Chapter 24

COMPUTER AIDED DETECTION & QUANTIFICATION

Concepts and Results with Respect to Pulmonary Nodules in High Resolution CT Data

Rafael Wiemker[1], Patrik Rogalla[2], Dag Wormanns[3], Thomas Bülow[1], Roland Opfer[1], Ahmet Ekin[1], Thomas Blaffert[1], Ori Hay[4], Ekta Dharaiya[5], Roel Truyen[6], Joost Peters[6], Eike Hein[2], Valentina Romano[2], Florian Beyer[3]

[1]Philips Research, Hamburg, Germany; [2]Charité Hospital, Humboldt University, Berlin, Germany; [3]University Hospital Münster, Germany; [4]Philips Medical Systems, Haifa, Israel; [5]Philips Medical Systems, Cleveland, OH, USA; [6]Philips Medical Systems Medical, Best, The Netherlands

Abstract: With the superb spatial resolution of modern multi-slice CT scanners and their ability to complete a high resolution thoracic scan within one breath hold, software algorithms for computer aided detection (CAD) of pulmonary nodules are now reaching high sensitivity levels at moderate false positive rates. Pilot studies indicate that CAD software modules can serve as a powerful tool for diagnostic quality assurance. Equally important are tools for fast and accurate automatic three-dimensional volume measurement of detected nodules. Computer aided diagnosis (CADx) tools such as automated three-dimensional quantification of contrast enhancement in dynamic CT help to exclude benign nodules and reduce biopsies.

Keywords: Computer aided diagnosis, lung cancer screening, differential diagnosis, pulmonary nodules, quantitative contrast enhanced CT, ultra-low-dose CT

1. INTRODUCTION

Computer aided detection and automatic marking of lesions and anomalies in medical image data is a software technology that has gained rising interest in the last years. In principle, it is applicable to all kinds of

G. Spekowius and T. Wendler (Eds.), Advances in Healthcare Technology, 385-401.

medical images (2D, 3D, and higher dimensional) and signals (1 dimensional) from all kinds of scanners (e.g. CT, MR, US, PET, SPECT, ECG) and for all kinds of organs (lung, colon, kidneys, liver, brain, vascular system, etc). In this chapter we want to concentrate on concepts related to pulmonary nodules and their manifestation on CT, for the medical reason that lung cancer is the cancer with the highest mortality, and the technical reason that, after X-ray mammography, CT is currently seen as the modality with the next highest potential for CAD software.

Two main areas have to be distinguished where computer assistance can be used. The *computer aided detection* (CAD) of pulmonary nodules as such, be they malignant or benign, calcified, solid or sub-solid. The results of CAD are markers that draw the attention of the reader to locations of suspicious anomalies (Figure 24-1). The second area is *computer aided quantification (CAQ)* or even more ambitious *computer aided diagnosis* (CADx) of a detected nodule, and aims at the differential diagnosis between malignant and benign pulmonary nodules. Only a fraction of the pulmonary nodules are malignant carcinomas from lung cancer or metastases from cancers in other organs. It is well known that the fraction of nodules which are actually malignant decreases when smaller and smaller nodules are considered[1,2] as they become detectable by the still increasing resolution of multi-slice CT scanners[3].

As software technologies, computer aided detection and diagnosis aim for three main objectives:

- **Diagnostic quality assurance:** By detecting and marking suspicious lesions, CAD can help avoid potential nodules from being overlooked by the radiologist.
- **To increase therapy success by early detection of cancer:** By down-staging the typical stage when a cancer is diagnosed; it is hoped that detection at an earlier stage increases the survival rates.
- **Reduction of biopsies:** By computation of growth rates and doubling times of lesions between follow-up examinations, for non-invasively differential diagnosis to avoid the risks associated with invasive procedures like needle-biopsies or resection surgeries.

Within the context of CAD and CADx for pulmonary nodules, a number of separate technical tasks can assist the reading radiologist. In this chapter we want to address several concepts and discuss the underlying principles, problems and preliminary results:

- Enhanced viewing for optimal visual detection of lung nodules
- Automated detection and prompting of nodules

- Automated three-dimensional volumetry and follow-up matching of nodules for growth-rate computation
- Contrast-uptake measurement with dynamic CT to differentiate benign and malignant lung nodules.

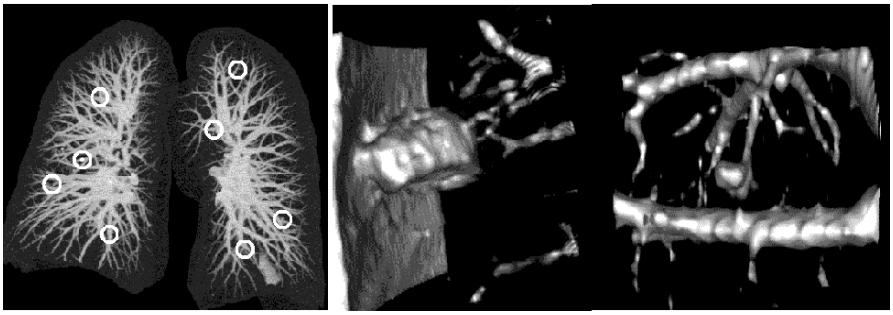

Figure 24-1. CAD markings of lung nodules (left), and renderings of nodules attached to the lung wall (middle) and to pulmonary vessels (middle, right).

