RadioGraphics

Informatics in Radiology (*info*RAD)

New Tools for Computer Assistance in Thoracic CT Part 2. Therapy Monitoring of Pulmonary Metastases[1]

Lars Bornemann, Dipl CS • Jan-Martin Kuhnigk, Dipl CS • Volker Dicken, PhD • Stephan Zidowitz, PhD • Bernd Kuemmerlen, Dipl Phys Stefan Krass, PhD • Heinz-Otto Peitgen, PhD • Berthold B. Wein, MD Henning Schubert, MD • Hoen-oh Shin, MD • Dag Wormanns, MD

Owing to the rapid development of scanner technology, thoracic computed tomography (CT) offers new possibilities but also faces enormous challenges with respect to the quality of computer-assisted diagnosis and therapy planning. In the framework of the Virtual Institute for Computer Assistance in Clinical Radiology cooperative research project, a software application was developed to assist the radiologist in the analysis of thoracic CT data for the purpose of evaluating the response to tumor therapy. The application provides follow-up support for monitoring of tumor therapy by means of volumetric quantification of tumors and temporal registration. In addition, anatomically adequate three-dimensional visualization techniques for convenient examination of large data sets are included. With close cooperation between computer scientists and radiologists, the application was tested and optimized to achieve a high degree of usability. Several clinical studies were carried out, the results of which indicated that the application improves therapy monitoring with respect to accuracy and time required.

Abbreviations: RECIST = Response Evaluation Criteria in Solid Tumors, 3D = three-dimensional, 2D = two-dimensional, VOI = volume of interest

RadioGraphics 2005; 25:841–848 • **Published online** 10.1148/rg.253045163 • **Content Codes:** CH CT HP

[1]From the MeVis Center for Medical Diagnostic Systems and Visualization, Universitaetsallee 29, 28359 Bremen, Germany (L.B., J.M.K., V.D., S.Z., B.K., S.K., H.O.P.); the Department of Diagnostic Radiology, RWTH Aachen University Hospital, Aachen, Germany (B.B.W., H. Schubert); the Department of Diagnostic Radiology, Medical School Hannover, Germany (H. Shin); and the Institute for Clinical Radiology, University Hospital Muenster, Germany (D.W.). Presented as an *info*RAD exhibit at the 2003 RSNA Scientific Assembly. Received April 7, 2004; revision requested June 30 and received August 20; accepted September 10. Supported by grant 01EZ0010 from the German Federal Ministry of Education and Research. All authors have no financial relationships to disclose. **Address correspondence to** L.B. (e-mail: *bornemann@mevis.de*).

See Kuhnigk et al in the March 2005 issue of *RadioGraphics* (pp 525–536) for Part 1 of this two-part series of articles.

Introduction

The influence of the progress in the image quality of thoracic computed tomography (CT) over the last few years has already been discussed in Part 1 of this two-part series of articles (1).

Because of the described rapid development of scanner technology, thoracic CT offers completely new possibilities but also faces enormous challenges concerning the quality of computer-assisted diagnosis and therapy planning. In the framework of the German VICORA (Virtual Institute for Computer Assistance in Clinical Radiology) research collaboration (2,3), applications were developed that offer solutions in the following areas of thoracic CT: *(a)* improved CT-based functional diagnosis with quantitative CT parameters for each lobe and segment and methods for quantification and classification of emphysema, *(b)* examination of large data sets by means of anatomically adequate three-dimensional (3D) visualization techniques, and *(c)* follow-up of tumor therapy by volumetric quantification of tumors and temporal registration. These functionalities are implemented in two new prototypical applications: MevisPULMO for functional analysis of pulmonary CT data (1) and PulmoTREAT for allowing therapy monitoring in metastatic lung disease.

TAKE-HOME POINTS

- The prototypical software application PulmoTREAT assists the radiologist in the analysis of thoracic CT data for the purpose of evaluating the response to tumor therapy.
- A fast automatic segmentation and volumetry method for lung nodules was developed that is robust and fast with reproducible results in cases of large, irregular nodules that are connected to other structures.
- By using marker registration, automatic comparison of nodule volumes, calculation of doubling times, and report generation, the examination is more convenient and faster than RECIST measurement.
- Estimation of nodule growth by means of 2D measurements is associated with some pitfalls.

