Detection, modeling and matching of pleural thickenings from CT data towards an early diagnosis of malignant pleural mesothelioma

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ABSTRACT

Pleural thickenings can be caused by asbestos exposure and may evolve into malignant pleural mesothelioma. While an early diagnosis plays the key role to an early treatment, and therefore helping to reduce morbidity, the growth rate of a pleural thickening can be in turn essential evidence to an early diagnosis of the pleural mesothelioma. The detection of pleural thickenings is today done by a visual inspection of CT data, which is time-consuming and underlies the physician's subjective judgment. Computer-assisted diagnosis systems to automatically assess pleural mesothelioma have been reported worldwide. But in this paper, an image analysis pipeline to automatically detect pleural thickenings and measure their volume is described. We first delineate automatically the pleural contour in the CT images. An adaptive surface-base smoothing technique is then applied to the pleural contours to identify all potential thickenings. A following tissue-specific topology-oriented detection based on a probabilistic Hounsfield Unit model of pleural plaques specify then the genuine pleural thickenings among them. The assessment of the detected pleural thickenings is based on the volumetry of the 3D model, created by mesh construction algorithm followed by Laplace-Beltrami eigenfunction expansion surface smoothing technique. Finally, the spatiotemporal matching of pleural thickenings from consecutive CT data is carried out based on the semi-automatic lung registration towards the assessment of its growth rate. With these methods, a new computer-assisted diagnosis system is presented in order to assure a precise and reproducible assessment of pleural thickenings towards the diagnosis of the pleural mesothelioma in its early stage.

Keywords: Malignant pleural mesothelioma, pleural thickening, thoracic computed tomography, computer-assisted diagnosis, automatic image processing algorithms, semi-automatic registration, spatiotemporal matching, modeling

1. INTRODUCTION

It is well proven that 70%-90% of occurrences of pleural mesothelioma, high-grade malignant tumors of the pleura, can be traced back to asbestos exposure. After a statutory prohibition in the year 1993 in Germany, occurrence of malignant pleural mesothelioma morbidity and mortality in Germany is expected to peak during 2010s, due to a long latency period of - on the average - 35 years. In addition, an early diagnosis of pleural mesothelioma is crucial for extending the patient's life expectancy. In case of lack of a proper treatment, the disease can rapidly lead to the patient's death.

Pleural thickenings (Fig. 1) caused by asbestos exposure may evolve to aggressive pleural mesothelioma [1]. For non-invasive diagnostics, they can be identified by inspecting CT-data of the patient’s thorax. Depending on the layers’ 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. The physician inspects each slice on a workstation in order to find pleural thickenings. This procedure is very time-consuming, taking about 20 to 30 minutes per data set, and underlies inter-reader and intra-reader variability [2].

Worldwide, only semi-automated systems which carry out computerized segmentation and measurement of malignant pleural mesothelioma are reported [3]. Moreover, the integration of computer-assisted volumetry of malignant pleural mesothelioma during a therapy is absolutely essential [4]. Therefore, to increase the accuracy of the localization and of the topological information of these quite small image regions within a subjective visual evaluation, a computer-aided diagnosis (CAD) system towards the automated detection of pleural thickenings within CT data is needed. In this work, a pipeline based on a tissue-specific detection has been developed, allowing the 3D segmentation of pleural thickenings from the surrounding thoracic tissue. Together with 3D assessment, the developed tool includes follow-up observations to provide change detection with precise volumetry to facilitate the diagnosis of pleural mesothelioma in its early stage.

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2. METHODS

In order to improve the precision and reproducibility of both the detection and follow-up assessment of the pleural thickenings towards an early diagnosis of a malignant pleural mesothelioma, a new workflow to automatically detect as well as match pleural thickenings from consecutive CT data is proposed (Fig. 2). A 3D detection technique based on a tissue-specific classification has been developed, allowing the segmentation of pleural thickenings from the surrounding thoracic tissue. 3D volumetry provides physicians necessary information onwards the follow-up observations which is based on a semi-automatic registration. After the matching step, physicians can make decision on the change follow-up table from the algorithmic process and therefore still have control on the software output whether or not a pleural thickening has gained its volume increase. Details of each step will be given in this section.

Figure 1. An example of a pleural thickening which was automatically detected (marked with green contours) through the implemented algorithm on a CT slice from each of the consecutive CT data sets from the same patient. Pleural thickenings as biomarker of exposure to asbestos may evolve into malignant pleural mesothelioma. Observation on any change over time is essential to the diagnosis of malignant pleural mesothelioma in its early stage. A decisive diagnosis, in turn, plays the key role on its consequential treatment and therapy.