1.1 Lung cancer

Cancer of the lung and bronchus is the second most common cancer type. However, due to its aggressiveness, lung cancer is the number one cause of all cancer-related deaths, with more than 150 000 deaths in the USA each year[4].

Pulmonary nodules are among the most common focal pulmonary lesions. The presence or absence of pulmonary nodules is of great importance in the differential diagnosis of lung diseases[5,6]. Therefore the detection and diagnosis of pulmonary nodules in CT data sets of the thorax is a standard procedure in radiological practice. Pulmonary nodules are often benign, or may be metastases from various cancer types, but they may also be an indication for primary lung cancer.

The early detection of lung nodules is crucial, both for close observation or biopsy to differentiate between benign or malignant nodules, and for timely therapy. Among the most common methods to detect pulmonary nodules are chest X-ray and CT. Fiber optic bronchoscopy is also used but has limited value for finding nodules other than those directly attached to the larger airways. CT offers better contrast than chest X-ray between nodule and background with no overlapping structures, and several studies have shown that CT can detect smaller, earlier stage nodules with a higher sensitivity than chest X-ray[7].

In the last years CT technology has undergone a major evolution with the introduction of multi-slice technology. With multi-slice CT, a full lung, thin-slice (<1 mm) scan can be done within a single breath-hold. It is hoped that with the high-resolution CT data available from multi-slice CT scanners cancerous nodules can be recognized while still small and in an early stage of lung cancer. Many researchers assume that this down-staging effect by early detection of lung cancer will ultimately improve the survival rate[1,2].

Moreover, it is hoped that lung cancer screening of high-risk patient groups may significantly increase the rate of lung cancer cases that are diagnosed before the cancer has metastasized. These propositions will be investigated during a large-scale randomized 9-year trial conducted by the US National Cancer Institute (NCI): The National Lung Screening Trial (NLST)[8] has enrolled enroll nearly 50,000 current or former smokers at a total of 30 clinical sites throughout the USA. Similar trials are underway in the Netherlands (NELSON, 24,000 people), the United Kingdom (LUCAS, 40,000 people), and France (DEPISCAN, 21,000 people)[9].

1.2 Differential diagnosis of pulmonary nodules

Once one or several pulmonary nodules have been detected in a patient, the likelihood of malignancy has to be determined. A number of different clinical approaches are aimed at differential diagnosis: biopsy, observation of possible growth by follow-up examinations[10], appraisal of morphological features (such as spiculated or smooth margins), measurement of contrast enhancement in a dynamic CT series[11], use of additional modalities such as positron emission tomography (PET), etc. For all these clinical approaches, software modules for *computer aided quantification* can be used, not only to speed up the workflow, but also to make the necessary measurements themselves more accurate, less prone to error, and more repeatable. Going beyond pure quantification, *computer aided diagnosis* software (CADx) can then estimate likelihood for malignancy versus benignity.

From the various needs for quantification of lung nodules in CT, the volume measurement (volumetry) of a detected nodule is the most immediate (for reporting) and the most basic (for detection of possible growth in a follow-up examination).

2. COMPUTER ENHANCED VISUALIZATION FOR OPTIMAL VISUAL DETECTION

Lung nodules can be detected particularly well by CT, since they show good contrast in the lung parenchyma and – in contrast to projection X-ray –

cannot be hidden by ribs or other overlying structures. Although in principle detectable in CT, a non-negligible fraction of small nodules may be overlooked by the radiologist, particularly if they are located centrally and hidden in a maze of vessels of similar size (Figure 24-2). This may be even more of an issue, as modern multi-slice scanners can produce up to 800 slices for a thoracic CT exam with sub-millimeter slice thickness. All the small vessels have to be checked for their 3D-connectivity in order to rule-out the presence of possible nodules.

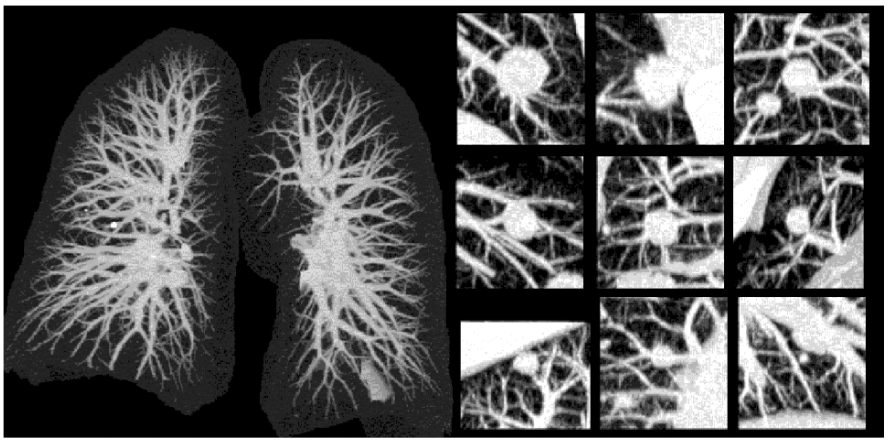

Figure 24-2. Left: Maximum intensity projection (MIP) of the lung segmented out of a high-resolution CT data set. Right: Examples of nodules of varying size (2–20 mm diameter), hidden in the maze of vessels.