In this article, we discuss the motivation for the development of PulmoTREAT, describe the use of PulmoTREAT, and provide the results of evaluations of PulmoTREAT.

Motivation

When one considers that lung cancer is the leading cause of cancer death (an estimated 160,440 deaths and an estimated 173,770 new cases in 2004 in the United States [4]), it becomes apparent that accurate monitoring of therapy response is of particular importance.

Although surgery is the treatment of choice for many localized cancers, in many cases the disease has already spread by the time of discovery. In those cases, radiation therapy and/or chemotherapy are mostly performed. Since these treatment options are expensive and associated with severe stress for the patient, it is necessary to evaluate the success of the treatment as reliably as possible and change poorly performing therapy options as soon as possible.

A key indicator for the success or failure of treatment and, thus, for continuation or modification of the current therapy is tumor growth. Given that most thoracic CT scans provide a large number of sections (about 400–500), it is prohibitive to measure the volume of each nodule manually. Therefore, according to current World Health Organization (WHO) and RECIST (Response Evaluation Criteria in Solid Tumors) (5) criteria, nodule growth is estimated by measuring the largest axial diameter of the largest nodules and observing the change of those parameters in two CT scans performed within an interval of 3–6 months. A diameter increase of 20% indicates progressive disease and implies modification of the treatment. In contrast, a nodule diameter decrease of 30% indicates therapy success. Unfortunately, the quantification of a 3D object by measuring a two-dimensional (2D) parameter implies some pitfalls.

First, deducing the growth of a spherical nodule from a 2D parameter change means that—considering the RECIST thresholds—the nodules have already grown in volume by 70% (equivalent to a 20% diameter change) before the failure of therapy is recognized. Second, this method assumes that oncologic lung nodules tend to grow symmetrically, which is not always valid. Third, both finding the section with the largest diameter and measuring it might be difficult—especially for complex, nonspherical nodules—and therefore this process is subjective and error-prone.

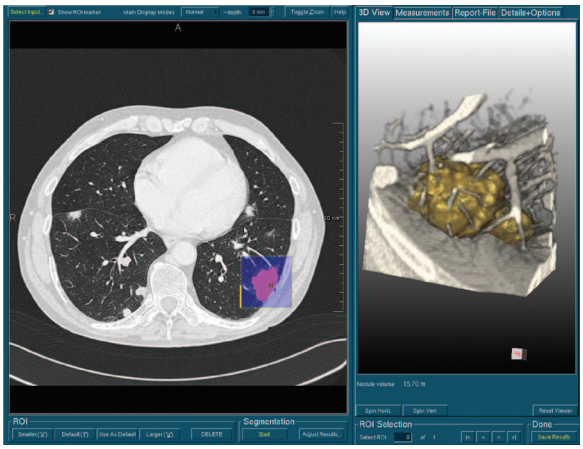

Figure 1. Baseline scan mode of PulmoTREAT. The user can slice through the image data (left) and identify nodule positions with the mouse. The segmentation of the currently selected nodule can be roughly verified in a zoomed 3D view (right).

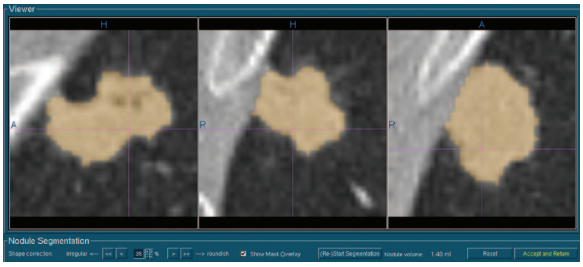

Figure 2. Convenient correction of nodule segmentation in PulmoTREAT. In the "adjust results" panel, the radiologist can obtain a more detailed view of the segmentation in three orthogonal viewers, which show sagittal (left), coronal (center), and axial (right) images. The segmentation can be easily modified by adapting a single shape correction parameter.

Finally, it is still a tedious and time-consuming job to find and measure the largest axial diameter of even a few nodules manually.

