Computer-assisted Diagnosis for Early Stage Pleural Mesothelioma: Towards Automated Detection and Quantitative Assessment of Pleural Thickenings from Thoracic CT Images


Institute of Imaging and Computer Vision
RWTH Aachen University, 52056 Aachen, Germany
tel: +49 241 80 27860, fax: +49 241 80 22200
web: www.lfb.rwth-aachen.de

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Computer-Assisted Diagnosis for Early Stage Pleural Mesothelioma: 
Towards Automated Detection and Quantitative Assessment of Pleural Thickenings 
from Thoracic CT Images

K. Chaisaowong\textsuperscript{(1,2)}, P. Jäger\textsuperscript{(1)}, S. Vogel\textsuperscript{(3)}, A. Knepper\textsuperscript{(1)}, T. Kraus\textsuperscript{(4)}, and T. Aach\textsuperscript{(1)}

\textsuperscript{(1)} Institute of Imaging & Computer Vision, RWTH Aachen University, Germany
\textsuperscript{(2)} The Sirindhorn International Thai-German Graduate School of Engineering, King Mongkut’s Institute of Technology North Bangkok, Thailand
\textsuperscript{(3)} Chair for Medical Information Technology, RWTH Aachen University, Germany
\textsuperscript{(4)} Institute and Out-Patient Clinic for Occupational Medicine, University Hospital Aachen, Germany

Website:  http://www.lfb.rwth-aachen.de/en/projects/pleuramesothelioma/

Correspondence to:
Name: Dipl.-Ing. Kraisorn Chaisaowong
Address: Institute of Imaging & Computer Vision - Lehrstuhl für Bildverarbeitung
RWTH Aachen University
Templergraben 55
52056 Aachen
Germany
Tel.: +49 (241) 80-27862
Fax.: +49 (241) 80-22200
Email: Kraisorn.Chaisaowong@lfb.rwth-aachen.de
Summary

Objectives: Pleural thickenings as biomarker of exposure to asbestos may evolve into malignant pleural mesothelioma. For its early stage, pleurectomy with perioperative treatment can reduce morbidity and mortality. The diagnosis is based on a visual investigation of CT images, which is a time consuming and subjective procedure. Our aim is to develop an automatic image processing approach to detect and quantitatively assess pleural thickenings.

Methods: We first segment the lung areas, and identify the pleural contours. A convexity model is then used together with a Hounsfield unit threshold to detect pleural thickenings. The assessment of the detected pleural thickenings is based on a spline-based model of the healthy pleura.

Results: Tests were carried out on 14 data sets from 3 patients. In all cases, pleural contours were reliably identified, and pleural thickenings detected. PC-based Computation times were 85 min for a data set of 716 slices, 35 min for 401 slices, and 4 min for 75 slices, resulting in an average computation time of about 5.2 s per slice. Visualizations of pleurae and detected thickenings were provided.

Conclusion: Results obtained so far indicate that our approach is able to assist physicians in the tedious task of finding and quantifying pleural thickenings in CT data. In the next step, our system will undergo an evaluation in a clinical test setting using routine CT data to quantify its performance.

Keywords

Malignant pleural mesothelioma, pleural thickening, thoracic spiral computed tomography, computer-assisted diagnosis, automatic image processing algorithms.
1 Introduction

For almost a century, asbestos was widely used in the industrialized countries of Western Europe and Northern America [1][2][3][4], without its users being aware of the fibrotic and carcinogenic potential of inhaled asbestos fibers. As a consequence, malignant pleural mesothelioma, which normally is a rare tumor, was found thousand times more often in persons exposed regularly to asbestos during their daily work than in the normal population [5]. Today, it is statistically documented that 70-90% of malignant pleural mesotheliomata can be traced back to asbestos exposure. At least three decades elapsed until it came to a statutory prohibition, for instance in the year 1993 in Germany [6]. There are several types of asbestos, differentiated by their filament forms. The narrow and needle-like type (amphiboles such as crocidolite and amosite, the so-called blue asbestos) was classified to be more carcinogenic than the curled and pliable fibers of chrysotile, the so-called white asbestos, which is biologically more degradable and less harmful. Both types were widely applied in various industrial branches. Because of the industrialization after the Second World War, use of asbestos reached its maximum during the late 1970’s for example in Germany. Due to a long latency period of - on the average - 35 years (range between 10 to 60 years) after asbestos exposure, occurrence of malignant pleural mesothelioma morbidity and mortality in Germany is expected to peak during 2010s. Worldwide, asbestos related deaths are expected to rise in total to a million over the next 30 years [4].