For the human observer, a major difficulty in visual detection of lung nodule lies in the fact that in axial slice images the lung nodules can easily be confused with the cross sections of pulmonary vessels. Displaying maximum intensity projections (MIPs) of the lung region is of limited use since nodules will be occluded in the maze of the pulmonary vessels due to their similar Hounsfield (HU) values.

We propose a visualization technique[12] which removes the disturbing vessel structures from the MIP and thus provides a clear view of the lung nodules. The structures that obscure the view are all the structures outside the lungs (the chest wall including bones, the heart, etc.) on the one hand and the pulmonary vessels on the other hand. Consequently, an automatic segmentation of the lungs is performed in order to exclude all exterior structures from the display. Secondly, the pulmonary vessel tree is automatically extracted and then suppressed.

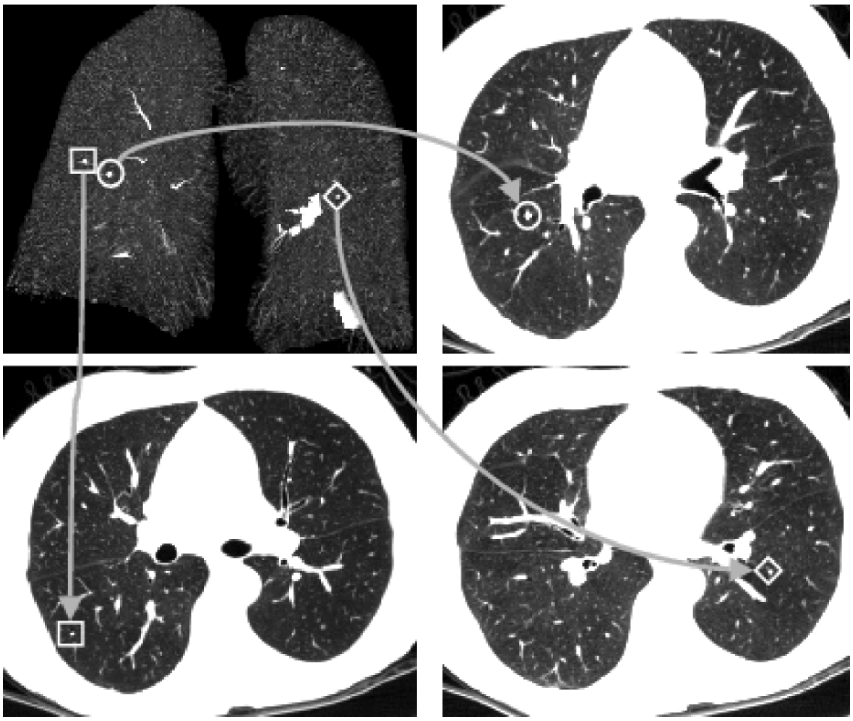

Figure 24-3. Upper left: A coronal MIP of the lung with suppressed vessel tree (compare Figure 24-2). A mouse click on one of the nodules which stand out prominently in the display transfers to the corresponding axial slice.

The principal technical challenge is a careful segmentation of the vessel tree, such that no vascularized nodules that are connected to the vessel tree are erroneously suppressed.

Figure 24-3 shows the method applied to CT datasets acquired with a Philips Brilliance 40-slice scanner (in-plane resolution 0.7 mm, reconstruction interval 0.45 mm, slice thickness 0.9 mm). In the maximum intensity projection (MIP) of the extracted lung after suppression of the segmented vessel tree, lung nodules down to absorption values of about -600 HU are clearly visible. The effect is most striking in interactive mode, where the user can change the viewing direction. It can also be noticed that some vessel segments have been missed by the extraction step. Also some chest wall tissue is still visible. Nevertheless, most overlying tissue is excluded from the MIP and lung nodules become clearly visible at a single glance.

The enhanced visualization scheme suggested here appears promising to reduce the number of false negatives (missed nodules) in visual lung nodule detection.

3. COMPUTER AIDED DETECTION

In contrast to optimal visualization as described in the last section, the concept of computer aided detection (CAD) means that a visual prompt like an arrow or an ring is drawn at distinct locations of the displayed image in order to call the attention of the reading physician to potential anomalies.

Computer assistance for detecting lung nodules in CT data sets is a straightforward concept and has been suggested and investigated as early as 1989[13,14,15]. The underlying idea is not that the diagnosis is delegated to a machine, but rather that a machine algorithm acts as a support to the radiologist and points out locations of suspicious objects, so that the overall sensitivity (detection rate) is raised. This could be important particularly in screening situations with a massive reviewing load of CT studies, to detect single so far unknown nodules, but also as a significant workflow improvement in oncology therapy follow-up situations, where a multitude of already known nodules have to be assessed for monitoring therapy success.

The principal problem of CAD is that inevitably false markers (so called false positives, pointing to structures which are either not nodules or medically irrelevant) come with the true positive marks. The aim then is to develop software algorithms that hold the false positive rate per patient data set as low as possible while retaining a high sensitivity (detection rate)[16].

The CAD algorithm we have suggested[17] works on pure geometric reasoning. It assumes that any blob-like solid structure (which may also be on one side attached to a plane-like structure, the lung wall) may be a candidate for a pulmonary nodule, if all connecting vessels are significantly smaller in diameter than the central blob-like structure.