Therefore, it is important to have a software tool that supports decision making in treatment planning and monitoring with respect to convenience, accuracy, and time consumption.

At present, some commercial tools are available for tumor volumetry and follow-up in the lung (eg, by manufacturers such as R2 Technology, Siemens Medical Solutions, GE Healthcare, and Philips Medical Systems). However, these tools were designed predominantly for screening purposes, concentrating on the segmentation of small spherical nodules. The segmentation of large, irregularly shaped nodules connected with other structures of similar density (pleura, vessels) does not work sufficiently well in many cases or only with high effort and user interaction.

PulmoTREAT

The application prototype "PulmoTREAT" (*TREAT* = tumor therapy response evaluation tool), presented in this article, allows robust and reproducible volumetry of lung nodules even for large, nonspherical, pleurally attached and/or vascularized lung nodules in CT scans.

The tool has been evaluated in several studies and features a convenient and intuitive work flow by avoiding time-consuming computations or complex interactions on behalf of the radiologist or radiology technician.

Owing to the different work flow requirements of the baseline scan and subsequent follow-up examinations, the software assistant runs in two modes. In the "baseline scan" mode, the user can identify nodules with the mouse (each of them representing a "nodule VOI" [volume of interest] for the segmentation calculation) by pointing and clicking. Another mouse click starts the computation, which takes about 1–2 seconds on a common personal computer (PC). For some large nodules, the size of the VOI needs to be adapted before starting the segmentation. This can be easily achieved via buttons or shortcuts. After segmentation, the result can be verified in a 3D overview of the VOI (Fig 1) or more detailed in three orthogonal viewers (showing the axial, coronal, and sagittal sections). If the user is not satisfied with the automatic segmentation, he or she can easily modify the result by adapting a single "shape" parameter (Fig 2).

The analysis results of the currently selected nodule (including volume, mean density, and a histogram of the nodule voxel values) are made available for the user. All information about the processed nodules is summarized in a text report, which includes a table containing nodule volumes. The report can be saved as a formatted text file.

The work flow in "follow-up" mode is essentially the same as in the baseline scan mode, with the exception of two additional features. First, the possibility exists to register the nodule markers of

Figure 3. Follow-up mode of PulmoTREAT. The viewer on the left shows the baseline data set including the nodule markers from the corresponding examination. The viewer in the center shows the new data set and the registered marker. This mode is similar to the baseline scan mode in that the user can select nodules and start the segmentation. On the right side, a detailed follow-up report is presented.

a former examination in order to support localization of the nodules in the new scan. In addition, the data, nodule markers, and segmentation masks from the previous scan can be shown in an extra viewer synchronously to the viewer of the current scan.

Second, the volumes of each processed nodule are compared automatically with the corresponding measurements from the previous examination. The calculated information (volume, relative growth, doubling time, etc) is gathered in an extended follow-up report (Fig 3).

Finally, to assist the radiologist in nodule detection, alternative visualization modes such as MIP (maximum intensity projection) are provided. CAD (computer-aided detection) is not included in the software.

Methods and Algorithms

Visualization

To simplify the reading of high-volume thoracic CT data sets comprising several hundred sections, novel visualization techniques have been developed. On the basis of a fully automatic segmentation of the lungs, we compute distance maps of the orthogonal distance from the lung surface to the data set boundary for the six faces of the data cuboid. Using these distance maps, we compute the following views: *(a)* Gradient filtered distance maps highlight nonsmooth parts of the lung surface, which are often related to pleural nodules. In these views, even tiny pleural nodules become easily visible (Fig 4 [left]). *(b)* Maximum intensity projection (MIP) images of the segmented lungs provide an easy overview of the total tumor load and may help detect more subtle cases of pulmonary embolism (Fig 4 [center]). *(c)* An image of anatomically reformatted thoracic data shows all voxels having the same distance along the viewing direction to the lung surface. A stack of these images provides what may be called a "peeling view" of the data, that is, an arrangement in an onion skin layering that creates very homogeneous images of tissue in anatomically similar positions wherein even subtle pathologic conditions are easy to spot (Fig 4 [right]).

More information on these visualization techniques can be found in reference 6.