At present in Germany, an assessment program is applied to the asbestos exposed group of persons. This assessment program includes thoracic CT imaging [7] for non-invasive diagnostics in high risk groups. Physicians usually have to manually investigate over 80 layers of thoracic images to find all kinds of pleural or pericardial thickenings. After diagnosis of malignant pleural mesothelioma, survival time was documented to be between 4 to 18 months without any therapy. For early stage pleural mesothelioma however, pleurectomy together with perioperative treatment can reduce the morbidity and delay the mortality [8]. Thus, efficient and reliable diagnosis of early stage pleural mesothelioma is a key factor to moderate the consequences of the expected peak of malignant pleural mesothelioma.

2 Objectives

A typical mesothelioma related clinical non-invasive diagnosis is based on thoracic axial CT images. Depending on the layer’s thickness, the number of images varies between 80 slices with a thickness of 5 mm to about 700 slices with a thickness of 0.5 mm. Physicians view each slice on a computer workstation in order to find pleural thickenings. A simultaneous second diagnostic aim is to find potential lung nodules. The diagnostic findings are documented in a standardized form containing data such as their size, position, and growth rate. This visual diagnostic approach is a very time consuming procedure, taking about 20 to 30 minutes per data set, and it is considered as often being subjective. Indeed, studies have shown that the inherent complexity of tumor measurements impair an accurate assessment [9]. Furthermore, differences in the diagnostic results were found between different investigating clinicians (inter-reader variability) [10]. To increase the accuracy of the localization and of the topological information of these quite small image regions within a subjective visual evaluation, an even longer investigating time would be needed for each data set. However, due to the increasing number of investigations and high work load of the physicians involved, this solution is not practicable. Therefore, a method is needed to provide a more accurate assessment of pleural mesothelioma at an early stage, which is reliable, consistent, and reproducible.

To date, worldwide only one solution based on a semi-automated method is available [11], which was applied to measure thickness of mesothelioma tumors. This method requires the manual
selection of a point along the outer margin of the tumor in a CT slice, followed by the application of an automated lung segmentation method. The aim of our work is to develop an image analysis system [12] to automatically detect and quantitatively assess pleural thickenings in axial thoracic CT images, hence without any interaction of the user during the calculation processes. For the therapy after a positive diagnosis of pleural mesothelioma, an accurate and reliable documentation of the evolution over time, such as growth rate, is essential.

3 Methods and Materials

Within a preventive medical assessment program, axial tomograms were acquired by a spiral CT for those patients where initial findings in a thorax radiograph required a follow-up diagnosis. The major steps of the developed image analysis system are [13][14]:

1. Segmentation of pleural contours,
2. Detection of potential pleural thickenings,
3. Identification of pleural thickenings,
4. Assessment of characteristic properties, and
5. 3D Visualization of pleural thickenings.

Within our system, algorithms are applied to process data on both 2D and 3D levels. Segmentation, detection and identification of the pleural thickening candidates are carried out slice-by slice on a 2D level, while classification and size measurements were done on a 3D level.

3.1 Segmentation of pleural contours

After loading the axial CT data set, segmentation of the pleural contours is carried out as follows:

**Lung tissue segmentation:** Based on the observation that in our data sets, lung tissue with Hounsfield units in the range between -180 to -910 HU is reasonably well separated from other, surrounding tissues such as fat ranging between -50 to -220 HU [15], a first estimate of the lung areas is obtained by thresholding at -550 HU. Spurious remaining artifacts are eliminated by consecutive application of morphological openings and closings [16][17]. Such artifacts due to, e.g., noise and vessels of up to $5 \times 5$ pixels are removed by threefold opening with a $3 \times 3$ structuring element, followed by twofold closing to compensate the segment boundary shifts caused by opening.

**Contour computation:** Within the resulting binary image, closed contours were computed using the following adjacency tree of connected components: background surrounds components, components may include holes and holes may, in turn, surround objects, and so on [18][19]. The adjacency tree thus describes the relation and hierarchy of connected regions - also called components - surrounding each other within a binary picture. While using the Freeman code to describe the local contour directions of lung tissue in binary pictures, connectivity in the regions of interest is described by a four-pixel neighborhood, so that both types of components do not overlap each other. The algorithm discriminates between the outer and inner contours of these regions. To ensure that the contours indeed describe the outer contour of thoracic tissues, only the outer contours of the white regions (the objects of interest) are taken into account for the subsequent determination of pleural contour. Outlines of the hole regions, hence, are rejected.