A pilot study of a lung nodule CAD system was conducted on images from the radiology department at the Charité university hospital Berlin. The images were acquired in the years 2000–2001 by a 4-slice scanner over the entire thorax at 1 mm slice thickness, 120 kV and 100 mAs.

The automated detection showed a sensitivity of 84% (detection rate including nodules of all sizes). If the minimum nodule size for detection was set to 2 mm, the sensitivity was 95% with 4.4 false positives per patient. For nodules greater than 4 mm, the sensitivity was 96% with 0.5 false positives per patient.

However, we would not necessarily expect such a high detection rate at an equally low false positive rate in all clinical settings. Exams may be taken with low-dose or ultra-low dose imaging protocols. Patient compliance with regard to breath hold and lying still may be poor. Also the delineations and regularity of the nodule population in question may vary considerably.

3.1 CAD performance comparison

In the medical context, the term true positive often refers to a detected nodule that has turned out to be truly malignant. In the context of CAD, a marker is considered as a true positive marker even it points at a benign or calcified nodule; false positive markings are then those which do not point at nodules at all (but at scars, bronchial wall thickenings, motion artifacts, vessel bifurcations, etc). The outcome of computer aided detection is not a yes/no decision for a given image, but rather markings at certain locations; therefore the term 'true negative' is not defined and a normalized specificity cannot be given. Instead, the performance of CAD is usually given as sensitivity (detection rate) and false positive rate (false positive markings per CT study).

Experience with clinical studies has shown that the measured detection rates achieved by CAD systems as well as by radiologists themselves clearly depend on the number of co-reading radiologists: the more co-readers participate, the more suspicious lesions will inevitably be found, and thus the individual sensitivity of each participating radiologist and CAD system will decrease. But even though the absolute sensitivity figures have to be appreciated with care, all clinical studies have agreed in that a significant number of nodules have been detected by the additional CAD software alone, while being overlooked by all co-reading radiologists[18]. Therefore, CAD can be seen as a strong quality assurance tool.

Up to now it is hard to compare the performance of the different CAD algorithms, as they have all been tested in different settings, on different patient data sets, and acquired with different scanners and imaging protocols.

In order to allow a more objective comparison of CAD performance, the US National Cancer Institute has formed a consortium to build up a lung image database with consensus based diagnostic findings, which could then be used to validate and improve computer aided detection software[19].

3.2 CAD performance on ultra-low-dose CT

For lung cancer screening with CT, i.e. for asymptomatic patients, the feasibility of low-dose or even ultra-low-dose CT exams is of particular interest. Therefore we have tested CAD algorithms on ultra-low-dose scans of the Charité University Hospital Berlin, which were recorded with the very low tube current setting of 5-9 mA. It was possible to directly compare the CAD performance to the standard dose images that were acquired of each patient in the same exam session. The double CT examination of the patient was possible because the ultra-low-dose data was reconstructed from the raw

data of the scout scan (which was performed with a rotating CT gantry), so that the patient was not exposed to more ionizing radiation than usual.

A pilot study was conducted on 18 patient data sets, for which both standard and ultra-low-dose scans were available. Double reading of two experienced thoracic radiologists revealed a total of 44 lung nodules.

For any CAD algorithm, the trade-off between false positives and detection rate leads to a range of possible operating points. A performance comparison that is independent of a specific operating point can be made by virtue of an FROC curve (free response receiver operating characteristic)[16]. The performance of our CAD algorithm for nodules with a diameter ≥2.5 mm is shown in Figure 24-4. The CAD algorithm was applied without any change to both standard-dose and ultra-low-dose images. At one operating point on standard dose images, a sensitivity of 90% was achieved at a rate of 10 mean false positives per patient, a sensitivity of 80% was achieved at a rate of 5 mean false positives per patient. For the ultra-low-dose data the CAD software achieved 83% sensitivity at a rate of 10 mean false positives per patient, and a sensitivity of 76% at a rate of 5 mean false positives per patient.

Appraisal of the two FROC curves indicates that the CAD shows only a slight performance decrease on ultra-low-dose CT images, but seems generally feasible. This is particularly interesting with respect to lung cancer screening of asymptomatic patients.

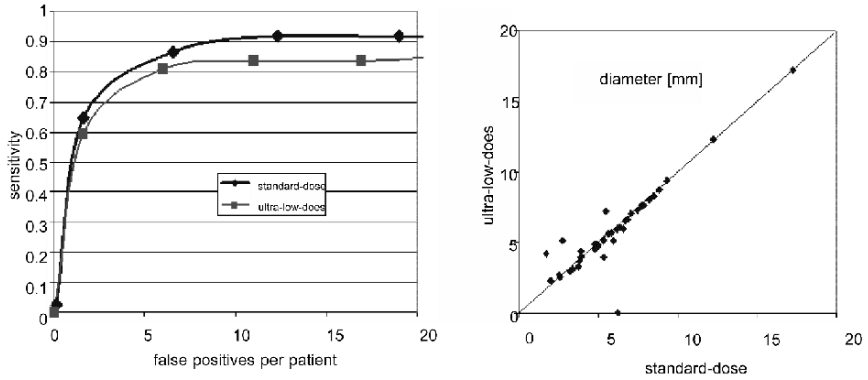

Figure 24-4. Left: FROC curves describing the performance trade-off between detection rate and false positive rate for standard-dose and ultra-low-dose CT (lower curve), for nodules larger than 2.5 mm diameter. Right: Correlation between computer measured volume-equivalent nodule diameter in standard-dose and ultra-low-dose CT (correlation 0.92).