Segmentation and Volumetry

Owing to the problem that—especially in oncologic cases—many lung nodules are connected with other structures of the same density, a straight gradient-based approach for segmentation would not yield satisfying results. For that reason, a hybrid algorithm was developed that makes use of the high contrast between a nodule and lung parenchyma for a coarse segmentation. Afterward, adjacent structures are separated from

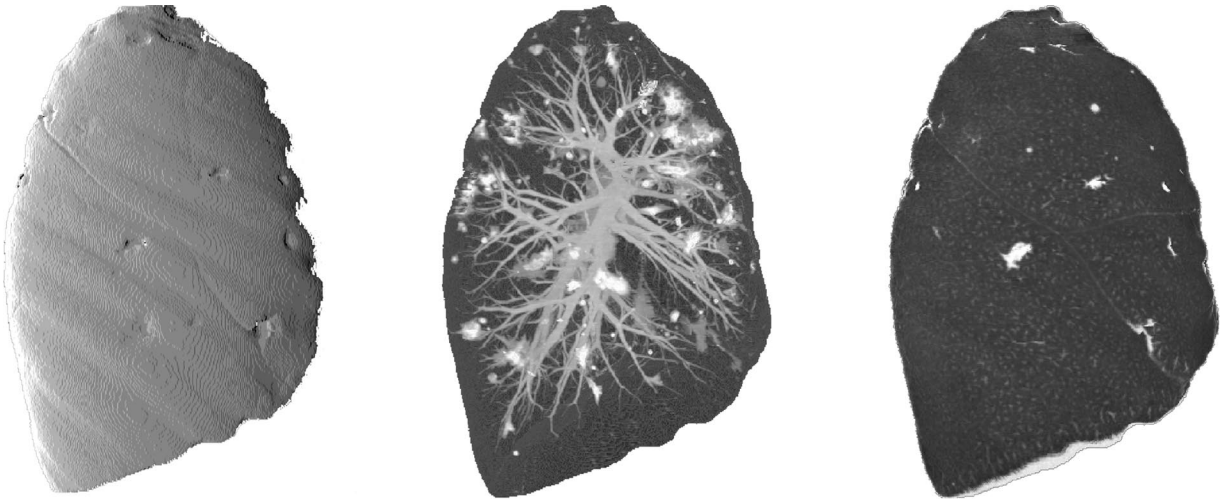

Figure 4. Novel visualization techniques for lung CT data. Left: Filtered distance map of the right lung. Center: Maximum intensity projection view of the right lung shows multiple calcified metastases. Right: Image of reformatted data close to the surface of the right lung.

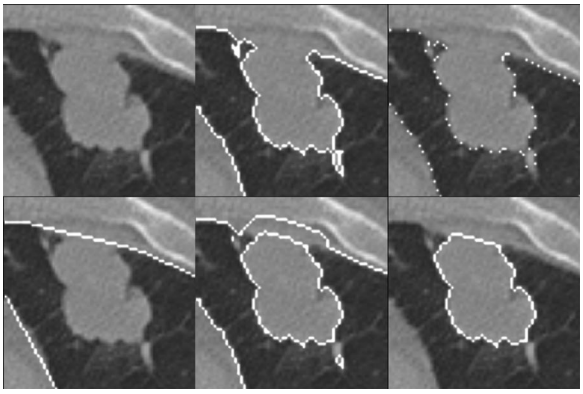

Figure 5. Automatically calculated intermediate results for separation of the pleura and nodule. The parenchyma mask is calculated from the original nodule VOI (top left) by using region growing (top center). To reduce calculation time, the parenchymal contour is thinned out (top right). Afterward, the convex hull of the remaining contour voxels is calculated to obtain the "healthy" parenchyma mask (bottom left). This mask is combined with the region growing mask to separate the nodule and pleura (bottom center), resulting in the final nodule segmentation (bottom right).

the nodule using morphologic operations. This separation of the pleura and vessels will be outlined in the following sections to convey the rough idea of the developed segmentation method. All of the segmentation steps mentioned do not require any kind of user interaction. As described earlier in this article, the only user interaction needed is a mouse click to identify the nodule. Since all the calculation steps of the segmentation method are performed only on the VOI around the nodule, the algorithm is fast enough for clinical use and takes 1–2 seconds on a standard personal computer.