Figure 2. Schematic view of the semi-automatic workflow to detect and assess pleural thickenings as well as follow-up their change in consecutive CT data from the same patient. Except one single semi-automatic algorithmic step, all other implemented methods are based on fully automatic processing. Only the registration step requires the manual definition of anatomic fix points from lung to map consecutive lung data into the same matching space towards the change follow-up of the detected thickenings.
2.1 Automatic detection of pleural thickenings

2.1.1 Delineation of pleural contour

The delineation of the pleural contours is done by 2-steps-application of the supervised range-constrained Otsu thresholding using 3D CT data to first extract thorax, and then pulmonary organs therein [5]. Classification of that pulmonary region leads to the removal of trachea and bronchi [6]. Contour refinement via 2D contour relaxation removes motion artifacts and partial volume effects (Fig. 3). The resulting 3D model of the pleura is used as the input for the next step.

![Figure 3. The 2-steps-application of the supervised range-constrained Otsu thresholding using 3D CT data (from left to right) led to the extraction of thorax, and then pulmonary organs therein. Classification of that pulmonary region (most right image) leads to the removal of trachea and bronchi.](image)

2.1.2 Tissue-specific 3D segmentation after the topology-oriented anisotropic diffusion smoothing

The adaptive surface-based smoothing takes the assumption of the convexity of the contour surface into account, since pleural thickenings can be understood as fine-scale occurrences on the rather large-scale pleural surface [7]. The smoothing algorithm creates a convex “healthy” volume model of the pleura. Concave differences between the healthy model and the original data are considered to be candidate of pleural thickenings (Fig. 4).

The topology-oriented anisotropic diffusion smoothens the region-of-interest of each initially detected thickening, which is enhanced with a topology-oriented conduction coefficient function due to the influence of the directional topology of each thickening in order to enable additional smoothing along the local orientation of each thickening.

For a tissue-specific segmentation of pleural thickenings, a probabilistic Hounsfield Unit model for pleural plaques was constructed, using “virtual” biopsy data manually excerpted by a professional physician. The resulting intensity distribution of pleural plaques was then modeled by a finite mixture of Gaussian distributions (Fig. 5). The parameters were estimated by applying the Expectation-Maximization algorithm. The consequent application of a model fitting technique then allows an initial tissue-specific segmentation of pleural plaques from the surrounding thoracic tissue.

![Figure 4. Lung surface before and after the adaptive surface-based smoothing and the differences as initial thickenings.](image)
Figure 5. The tissue-specific probabilistic Hounsfield Unit model $p(Y|P=\text{Plaques})$ for pleural plaques (upper left) classifies within a region of interest (upper right) against the probabilistic Hounsfield Unit model $p(Y|T=\text{Thorax})$ of thorax tissue (lower left) after the topology-oriented anisotropic diffusion smoothing each pixel to thickening tissue $X=1$ (red-colored) or not $X=0$ (blue-colored zero value) (lower right).

2.1.3 Multiple refinement of the detected thickening

Markov random fields are widely used in medical image processing applications as they are particularly useful in image segmentations because they take into account the labels of neighboring elements to classify the element under consideration. In this step, a 3D Gibbs-Markov random field model is introduced to be applied on the initial tissue-specific segmentation result of the previous step in order to achieve a high precision segmentation of pleural plaques.

For this purpose, a 3D neighborhood has been introduced, where each center point has 26 neighbors. Based on the selection of the second order neighborhood, configurations of each two-points clique are defined (Fig. 6). While each CT slice is an equidistant grid, the distance between layers varies according to the number of existing slices; therefore the 3D distance-weighted factor for each clique configuration has to be adjusted correspondingly [8].

At the same time to achieve the most reliable result, 2D Gibbs-Markov random field is applied as well. At the final end, both refinement results will then be merged together.
2.2 Quantitative assessment

Since detected pleural thickenings are excerpt from CT slices, the volumetry of each detected pleural thickening requires therefore a 3D volume model. Mesh construction algorithm followed by surface smoothing is applied to create a close-to-reality 3D model of each detected pleural thickening and to overcome difficulty in constructing a complex branch structure. The volume of smoothed mesh model is then calculated by mean of the divergence theorem and representing volume of each detected pleural thickening.

2.2.1 Mesh construction

For the mesh construction, various mesh algorithms exist. The marching cube algorithm can lead to the reconstructed volume close to the original voxel-based structure [9]. The cuberille (opaque cubes) technique is based on an idea to have vertices and faces of a surface to represent a volumetric data [10][11]. In the view of shape, another technique such as thin plate spline can be used to create a simple thickening structure [12][13], but cannot handle a complex branch structure.