4. COMPUTER AIDED VOLUMETRY OF PULMONARY NODULES

Nodule volumetry is important for the detection of possible growth between follow-up examinations and computation of growth rates (volume doubling times) for small indeterminate nodules to evaluate the likelihood of malignancy. It is also important in oncology for monitoring the success of cancer therapy. Follow-up of small lung nodules becomes even more important with the increasing number of small nodules detected in thin-slice CT data.

Computer-aided three-dimensional volumetry promises a better sensitivity than manually guided diameter-measurements in a single image slice, since an actual doubling of the nodule volume means a diameter increase of a factor of only $\sqrt[3]{2}$ or 26%, which for small nodules might easily be overlooked in the measurement error range.

The main technical challenge for automatic three-dimensional segmentation of nodules is that the image processing algorithm must be able to separate the nodule from the lung wall or attached vessels in a consistent way. The automated segmentation should also yield consistent results when the nodule is imaged with different CT slice thickness settings[20, 21].

For validation of automatic volumetry, we have conducted comparisons of manual measurements between two radiologists, and between manual versus automated volume segmentation. The correlation between the manual measurements by two radiologists was 0.987. There was also a strong correlation between automated and manual segmentation with the correlation coefficient equal to 0.972 and 0.986 for the two radiologists respectively. So the agreement between manual and computer aided volumetry proved to be equally good as the agreement between the two human readers. The automated measurements required minimal user interaction with average volume estimation time per nodule of about a second. Slicewise manual measurements on the other hand took an average of five minutes per nodule[22].

4.1 Nodule volumetry with ultra-low-dose CT

It is an important question whether computer aided nodule volumetry is also feasible on ultra-low-dose CT data, despite its higher image noise. Therefore we have compared the nodule volumetry results for patients scanned twice with standard-dose and ultra-low-dose CT (data material as described in section 3.2). The computer-estimated volume-equivalent diameters show good correlation between ultra-low-dose and standard-dose

(see Figure 24-4, correlation coefficient of 0.92), so that both protocols could be used for follow-up monitoring.

4.2 Follow-up registration and matching of nodules

Evaluating the potential growth or shrinkage of pulmonary nodules between a former CT exam and a current follow-up exam is a routine task in radiology practice, not only for diagnosis of detected nodules, but also for monitoring the response to oncological therapy. The typical manual matching procedure is quite time consuming; the user has to separately scroll through the slice stacks of the two studies and locate each nodule and then locate the same nodule in the follow-up study, perform the volumetry and copy down the results. In contrast, the computer assisted matching indicates the corresponding nodule location in the other dataset when the user points to the nodule in either one of the datasets (see Figure 24-5). Moreover, a list of matching pairs is automatically compiled for all nodules found in the two datasets (detected both manually and/or by CAD).

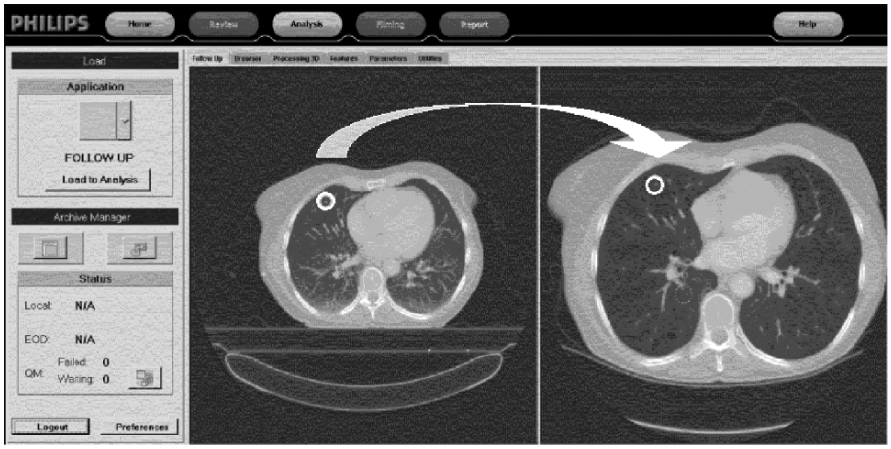

Figure 24-5. Automated matching of a nodule between follow-up exams reconstructed with different imaging protocol parameters (field-of-view).

To perform such a statistical growth analysis with measurement and matching in a manual fashion is of course possible, but might simply not be undertaken for all cases in the clinical practice with high caseload pressure. Therefore, the computer aided follow-up matching may be more than a convenience tool but indeed contribute to diagnostic quality assurance.

The automatic nodule matching approach described by Blaffert[23] starts out by segmenting the lungs out of the overall thoracic CT data volume of

the current and former study. The two lung volume images are geometrically registered (aligned) using an affine coordinate transformation until optimal cross-correlation is reached. Using highly optimized image processing methods, the optimal alignment of the two lung volumes can be reached in typically 5 seconds.