Separation of the Pleura.—First, simple threshold-based region growing (based on the user-defined nodule marker) is performed to obtain a mask that contains both the nodule and pleura. On the basis of this mask, the parenchyma mask is generated using a connected component analysis of the nonsegmented regions. Connected component analysis is a method of finding homogeneous regions in an image—in this case a binary image. This method is used to identify the largest connected homogeneous region of voxels not belonging to the nodule and pleura mask. It will be called the *parenchyma mask* in this article. This parenchyma mask contains a gap caused by the nodule. The basic idea is now to fill this gap in the mask by applying a convex hull operation to the parenchymal contour. The convex hull of a given set of voxels is the smallest convex object that contains the complete voxel set. The result of the convex hull operation is a mask that describes approximately how the parenchymal contour would appear if no nodule was attached to the pleura. This resulting "healthy" parenchymal contour is used to separate the nodule and pleura (Fig 5).

A question that might be raised is that tumorous infiltrations are left out when this method is used. However, such infiltrations are usually not visible in CT scans, making it impossible to measure or even segment them reliably at present. Therefore, we concentrate on the reproducible segmentation of the nodule component located within the lung.

Separation of Vessels.—Similarly to the method in the preceding section, the algorithm for vessel separation starts with threshold-based region growing. Subsequently, an erosion operation is calculated for the resulting nodule and vessel mask to eliminate the components not belonging to the nodule. Afterward, the resulting mask image is transformed into an approximation of the nodule contour by dilation. In combination with the original mask, this contour is refined to the nodule contour without connected vessels (Fig 6).

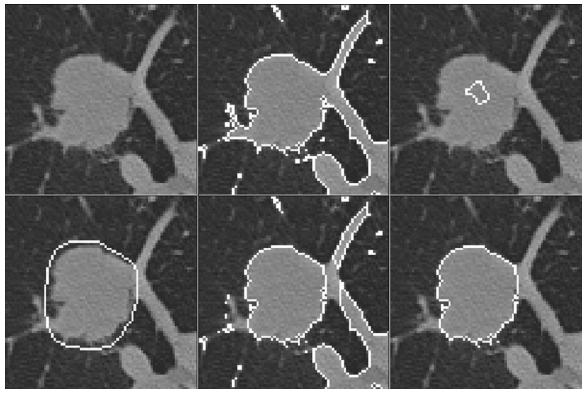

Figure 6. Automatically calculated intermediate results for separation of the vasculature and nodule. A mask that includes both vessels and the nodule is computed from the original VOI (top left) by using region growing (top center). Afterward, erosion (top right) and dilation (bottom left) are performed, resulting in an improved approximation of the nodule. Combination with the original nodule mask (bottom center) leads to the final nodule segmentation (bottom right).

Volumetry.—Mainly because of partial volume effects, the straightforward method of calculating the volume by counting voxels in the segmentation mask and multiplying the result by the volume of a single voxel is not suitable for reproducible volumetry. Therefore, a variation of the partial volume method (PVM) described in reference 7 was developed. On the basis of the segmentation result, three different areas are defined automatically: the nodule core, a parenchyma area, and a partial volume region. Mean attenuation values are calculated from the parenchyma area and the nodule core, allowing calculation of a weighted contribution of the voxels within the partial volume region to the nodule volume.

Temporal Registration

The temporal registration of nodule markers from a previous scan is based on automatic segmentation of the lung mask (8). The lung mask calculated in a preprocessing step is used to define a coordinate system that describes positions within the lung depending on the boundaries of the lung mask. The nodule markers of the previous examination are transformed into these "relative lung coordinates." They are then transformed back into world coordinates by using the corresponding lung mask of the current scan.

This registration is fast and accurate enough to assist the user in finding the nodules in the new scan and allows identification of the corresponding nodule in the baseline scan for the currently selected follow-up nodule automatically. For the available follow-up data, the accuracy of the nodule marker registration ranged between 0 and 20 mm, depending on the position of the nodule marker within the lung.

Evaluation

During the development process, the tool and the implemented segmentation were tested and improved continuously by using a database of more than 50 patient CT scans performed with different scanners and containing about 700 nodules. These nodules were not used in the reproducibility studies described in this section.