**Determination of pleural contour:** In addition to the sought lung boundaries, the contour computation algorithm also yields a variety of other closed contours, such as those of other, vessel-related regions, and the edges of the patient table (see Fig. 1). Usually, the sought pair of pleural contours is the largest among these. These are detected as the pair of contours whose bounding boxes exhibit the largest areas in comparison to any other existing bounding boxes. Since this
reasoning is valid for the central slices (between the 15-85 % of all available layers) of the data set, pleural contours are first identified in these, and then propagated towards the upper and the lower slices. In the latter, pleural contours are found as the contours with largest bounding boxes which share at least one point with the pleural boundary in the adjacent slice.

In slices of the lower thorax, the lung lobes may be connected. To detect the occurrence of connected lung lobes and to separate these, we first track all closed contours. Points encountered twice during this tracking process (except the starting point) must belong to two different closed contours which are linked via these points (see Fig. 2). The contour loops are then disconnected in a subsequent step at these positions. A second, related problem is the connection of the segments of the two lung lobes via a constriction (see Figs. 3a, b). These bottleneck-like constrictions are detected by seeking pairs of contour points whose Euclidean distance is low (here less than 15 pixels), while their distance along the contour is large (here larger than a quarter of the total contour length). Such point pairs are then linked by a straight line (see Figs. 3c, d) to separate the contours (see Figs. 3e, f).

As shown in Figure 1, the lung contours exhibit a rather smooth shape except for the boundary along mediastinum and bronchus. Since this irregular shape would make the subsequent detection of pleural thickenings more difficult, while at the same time pericardial tumorous infiltrations are very rare, the detected contour along mediastinum and bronchus is replaced by a straight line, as shown in Figure 4.

3.2 Detection of potential pleural thickenings

From this stage on, the contour of healthy pleura can be modeled as being convex shaped. Pleural thickenings appear as concave irregularities on the outer surface of the three-dimensional convex pleural model, which locally violate convexity. Candidate pleural thickenings thus are those points, where connection lines between pairs of contour points traverse the outside of the detected pleural contour.

The convex hull of a set of points, in this case the lung tissue, is the smallest convex set that geometrically includes all points of that set [20][21]. For a two-dimensional set of points, the convex hull can be represented by a convex polygon. In comparison to the detected pleural contour, the convex hull then is the smallest convex polygon, which envelopes the pleural contour totally. Finding the convex hull is equivalent to a sorting task. Given a set of points on a plane, those points composing the convex hull need to be found, whereas the composed convex hull must contain all remaining points. The algorithm must identify points that are not part of the hull as efficiently as possible. The algorithm hence has to search the points with the maximum and minimum coordinates, since these points must be on the hull. Finding the maximum and minimum of coordinates corresponds to sorting the coordinates of those points. The QuickSort algorithm is employed for this process, which solves the task with $O(n \log n)$ operations, where $n$ is the number of points. Once the convex hull is found, candidate pleural thickenings are found by calculating the difference between the new convex hull and the existing contour (see Fig. 5).

3.3 Identification of pleural thickenings

The above procedure provides a set of candidates for pleural thickenings, from which the subset of actual pleural thickenings is selected according to the following criteria:
1. A pleural thickening extends over several slices. A candidate thickening therefore can only form a pleural thickening if it extends over at least three slices.
2. Pleural thickenings consist of tumorous connective tissue, whose Hounsfield values range between 20 to 60 HU, sometimes impregnated with calcium carbonate. A candidate region is classified as a pleural thickening only if at least 10 percent of its voxels exhibit a Hounsfield unit
larger than a given threshold. With fat, as mentioned above, ranging between -220 HU to -50 HU, this threshold is set to 10 HU.

### 3.4 Assessment of characteristic properties

The above detection procedure provides information such as the position of each pleural thickening and the number of pleural thickenings found. To determine characteristic values of each pleural thickening, such as maximal width and volume of the thickening, a more accurate model of pleura without pleural thickenings is locally needed. Based on this pleura model, the necessary comparisons and calculations of these characteristic values can be made. To create this model, the pleural contour is refined by a more sophisticated interpolation replacing the linear interpolation originating from the convex hull calculation at those locations where pleural thickenings were detected. The interpolation is based on a thin plate spline model [22][23], which is reported to be suitable for the deformation of biological tissues [24]. A result is shown in Figure 6.