In general, an affine coordinate transformation is not expected to always suffice for the alignment of the same lung between a former and current CT study, since the possibly different respiratory state and patient pose on the CT table may necessitate the use of elastic registration. Current state-of-the-art elastic image registration algorithms are still too time consuming, but are expected to reach the performance required for clinical real time applications soon.

5. CONTRAST UPTAKE MEASUREMENT FOR DIFFERENTIAL DIAGNOSIS

Differential diagnosis of incidentally found pulmonary nodules is a very common clinical problem. The widespread use of multislice CT scanners has led to an increase of incidentally detected small nodules. Possible options to differentiate benign and malignant nodules are follow-up with growth assessment, biopsy, surgical resection, analysis of the nodule morphology on high resolution CT images, contrast enhanced dynamic CT, and PET/CT examinations. However, CT-guided or bronchoscopic biopsy of small nodules is difficult to perform, and surgical resection is a very invasive procedure (in relation to the highly probably benign nature of small nodules). Thus, non-invasive tests for reliable distinction between benign and malignant nodules are highly desirable. Analysis of nodule morphology alone is currently not known to be sufficiently reliable, and PET/CT shows a lack of sensitivity for detection of malignancy in small nodules[24].

Swensen et al.[11] have suggested that due to angiogenesis every malignant pulmonary nodule visible at CT should exhibit enhancement after intravenous injection of contrast media. Inversely, lack of enhancement should virtually exclude malignancy. Even though the sensitivity of this quantitative contrast-enhanced CT (QECT) is high (above 90%), the specificity of dynamic CT is known to be moderate (below 50%). However, despite its known moderate specificity, dynamic CT serves to effectively reduce the number of necessary biopsies, since all non-enhancing nodules do not require work-up.

Quantitative contrast-enhanced CT (QECT) requires precise density measurement in pulmonary nodules at CT for reliable detection of enhancement, which is suspicious for malignancy. The mean Hounsfield value of the

nodule in question is measured in a native scan and in e.g. four subsequent CT scans 1, 2, 3, and 4 minutes after administration of contrast agent. However, the measurement of the mean Hounsfield value is not without pitfalls. The estimated mean Hounsfield number of a nodule may easily vary in an interval of ±100 HU (depending on the selected volume of interest or segmentation of the nodule, Figure 24-5), which is 10 times higher than the expected enhancement, which we want to quantify. Here, computer aided quantification can be a valuable tool for diagnostic quality assurance.

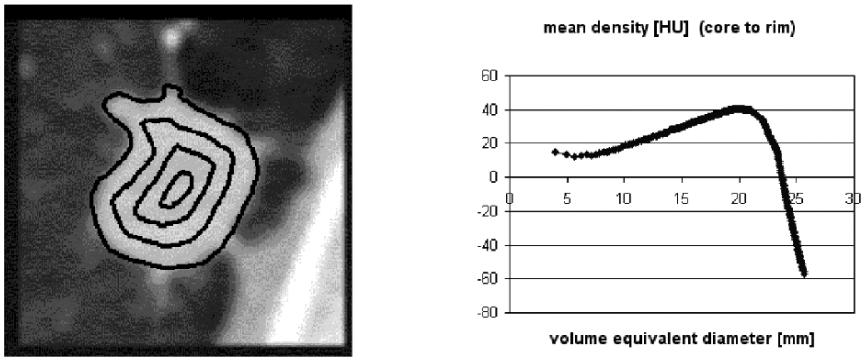

Figure 24-6. Computer aided three-dimensional measurement of the mean Hounsfield value from nodule core to boundary, showing the functional dependence of the estimated mean Hounsfield value and the estimated volume of a nodule.

In contrast to an average enhancement number from an arbitrary volume of interest, we suggest a radially resolved enhancement curve[25] which is capable to convey more detailed information, and more reliable comparison between pre- and post-contrast scans, e.g. for partial enhancement such as rim enhancement. This measurement and visualization method promises to be a valuable tool for differential diagnosis between malignant and benign lesions.

Figure 24-6 shows a malignant lesion (carcinoma), which was automatically segmented in 3D. Lung wall and attached vessels were cut-off. Successively large Volumes of Interest (VOI) are defined from the center of the segmented region moving outward. The Hounsfield values within each of the growing volumes of interest are averaged to yield a mean Hounsfield value. Then the distance to the boundary is gradually lowered, and more and more voxels are continuously added to the VOI, leading to a gradual inflation of the VOI towards the segmentation boundary until it completely fills the segmented nodule. For each VOI a cumulative mean Hounsfield

value is computed from all voxels aggregated so far, yielding a continuous mean-Hounsfield-curve (Figure 24-7), which can be plotted as a function of volume-equivalent diameter.

