wall.</td>
</tr>
<tr>
<td>Areas of ground-glass opacity</td>
<td>Areas of increased attenuation in which the vessels and the bronchial walls remained visible.</td>
</tr>
<tr>
<td>Honey combing</td>
<td>Area of lung containing cystlike spaces with thickened walls. Cystic air spaces, with bronchiectasis or traction bronchiectasis had a diameter of several mm to 1 cm and were separated by well-defined walls.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nodules</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant lung nodules</td>
<td>All nodules measuring at least 5mm, and/or which were not entirely calcified and/or which were not scissural, according to advice offered by the Fleischer Society</td>
</tr>
</tbody>
</table>
Table 3: Diagnostic confidence

<table>
<thead>
<tr>
<th>Mark</th>
<th>Diagnostic Confidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 A too hazardous interpretation</td>
<td>Less than 50 %</td>
</tr>
<tr>
<td>2</td>
<td>Between 50 and 75 %</td>
</tr>
<tr>
<td>3</td>
<td>Between 76 and 90 %</td>
</tr>
<tr>
<td>4</td>
<td>Between 91 and 95 %</td>
</tr>
<tr>
<td>5 Optimal conditions</td>
<td>More than 95 %</td>
</tr>
</tbody>
</table>

Table 4: Evaluation of the quality of CT images

<table>
<thead>
<tr>
<th>Mark</th>
<th>Evaluation of the quality of CT images</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Quality of the image is mediocre and is unable to make a diagnosis</td>
</tr>
<tr>
<td>2</td>
<td>Very blurred, creating an uncertain reading</td>
</tr>
<tr>
<td>3</td>
<td>Moderately blurred, only slightly preventing an evaluation</td>
</tr>
<tr>
<td>4</td>
<td>Weak artifact which does not interfere with the interpretation</td>
</tr>
<tr>
<td>5</td>
<td>Excellent image quality without any artifacts</td>
</tr>
</tbody>
</table>
Results

POPULATION

55 patients were ultimately included, all of which were male. They were aged (mean ± standard deviation) 55.7 ±8 years.

Asbestos exposure was 14.7 ±9 years.

Approximately 49% of participants were active smokers.

DIAGNOSTIC PERFORMANCE of the ULD CT

The prevalence of global abnormalities was 20% (11 patients out of 55). The request for the third reader was necessary in 5 cases for the full dose images, and 6 cases for the ULD images.

Results from the joint analysis showed that the performance of the ULD CT for the primary endpoint was excellent (Table 5 on page 9). Out of the 55 patients, there were 44 true negatives, 10 true positives, 1 false negative and no false positive. The non-inferiority of the ULD CT in the detection of global pleuropulmonary abnormalities related to asbestos was demonstrated in a significant way, with an inferior threshold lower than 10%.

Diagnostic performance for the secondary endpoints was also excellent and is summarized in Table 5 on page 9.

When comparing one reader’s interpretation of the ULD acquisition with his own interpretation of the reference full dose acquisition (Table 6 on page 10), the intra-reader accuracy for the primary endpoint was 98.2% for the senior reader, and 100% for the junior reader, demonstrating an extremely low intra-reader variability induced by the use of a ULD technique.

In the same way, no significant difference in diagnostic confidence was demonstrated between the ULD and the full dose acquisitions (p=0.6075, Wilcoxon signed rank test with continuity correction data). Indeed, the average diagnostic confidence of the two readers was 4.55 out of 5 for the ULD acquisition (Standard Deviation = 0.48, Median
= 4.5, Q1 = 4.25, Q3 = 5.0) and 4.52 for the standard acquisition (Standard Deviation = 0.56, Median = 4.5, Q1 = 4.25, Q3 = 5.0).

**AGREEMENT BETWEEN READERS**

For all criteria, which have been studied, the agreement between both readers ranged from substantial to almost perfect, according to Cohen's Kappa (Table 7 on page 10).

**IMAGE QUALITY**

Logically, there is a significant difference both in objective and subjective image quality to the expense of the ULD acquisition (Table 8 on page 11).

Examples are shown in Fig. 1 on page 11, Fig. 2 on page 12, Fig. 3 on page 13 and Fig. 4 on page 13.

**RADIATION EXPOSURE**

The radiation exposure was naturally significantly decreased in the ULD CT, with the radiation dose divided by 16 ($p \#2.2e^{-16}$, Wilcoxon test).