2.2.2 Smoothing technique

An optimal number of eigenfunctions in comparison to the number of vertices from the starting mesh structure as bases for the smoothing technique Laplace-Beltrami eigenfunction expansion has to be found out [14][15], where both the smoothness of the re-constructed model as well as a close-to-reality appearance of the model are the main criteria together with minimal volume difference from the original voxel-based volume.

2.2.3 Volumetry

In computational geometry, the volume of the closed surface of a polyhedron can be calculated from the divergence theorem which is the direct generalization of Green’s Theorem from 2D to 3D [16].

2.3 Spatiotemporal matching of pleural thickenings

Since the assessment of the growth of pleural thickenings is crucial for an early diagnosis of pleural mesothelioma, detected pleural thickenings in two temporally consecutive CT data-sets have to be compared to each other. In order to support the physician in comparing the same pleural thickening amid a number of detected pleural thickenings, spatiotemporal matching of each correct pair of pleural thickenings in two temporally consecutive CT data-sets has to be carried out through the implemented methods as well.

2.3.1 Semi-automatic lung registration

Sophisticated automatic registration technics indeed exist, requires however enormous computation time and hence leads to a longer processing time. The general idea of using barely moving bone structures like rips for a horizontal alignment is promising, and leads to the implementation of a real time semi-automatic landmark-based lung registration. Based on a manual definition of significant anatomic landmarks e.g. the Carina trachea, the Processus spinosus as well as lung borders, the transformation parameters are determined (Fig. 7). A non-rigid transformation with eight degrees of freedom was proposed, i.e. translation in x (transversal), y (sagittal), z (vertical), rotation around y, z and linear scaling in x, y, z [17]. The rotation around x can be ignored because the table, on which the patient is lying during the examination, prevents the body from moving around the transversal axis.
Figure 7. Principle of the implemented semi-automatic registration. In order to bring two consecutive CT data of lung into the same matching space, specific anatomic fix points such as Carina trachea (red hair cross) and Processus spinosus (green hair cross) are required to calculate the parameters for translation in x, y, and z and rotation around z axis, as well as the reconstruction of the horizontal cut to calculate the rotation of the sagittal plane (white line) around the y axis.

2.3.2 Matching through principal components analysis

Since physicians have to observe change of each thickening over time, manual follow-up can be interpreted as intertemporal collision of thickenings. For this purpose, axis aligned bounding box is applied while minimum principle components of an object is calculated [17]. Since CT data might not have the same spacing either for pixel spacing or slice spacing; only the maximum spacing will be taken into account. Moreover, pleural thickenings can be growing and overlap each other, the possibility that two or more thickenings are matched to the same thickening in the follow-up scan is guaranteed through the maximization of overlapping volume between the group of baseline and target thickenings.

3. RESULTS

Initially detected pleural thickenings are the difference between the original pleural contours and the “healthy” model created by the ASBS algorithm (Fig. 8). Subsequently, bounding box of each initial detected pleural thickening was considered as Region of Interest (ROI) for the next step. These ROIs are filtered through the orientation-based anisotropic diffusion. Initial labeling of each pixel within a ROI was then carried out through the reported issue-specific 3D segmentation, where thickening hypothesis has been tested against the residual thorax affinity.

Afterward, a 3D Gibbs-Markov random field model was applied on the initial tissue-specific segmentation result of the previous step in order to achieve a high precision segmentation of pleural plaques, so that the volume dependency on neighboring pixels within a 3D thickening can be taken into account. At the same time, 2D Gibbs-Markov random field relaxation was also applied since 2D connectedness of pixels within a 2D thickening appears to preserve the border on the same slice. The consequential superimposition of the both proposed contour relaxations determined finally the transition between the thickening and the surrounding thoracic tissue (Fig. 9).

For a fine scale detailed validation of the detection algorithms, 27 slices of pleural thickenings, marked by physician consisting of 4116 manually segmented pixels, were used. All thickenings were detected correctly. Difference reveals by the circumference of the detected contour, which appears mostly smaller than the gold standard and hence hits apparently the percentage detection rate evaluated by the number of pixels. 2147 pixels (52.16%) from the gold standard are detected correctly, while 96 pixels (4.28%) are wrongly detected (Tab. 1).

The experiment on 3D modeling reveals that using only 10-50% of the maximum eigenfunctions which is limited by the number of vertices from the starting mesh structure as bases via Laplace-Beltrami eigenfunction expansion yields the desired smoothness of the model as well as a-close-to-reality of the model with volume different less than 5% (Fig. 10). No matter either marching cube or cuberille mesh construction algorithm was applied, subjective appearance of
reconstructed and smoothed was satisfying surveyed physicians. Marching cube mesh construction algorithm however promises the most accuracy in term of the average Euclidean distance to the original mesh and the volume difference thereafter.