A reproducibility study was performed by using 16 CT scans (low dose, 0.8-mm reconstruction increment, standard lung reconstruction kernel) from eight patients with lung metastases; the scans were performed with a Volume Zoom scanner (Siemens Medical Solutions, Erlangen, Germany). Both scans of each patient were performed within a few minutes and independently from each other. Each case was processed twice, once by an expert radiologist and once by a radiology technician. Thus, the variability of the computer-assisted volumetry for different clinical users and different scans could be observed. The radiologist identified 105 lesions with a minimum diameter of about 4.6 mm.

For 96 nodules (91.4%), the segmentation was classified as successful by the radiologist; the remaining nine were excluded from evaluation. Bland and Altman statistics (9) were used to determine interobserver variability as well as the agreement of volume measurement in both CT scans. The mean volume of the measurements was used to estimate the unknown true volume.

The results of the study showed an interscan variability with a median of 4.7% and a 95% limit of agreement of 26.9% (which means that an increase in the volume of more than 26.9% would have a 95% likelihood of being real growth rather than measurement inaccuracy). As expected, the interobserver variability was considerably smaller, with a median of 0.1% and a 95% limit of agreement of 7.1%.

Furthermore, a phantom study with nodule phantoms 5, 10, and 20 mm in diameter was performed. The nodules were generated by a validated software tool and inserted in a thoracic CT scan (4 × 2.5-mm collimation, 2-mm reconstruction increment). In addition, nodules that simulated volume growth of 10% up to 50% (in steps of 10%) were generated. Linear regression showed a high agreement between the simulated and calculated increase in volume for nodules 10 and 20 mm in diameter. For 5-mm-diameter nodules, slight volume growth was underestimated. The proposed segmentation algorithm was able to reliably detect a 10% increase in volume in all 10- or 20-mm-diameter nodules. For 5-mm-diameter nodules, a 20% increase was reliably detected.

Discussion

To ensure a high degree of usability, the design and work flow have been developed and evaluated in close collaboration with our clinical partners and have been described as easy to use and convenient. Since the implemented computer-assisted volumetry is very fast and needs only little user interaction, the examination of a single data set does not take more time than RECIST measurement. In fact, by the use of marker registration and automatic comparison of volumes, calculation of doubling times, and report generation, the examination is more convenient and faster than RECIST measurement in the follow-up case.

In contrast to existing commercial applications, the developed tool is able to segment and measure even large, complex, irregular, vascularized, and pleurally attached tumors reliably. The high percentage of successfully segmented tumors (>91%) in the study shows the robustness of the proposed method. It is planned to integrate the possibility of computer-assisted RECIST measurement and a manual segmentation method to be able to measure even those nodules that cannot be successfully segmented by the presented algorithm. Thereby, all other advantages of the developed tool for the work flow (marker registration, automatic comparison of measurements and report generation) could be kept, even for the examination of those difficult cases.

The reproducibility study demonstrated good reproducibility of the segmentation and volumetry implemented in the presented software tool. In contrast to RECIST measurement, the automatic volumetry allows reliable detection of volume growth of about 25% or more (RECIST measurement, 70% or more). Therefore, the tool not only reduces user interaction and time consumption in follow-up examinations but also increases the reliability and significance of the results of lung tumor follow-up.

Conclusions

The two prototypical applications presented in this two-part series of articles exemplify the enormous potential of 3D image processing techniques. In both areas, there has been a substantial increase in diagnostic information because of the application of 3D image analysis. Since the first attempts to quantify lung function from CT data (10), this technique was applied exclusively to 2D CT sections, yielding no information about local pathologic conditions or lobar-specific diseases. Today, the combination of high-quality image data from multidetector CT with state-of-the-art image processing techniques allows the quantification of abnormalities related to anatomic regions of the lung such as lung lobes or bronchopulmonary segments. In addition, the fast and reproducible measurement of tumor volume and growth has clear advantages over one-dimensional or 2D measurements of diameters in terms of accuracy, reproducibility, and time effort, as was also shown in reference 11. Therefore, this method has the potential to complement or even replace the current RECIST standard (5).