#### The thin plate spline

Let $f$ be a function from $\mathbb{R}^2$ to $\mathbb{R}$, which has square integrable second derivatives, and let $\Omega = \{ \bar{x}_i : i = 1, 2, ..., n \}$ be a finite set of constraint points in $\mathbb{R}^2$ which are all different and which are not collinear. Then the thin plate spline interpolant to $f$ on $\Omega$ is the function $s(\bar{x})$, which minimizes the integral [23]

$$J(s) = \int_{\Omega} \left[ \left( \frac{\partial^2 s}{\partial x^2} \right)^2 + \left( \frac{\partial^2 s}{\partial x \partial y} \right)^2 + \left( \frac{\partial^2 s}{\partial y^2} \right)^2 \right] d\bar{x}$$

subject to the interpolation conditions $s(\bar{x}_i) = f(\bar{x}_i), i = 1, 2, ..., n$.

The energy function $J(s)$ measures the smoothness of a function $s$. This energy function is basically a measure of the aggregate curvature of $s(\bar{x})$ over the region of interest $\Omega$ (a portion of the plane). Creases or pinches in a surface will result in a larger value of $J(s)$. A smooth function that has no such regions of high curvature will have a lower value of $J(s)$. Note that because there are only squared terms in the integral, the value for $J(s)$ can never be negative. The thin-plate solution to an interpolation problem is the function $s(\bar{x})$ that satisfies all of the constraints and that has the smallest possible value of $J(s)$ [22]. We may also say that the function $s(\bar{x})$ has minimum bending energy. The thin plate spline is the two-dimensional analog of the cubic spline in one dimension [25], which we have applied in our algorithm. In our case, we decided to use the beginning and ending pixels as well as each two further neighboring pixels of the found pleural thickening as altogether six constraint nodes [26].

### Determination of pleural thickening's volume

There is no pathophysiological basis for the assumption that the determined thickening’s volume would be dependent on the respiratory phase, in which the CT images have been recorded. Moreover, as a pleural thickening is a fibrous connective tissue, its volume does practically not change with pleural motion. In each slice, the area occupied by a pleural thickening is given by the number of pixels lying between the interpolated pleura contour and the pleural thickening boundary, multiplied by the pixel size (see Fig. 7). The corresponding volume is calculated by multiplying with the slice thickness. Integration of these volumes over the slices, on which the investigated pleural thickenings are lying, yields the total pleural thickening’s volume. The necessary parameters, such as pixel size and slice thickness, are taken from the DICOM data header [27].

### 3.5 3D Visualization of pleural thickenings
One possibility to visualize the thickenings is to render a 3D image of the pleural hull. The segmented pleura is approximated by triangulation invoking the Marching Cubes algorithm [28]. Our visualization uses the Open Graphics Library (OpenGL) [29].

4 Results

Tests were carried out on 14 real data sets acquired from 3 patients. In all cases, pleural contours were reliably identified, visualized, and pleural thickenings were detected. Table 1 shows the number of CT-data and the number of patients which we analyzed. The tests were run on a PC using an Intel Pentium® processor at 2.80 GHz with 1.00 GB RAM. The operation system was WindowXP®. Table 2 lists the computation times needed. Figure 8 depicts results for an original CT image of the upper thoracic level. The first row shows on the left the original CT-slice, and on the right the binary image after thresholding to detect the lung area. Bronchi and pulmonary airways remain visible in the lung area. The subsequently found pleural contours are shown on the left in the middle row, while its right-hand side shows the lung contours after replacing the contour part along mediastinum and bronchus by a straight line. The last row depicts on its left side the detected concavities, and on the right the concavities actually classified as pleural thickenings. Note that the classification algorithm in its present form does not utilize information about the position of the detected pleural thickenings, what leads to a misclassification of a concave area near the spinal cord: here, a larger, concave thickening appears with Hounsfield units in the critical range, which is classified as a pleural thickening. Such classification errors are, however, easily removed in future versions by additionally taking into account position information of the detected thickenings. Figure 9 shows other results for a CT slice from the lower thoracic level of another patient.

The pleura can be visualized as 3D volume model, which, in addition to a visualization of the detected thickenings, allows the interactive examination of a patient’s pleura. An example is shown in Figure 10.