The average DLP was **17.9 mGy.cm** (effective dose of **0.3 mSv**) for the ULD CT (Standard Deviation = 1.2 mGy.cm, Median = 18 mGy.cm, Q1 = 17.2 mGy.cm, Q3 = 18.9 mGy.cm) and the average DLP was 288.8 mGy.cm (effective dose of 4.9 mSv) for the standard acquisition (Standard Deviation = 151.3 mGy.cm, Median = 242.5 mGy.cm, Q1 = 183.4 mGy.cm, Q3 = 345.5).

Images for this section:
### Table 5: Performance of the ULD CT for the primary endpoint

<table>
<thead>
<tr>
<th>Criteria</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Accuracy</th>
<th>Error rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global abnormalities</td>
<td>10</td>
<td>44</td>
<td>1</td>
<td>0</td>
<td>93.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>99.2%</td>
<td>99.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Thickening of the pericardial plaques</td>
<td>10</td>
<td>44</td>
<td>1</td>
<td>1</td>
<td>91.7%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>97.7%</td>
<td>99.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Calcified pleural plaques</td>
<td>6</td>
<td>49</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Significant lung nodules</td>
<td>3</td>
<td>52</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

### Table 6: The ULD’s Diagnostic Performance for Each Reader

<table>
<thead>
<tr>
<th>Criteria</th>
<th>TP</th>
<th>TN</th>
<th>FP</th>
<th>FN</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
<th>Accuracy</th>
<th>Error rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global abnormalities</td>
<td>6</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Thickening of the pericardial plaques</td>
<td>6</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Calcified pleural plaques</td>
<td>2</td>
<td>44</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Significant lung nodules</td>
<td>2</td>
<td>52</td>
<td>0</td>
<td>0</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>99.2%</td>
<td>100.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

### Formulas
- Accuracy = (TP + TN) / (TP + FP + TN + FN)
- Sensitivity = TP / (TP + FN)
- Specificity = TN / (FP + TN)
- Positive Predictive Value = TP / (TP + FP)
- Negative Predictive Value = TN / (FN + TN)

- Confidence interval (CI)
- True Positive (TP)
- True Negative (TN)
- False Positive (FP)
- False Negative (FN)

### Table 6: Inter-reader variability
Table 7: Agreement between readers

Table 8: Image quality
**Fig. 1:**

1 a: Standard acquisition: Pleural plaques, calcified (green arrow) or not (blue arrow) on the left
1 b: ULD acquisition: Pleural plaques, calcified (green arrow) or not (blue arrow) on the right

**Fig. 2:** Standard Acquisition (mediastinal window 2a, lung window 2c) versus ULD CT (mediastinal window 2b, lung window 2d) for a patient with pleural plaques, calcified or not, diffuse pleural thickening (parenchymal bands, blue arrows) and asbestosis (subpleural and centrilobular micronodules and subpleural opacities, intralobular lines and septal lines, green arrows).
(subpleural and centrilobular micronodules and subpleural opacities, intralobular lines and septal lines, green arrows).

**Fig. 3:** Only false negative patient showing fine poster basal interstitial abnormalities Standard Acquisition (3a, top) versus ULD (3b, bottom)
Fig. 4: Standard Acquisition (4a, top) versus ULD (4b, bottom) for a patient with a significant solid nodule of 8mm (true positive)
Conclusion

This study has demonstrated the excellent diagnostic performance of the ULD CT in the detection of abnormalities related to asbestos exposure, with a radiation dose 16 times lower than with a standard CT acquisition.

For the primary endpoint which was the detection of global abnormalities related to asbestos, the ULD had a specificity and a PPV of 100%, a NPV of 97.8% and a sensitivity of 90.9% due to one false negative (Fig. 3 on page 18).

There was an almost-perfect inter-reader agreement on the ULD acquisition (Kappa = 0.810), which demonstrates an excellent reproducibility in the analysis of ULD acquisitions. The inter-reader agreement was also excellent in the reference full dose acquisition (Kappa = 0.756), confirming an excellent reproducibility of interpretation, as a result of a detailed standardised reading protocol [1, 13].

Regarding the secondary endpoints, the calcified pleural plaques seem to be the abnormalities that are the easiest to recognise. They were constantly detected by both readers (Fig. 1 on page 17 & Fig. 2 on page 17).

The ULD CT also performed extremely well for the detection of solid nodules greater than 5 mm, as they were also constantly detected by both readers (Fig. 4 on page 19). This is on par with what has already been proven in other studies [2, 8, 11, 12].

The interstitial abnormalities, suggesting asbestosis remained the most difficult to detect from the ULD as the sensitivity of the ULD CT was only 75% (out of only 4 cases). There was indeed one false negative where subtle subpleural micronodules and interlobular reticulations were undetected on the ULD by both readers (Fig. 3 on page 18). These abnormalities had been diagnosed by the senior reader in the standard protocol, but remained unnoticed in the ULD acquisition. These results are in agreement with the literature which highlights the limitations of the ULD CT in the detection of interstitial abnormalities and limited ground glass opacities [12].