Table 1. Evaluation of the implemented detection algorithm using the combination of 2D and 3D Gibbs-Markov random field relaxation at the end of the detection step using a sample of 27 slice-wise thickenings containing 4116 pixels.

<table>
<thead>
<tr>
<th>Gold standard</th>
<th>Detected number</th>
<th>Detection rate</th>
</tr>
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<tbody>
<tr>
<td>27 slice-wise thickenings</td>
<td>27 slice-wise thickenings</td>
<td>100.00%</td>
</tr>
<tr>
<td>4116 pixels</td>
<td>2147 true positive pixels</td>
<td>52.16%</td>
</tr>
<tr>
<td>4116 pixels</td>
<td>96 false positive pixels</td>
<td>4.28%</td>
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</table>

For the validation of the matching algorithm, two CT data sets containing 68 baseline thickenings (40 in the left and 28 in the right lung) and 81 follow-up thickenings (47 left and 34 right) has been used (Fig. 11). After the semi-automatic lung registration, thickenings are matched together versus manual comparison. Both sensitivity and specificity of 98% has been reached, while the accuracy was 76% (Tab. 2). For the matching using principal components analysis, the larger the tolerance the better the sensitivity, but the lower becomes the accuracy.

Repeating tests have been carried out to observe the influence of the manual definitions of anatomic fix points on the semi-automatic lung registration. There was no difference on the matching results after repeating the marking of required anatomic fix points.

Table 2. Evaluation of the implemented mapping technique based on principle components analysis.

<table>
<thead>
<tr>
<th>Mapping technique</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
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<tbody>
<tr>
<td>Principal components</td>
<td>98.46%</td>
<td>98.97%</td>
<td>76.19%</td>
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Figure 8. An example of a CT slice before and after automated detection of the bump-like pleural thickenings along lung border. Intrusive pulmonary indentation next to spinal cord is obviously a wrong detection, but it meets all implemented detection criteria of a pleural thickening.
4. CONCLUSIONS AND DISCUSSION

This paper proposes comprehensive computer-aided diagnosis algorithms for the detection, assessment, as well as matching of pleural thickenings from consecutive 3D CT data at different point in time. This method comprises fully automatic algorithm for both detection and assessment step, while the matching of the detected pleural thickenings was carried out automatically as well, however based on a semi-automatic registration of the 3D lung model. This step required solely the manual definition of selected anatomic fix points.

A new algorithmic pipeline to automatically detect pleural thickenings from CT data is developed in order to improve the precision and reproducibility of the diagnosis. For a further more fine-scale detection, a tissue-specific segmentation following by both 3D and 2D relaxation was executed. A close to reality 3D modeling is carried out via mesh construction followed by smoothing Laplace-Beltrami eigenfunction expansion. In order to follow-up the change, detected thickenings at different point-in-time can be automatically matched together as well, after the semi-automatic lung registration of two CT data.

While the results of fine scale evaluation yield 100% of true positive detected thickenings in comparison to gold standard, overall results however still include errors such as the inclusion of the tissue indentation through spinal cord as displayed in Fig. 8. This leads to the suggestion that an enhancement of the lung model with anatomic information might help reducing such a wrong thickening when anatomic position of detected thickening apparently does not belong to the anatomic part which would come into question. Moreover, discrepancy of pixel-wised detected true positive rate demands a new delineation strategy of each thickening in order to enhance the reliability of the volumetry.

The final target of this development is to create a fully automated system to observe change of pleural thickening from consecutive CT data from the same patient. Therefore, a registration using automatic approach has to be tested and integrated into the algorithmic pipeline with acceptable runtime.
Together with these working points to improve outcome reliability, clinical test with larger number of CT data sets is also inevitable.

Figure 10. 3D model of a simple (L104-2001) and a complex (L107-2001) pleural thickening. Both marching cube (upper row) and cuberille (lower row) mesh structure was initially applied then smoothed through Laplace-Beltrami eigenfunction expansion algorithm involving approximately 14% of eigenfunctions, namely 64 out of 865 eigenfunctions, resulting in volume difference less than 5% in comparison to the solely voxel-based volumetry.

Figure 11. Pleural thickenings from baseline (green) are mapped to those from follow-up CT (red), where the overlap (yellow) is shown after automatic matching via intertemporal collision of principle components in case that the thickening was detected.
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