Besides the presented diagnostic fields, multidetector CT is rapidly becoming the imaging modality of choice in the diagnosis of pulmonary embolism (12–14). This is one of the future areas for the development of advanced image analysis tools, an endeavor already being started (15). In addition, in the area of chronic obstructive pulmonary disease (COPD) diagnosis and therapy planning, there is high potential for medical image analysis, particularly by combining the presented methods for the quantification of emphysema with advanced analysis tools for the determination of bronchial wall thickness (16). The rapid progress in the development of modern image analysis in thoracic CT is now accompanied by the development of new applications in cardiac CT. This is also an important part of the current research program of the VICORA collaboration.

Acknowledgments: The research that led to the presented results was conducted as part of the cooperation project VICORA (Virtual Institute for Computer Assistance in Clinical Radiology) (*www.vicora.de*). We thank all partners who made this publication possible by their continuous support.

References

1. Kuhnigk JM, Dicken V, Zidowitz S, et al. New tools for computer assistance in thoracic CT: Part 1. Functional analysis of lungs, lung lobes, and bronchopulmonary segments. RadioGraphics 2005; 25:525–536.
2. Leppek R, Krass S, Bourqain H, et al. Virtual organization in the digital age of radiology: principle and solution for radiologic research? Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 2003; 175:1556–1563.
3. Peitgen HO, Krass S, Lang M. Computer assistance in clinical image-based diagnosis and therapy: a challenge for German research. Rofo Fortschr Geb Rontgenstr Neuen Bildgeb Verfahr 2004; 176:297–301.
4. American Cancer Society. Cancer Facts & Figures 2004 (serial online). Available at: *www.cancer.org/downloads/STT/CAFF_finalPWSecured.pdf.* Accessed March 31, 2004.
5. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000; 92:205–216.
6. Dicken V, Wein B, Schubert H, Kuhnigk JM, Krass S, Peitgen HO. Novel projection views for simplified reading of thorax CT scans with multiple pulmonary nodules. In: Lemke HU, Vannier MW, Inamura K, Farman AG, Doi K, Reiber JHC, eds. Computer assisted radiology and surgery. Amsterdam, the Netherlands: Elsevier, 2003; 59–64.
7. Ko JP, Rusinek H, Jacobs LA, et al. Small pulmonary nodules: volume measurement at chest CT—phantom study. Radiology 2003; 228:864–870.
8. Kuhnigk JM, Hahn HK, Hindennach M, Dicken V, Krass S, Peitgen HO. Lung lobe segmentation by anatomy-guided 3D watershed transform. In: Sonka M, Fitzpatrick JM, eds. Proceedings of SPIE: medical imaging 2003—image processing. Vol 5032. Bellingham, Wash: International Society for Optical Engineering, 2003; 1482–1490.
9. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1:307–310.
10. Kalender WA, Rienmueller R, Seissler W, Behr J, Welke M, Fichte H. Measurement of pulmonary parenchymal attenuation: use of spirometric gating with quantitative CT. Radiology 1990; 175: 265–268.
11. Kostis WJ, Reeves AP, Yankelevitz DF, Henschke CI. Three-dimensional segmentation and growth-rate estimation of small pulmonary nodules in helical CT images. IEEE Trans Med Imaging 2003; 22:1259–1274.
12. Herold CJ. Spiral computed tomography of pulmonary embolism. Eur Respir J Suppl 2002; 35: 13s–21s.
13. Muller NL. Computed tomography and magnetic resonance imaging: past, present and future. Eur Respir J Suppl 2002; 35:3s–12s.
14. Schoepf UJ, Costello P. Multidetector-row CT imaging of pulmonary embolism. Semin Roentgenol 2003; 38:106–114.
15. Masutani Y, MacMahon H, Doi K. Computerized detection of pulmonary embolism in spiral CT angiography based on volumetric image analysis. IEEE Trans Med Imaging 2002; 21:1517–1523.
16. Grenier PA, Beigelman-Aubry C, Fetita C, Preteux F, Brauner MW, Lenoir S. New frontiers in CT imaging of airway disease. Eur Radiol 2002; 12:1022–1044.