Even if the noise was increased by 30% in the ULD acquisition, the diagnostic confidence was not altered, as it was identical for both acquisitions for the junior as well as the senior reader. This showed that even being of a much lower quality, the ULD acquisition contained sufficient information to make a diagnosis, with as higher confidence as the full dose acquisition. Therefore, and even if the results are not perfect, this study allows
us to retain the very high sensitivity and NPV of the ULD CT in the screening of pleuropulmonary abnormalities related to asbestos.

It is therefore justifiable to suggest ULD CT as a **first line screening test**, to be completed only in cases of doubt or positivity by a full dose chest CT. If we consider a rough abnormalities prevalence of 20%, it means that 80% of patients could settle with only a ULD CT, whereas the remaining 20% would receive a full dose CT in addition to the initial ULD CT. In the end, such attitude would allow a reduction in the radiation exposure of the screening population of almost 75%.

The major problem induced by this suggested screening method is organisational: to avoid recalling 20% of the patients, the radiologist must be present when the screening takes place in order to interpret the images and to determine if a full dose CT is required. This is possible in France for instance, where the radiologist is present during the examination, but is highly difficult to carry out in other countries such as North America where the radiologist is not present during the examination.

**Our study has some limitations:**

The first one is the **limited size of the sample**, with 55 patients. This is indeed small, but has the advantage of being homogenous since all patients were managed in the same centre. The prevalence of the different abnormalities in our study corresponds to those expected on a national scale [1]. In particular, asbestosis prevalence was 7.2% (4 out of 55 patients), which is on par with recent studies [19, 20].

Another limitation is the **joint reading**. The rereading by an experienced third reader was only conducted in discrepant cases, instead systematically. However, we can assume from the near-perfect agreement between readers that the two radiologists displayed sufficient experience in the interpretation of these screening examinations.

**CONCLUSION**

This study has demonstrated the excellent performance of the ULD CT in the detection of pleuropulmonary diseases related to asbestos exposure, and particularly its high sensitivity and negative predictive value.

It seems justifiable to propose it as a first-line screening test, completed only in doubtful or positive cases by a full dose CT acquisition.
This would allow a reduced radiation dose of nearly 75% for the screening population.

Images for this section:

**FIGURE 1**

1 a: Standard acquisition: Pleural plaques, calcified (green arrow) or not (blue arrow) on the left

1 b: ULD acquisition: Pleural plaques, calcified (green arrow) or not (blue arrow) on the right

**Fig. 1:** 1 a: Standard acquisition: Pleural plaques, calcified (green arrow) or not (blue arrow) on the left 1 b: ULD acquisition: Pleural plaques, calcified (green arrow) or not (blue arrow) on the right
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Fig. 4: Standard Acquisition (4a, top) versus ULD (4b, bottom) for a patient with a significant solid nodule of 8mm (true positive)
Personal information

1: Marysa SCHAAL (Corresponding author)
marysa.jehl@free.fr
Tel: +33 6 77 10 02 09 Fax : +33 3 69 55 17 53
Professional address: Service de Radiologie B
Nouvel Hôpital Civil - Hôpitaux Universitaires de Strasbourg
1 place de l'hôpital
67000 Strasbourg - France

2: François SEVERAC
Service de Santé Publique
HOPITAL CIVIL - 1, place de l'Hôpital
67000 Strasbourg - France
francois.severac@chru-strasbourg.fr

3: Aissam LABANI
Service de Radiologie B
Nouvel Hôpital Civil - Hôpitaux Universitaires de Strasbourg
1 place de l'hôpital
67000 Strasbourg - France
aissam.labani@chru-strasbourg.fr

4: Mi-Young JEUNG
Service de Radiologie B
Nouvel Hôpital Civil - Hôpitaux Universitaires de Strasbourg
1 place de l'hôpital
67000 Strasbourg - France
Mi-Young.Jeung@chru-strasbourg.fr

5: Catherine ROY
Service de Radiologie B
Nouvel Hôpital Civil - Hôpitaux Universitaires de Strasbourg
1 place de l'hôpital
Catherine.Roy@chru-strasbourg.fr

6: Mickaël OHANA
Service de Radiologie B
Nouvel Hôpital Civil - Hôpitaux Universitaires de Strasbourg
1 place de l'hôpital
67000 Strasbourg - France
mickael.ohana@gmail.com
@macromik

Images for this section:
Fig. 5: Strasbourg Chest Team !!!
References