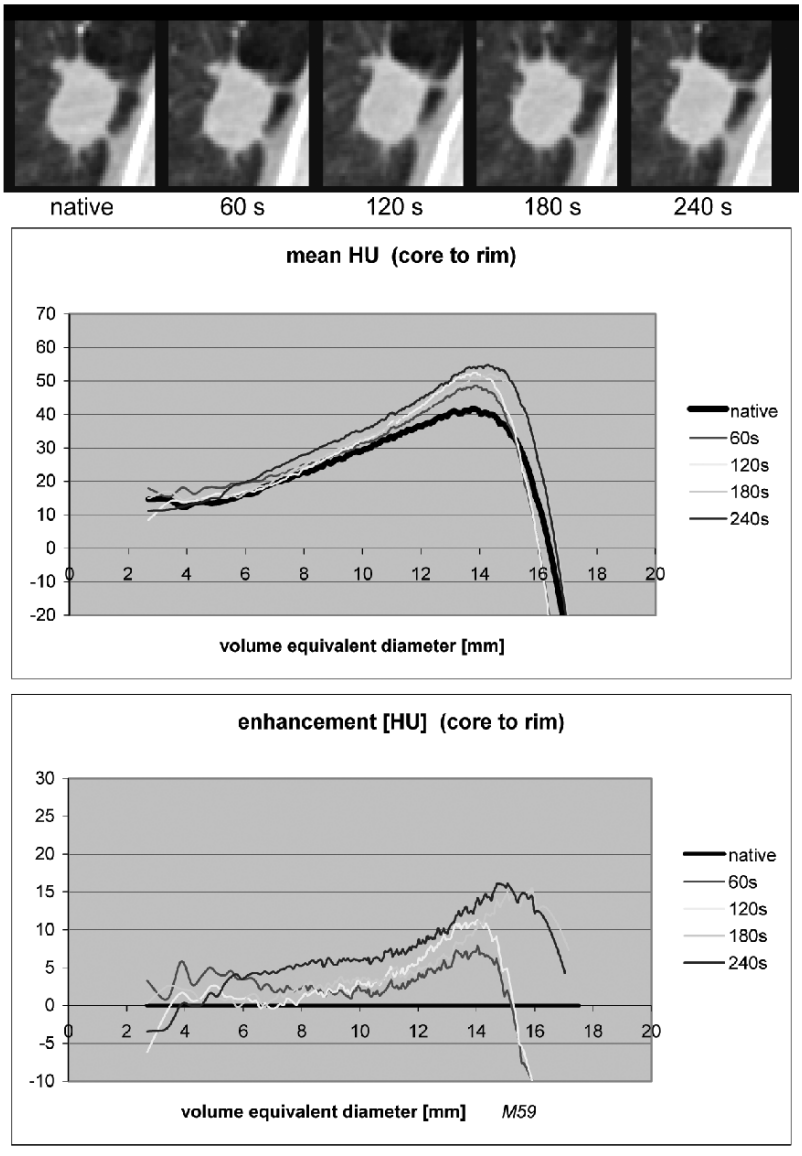

Figure 24-7. Example of radially resolved mean-Hounsfield and contrast-uptake curves for a malignant nodule exhibiting rim enhancement.

The resulting enhancement curves convey information to the reading physician whether there is significant enhancement present, and whether it is present more in the core or towards the rim of the nodule. Moreover, the ensemble of mean-Hounsfield-curves gives a good indication whether the measurements are stable (parallel course of the curves), or if the measurement is possibly unreliable due to problems of segmentation, misalignment (registration), cardiac motion artifacts, or incomparable respiratory state of the different series of the dynamic CT dataset.

6. OTHER AREAS OF INVESTIGATION

Going beyond detection and quantification of pulmonary nodules, *computer aided diagnosis* software (CADx) may be able to estimate a likelihood for malignancy versus benignity, by comparing the measured values in a multidimensional feature space to known benign and malignant example populations[26]. It may also be helpful to automatically retrieve similar cases with known diagnosis from a database and display them together with their findings to the radiologist[27].

Other CAD applications concerning thoracic CT imaging are the detection and quantification of pulmonary emboli[28], emphysema, airway diseases[29], and parenchymal infiltrations. Most of the tasks described in this chapter can in a similar fashion be applied to polyps in the colon, which may develop into colonic cancer[30].

7. CONCLUSION

With the advent of multi-slice CT scanners and the possibility to acquire sub-millimeter slice data over the whole thorax within a single breath-hold, software algorithms for computer aided detection and quantification start to reach a level of sensitivity and specificity which can make significant contributions to diagnostic quality assurance, and can provide radiology departments with the increased safety of a ‘second reader’ at low cost.

For computed tomography, the currently most advanced clinical CAD applications are related to lung as well as to colon cancer. The CAD applications provide automated and reproducible computer aided detection and three-dimensional volumetry of lesions, which is important for diagnostic quality assurance, acceleration of clinical workflow, and reduction of biopsies.

With ever refining spatial, dynamic, and temporal resolution of medical imaging scanners, more applications of computer aided detection and quantification are currently emerging.