5 Conclusions and Discussions

We described an image analysis system to automatically detect pleural thickenings and assess their characteristic values from patients’ thoracic spiral CT images. Algorithms are described to carry out the segmentation of pleural contours and to find the pleural thickenings. A subsequent algorithm was applied to automatically detect the pleural thickenings. In order to assess the growth rate of found pleural thickenings, a model of healthy pleura was created. Based on this healthy model, the size of the pleural thickenings was calculated. The graphical user interface allows also 3D visualization of the pleura to ease clinical interaction. The aim of the visualization is to facilitate the visual pre-investigation for the physician. The visualization even represents a quick instrument to give an overview of the state of the lung pleurae.

The results presented above are promising and indicate that our approach is able to assist physicians in the tedious task of finding and quantifying pleural thickenings in CT data. In the next step, the workstation will undergo an evaluation in a clinical test setting using routine CT data. Since histopathological findings from living patients are not available, we will seek to quantify its performance with respect to the detection of pleural thickenings as well as to measurements of their sizes in comparison to experienced physicians. Future algorithmic extensions, e.g. towards a direct 3D approach, as well as extensions of the user interface will depend on the outcome of this study.
Furthermore, an oncopathological assessment of the growth of a patient’s pleural thickenings is also desirable to provide an analysis of the morbidity. This requires the spatiotemporal matching of data, that means axial CT sets of the same patient taken at different points in time are to be matched (or registered). A first approach towards this end currently under development will consider the following degrees of freedom: translations along the three Cartesian axes, rotations around vertical and sagittal axes, and scaling of transversal, sagittal, and vertical axes caused by breathing.

References

Fig. 1: Result of thresholding, artifact removal and contour computation. White lines show remaining contours.
Fig. 2: a) Pleural contours of the right and the left lung may be joined together as shown within the circle. b) Point to be disconnected. c) and d) The right and the left lung after separation.
Fig. 3: a) Pleural contours of the left and the right lung may be joined via a bottleneck-like constriction as shown within the circle. b) Magnification of this area. c) A direct line connects adjacent points. d) Enlarged view. e), f) Application of the lung separation algorithm (see text).
Fig. 4: The pleural contour, with a line replacing the part along mediastinum and bronchus.

Fig. 5: Candidate pleural thickenings are the concave differences from the pleural convex hull, which is formed by a convex polygon.
Fig. 6: A delineated pleural thickening (outer contour) together with the pleural boundary behind the thickening as interpolated by a thin plate spline.

Fig. 7: Area and volume calculation of a pleural thickening in one slice, delineated by the outer contour, based on the interpolated contour behind the thickening. For the pleural thickening shown here, the area in this slice is 8.23 $mm^2$, its maximum thickness is 1.77 $mm$, and its total volume 6.60 $mm^3$, which was calculated over connecting slices.
Fig. 8: Original CT slice (a) from an asbestos exposed patient. After finding the pleural contours (b,c,d), concavities were detected (e). The thickenings which are finally classified as genuine pleural thickenings are shown in (f). The light gray color shows pleural thickenings with HU value larger than 10, and the dark gray color shows HU value smaller than 10.
Fig. 9: Original CT slice (a) of the lower thoracic level from another asbestos exposed patient. The pleural contours were segmented (b,c,d), concavities were detected (e). The pleural thickenings are determined (f).
Fig. 10: Three-dimensional visualization of the pleura. Pleural thickenings appear as concave depressions.
<table>
<thead>
<tr>
<th>Total number of CT-data</th>
<th>14 data sets</th>
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<tr>
<td>Total number of patients</td>
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</tr>
<tr>
<td>Sex</td>
<td>male</td>
</tr>
<tr>
<td>Number of patients undergoing second investigation</td>
<td>3 persons</td>
</tr>
<tr>
<td>Range of CT-acquisitions on the first investigation per each patient</td>
<td>1-4 sessions</td>
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<tr>
<td>Range of CT-acquisitions on the second investigation per each patient</td>
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<tr>
<td>Range of number of slices per each session</td>
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**Table 1: Data of the CT scans used for the evaluation.**

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<th>Computation time per one slice</th>
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<td>data set of 401 slices</td>
<td>35 min</td>
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<tr>
<td>data set of 716 slices</td>
<td>85 min</td>
<td>7.1 s per slice</td>
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| Total average computation time per one slice  | 5.2 s per slice |

**Table 2: Computation times needed for three example data sets.**