REFERENCES

1. C.I. Henschke, D.I. McCauley, D.F. Yankelevitz, D.P. Naidich, G. McGuinness, O.S. Miettinen, D.M. Libby, M.W. Pasmantier, J. Koizumi, N.K. Altorki, J.P. Smith, Early Lung Cancer Action Project: overall design and findings from baseline screening, *Lancet* **354**(9173), 99-105 (1999).
2. S. Diederich, D. Wormanns, M. Semik, M. Thomas, H. Lenzen, N. Roos, W. Heindel, Screening for early lung cancer with low-dose spiral CT: prevalence in 817 asymptomatic smokers*, Radiology* **222**(3), 773-781 (2002).
3. F. Fischbach, F. Knollmann, V. Griesshaber, T. Freund, E. Akkol, R. Felix, Detection of pulmonary nodules by multislice computed tomography: improved detection rate with reduced slice thickness, *European Radiology* **13**(10), 2378-2383 (2003).
4. United States National Cancer Institute; http://www.cancer.gov/statistics.
5. M. Prokop, M. Galanski, *Spiral and Multislice Computed Tomography of the Body,* (Thieme Medical Publishers, Stuttgart, 2003).
6. W.R. Webb, N.L. Müller, D.P. Naidich, *High Resolution CT of the Lung*, second edition, (Lippincott-Raven Publishers, Philadelphia, 1996).
7. P.B. Bach, M.J. Kelley, R.C. Tate, D.C. McCrory, Screening for Lung Cancer: A Review of the Current Literatur, *Chest* **123**, 72S-82S (2003).
8. National Lung Cancer Screening Trial, United States National Cancer Institute; http://www.cancer.gov/nlst.
9. S. Diederich, D. Wormanns, W. Heindel, Lung Cancer Screening with Low-Dose CT, *European Journal of Radiology* **45**(1), 2-7 (2003).
10. D. Wormanns, S. Diederich, Characterization of small pulmonary nodules by CT, *European Radiology* **14**(8), 1380-1391 (2004).
11. S.J. Swensen, R.W. Viggiano, D.E. Midthun, N.L. Muller, A. Sherrick, K. Yamashita, D.P. Naidich, E.F. Patz, T.E. Hartman, J.R. Muhm, A.L. Weaver, Lung nodule enhancement at CT: a multicenter study, *Radiology* **214**, 73-80 (2000).
12. T. Bülow, R. Wiemker, C. Lorenz, S. Renisch, T. Blaffert, A Method for Lung Nodule Visualization from Multi-slice CT data, *Proc Computer Assisted Radiology and Surgery CARS 2005,* 1127-1131 (2005).
13. F. Preteux, N. Merlet, P. Grenier, M. Mouellhi, Algorithms for automated evaluation of pulmonary lesions by high resolution CT via image analysis, *RSNA*, 416 (1989).
14. F. Preteux, A Non-Stationary Markovian Modeling for the Lung Nodule Detection in CT, *Proc Computer Assisted Radiology CARS 91*, 199-204 (1991).
15. M. Giger, K. Bae, H. MacMahon*,* Computerized Detection of Pulmonary Nodules in Computed Tomography Images, *Investigative Radiology* **29**(4), 459-465 (1994).
16. P.C. Bunch, J.F. Hamilton, G.K. Sanderson, A.H. Simmons, A free response approach to the measurement and characterization of radiographic observer performance, *Proc SPIE 1977*, **127**, 124-135 (1977).
17. R. Wiemker, P. Rogalla, A. Zwartkruis, T. Blaffert, Computer Aided Lung Nodule Detection on High Resolution CT Data, *Proc SPIE Medical Imaging 2002*, **4684**, 677-688 (2002).

18. C.L. Novak, J. Qian, L. Fan, D. Naidich, J.P. Ko, A.N. Rubinowitz, Inter-observer variations on interpretation of multislice CT lung-cancer screening studies and the implications for computer-aided diagnosis, *Proc SPIE Medical Imaging Conference 2002*, **4680**, 68-79 (2002).
19. S.G. Armato, G. McLennan, M.F. McNitt-Gray, C.R. Meyer, D. Yankelevitz, D.R. Aberle, C.I. Henschke, E.A. Hoffman, E.A. Kazerooni, H. MacMahon, A.P. Reeves, B.Y. Croft, L.P. Clarke, Lung image database consortium: developing a resource for the medical imaging research community, *Radiology* **232**(3), 739-748 (2004).
20. R. Wiemker, P. Rogalla, T. Blaffert, D. Sifri, O. Hay, E. Shah, R. Truyen, T. Fleiter, Aspects of computer-aided detection and volumetry of pulmonary nodules using multislice CT, *British Journal of Radiology* **78**, S46-S56 (2005).
21. R. Wiemker, P. Rogalla, E. Hein, T. Blaffert, P. Rösch, Computer Aided Segmentation of Pulmonary Nodules: Automated Vasculature Cutoff in Thick- and Thinslice CT, *Proc Computer Assisted Radiology and Surgery CARS 2003*, 965-790 (2003).
22. O. Hay, D. Sifri, Y. Srinivas, R. Wiemker, Evaluation of Automatic Volumetric Segmentation of Lung Nodules in Standard and Low Dose CT Scans, *RSNA* (2003).
23. T. Blaffert, R. Wiemker, Comparison of different follow-up lung registration methods with and without segmentation, *Proc SPIE Medical Imaging 2004*, **5370**, 1701-1708 (2004).
24. M.K. Gould, C.C. Maclean, W.G. Kuschner, C.E. Rydzak, D.K. Owens, Accuracy of Positron Emission Tomography for Diagnosis of Pulmonary Nodules and Mass Lesions, *Journal of the American Medical Society* **285**(7), 914-924 (2001).
25. R. Wiemker, D. Wormanns, F. Beyer, T. Blaffert, T. Bülow, Improved sensitivity of dynamic CT with a new visualization method for radial distribution of lung nodule enhancement, *Proc SPIE Medical Imaging Conference 2005*, **5746**, 486-497 (2005).
26. F. Li, M. Aoyama, J. Shiraishi, H. Abe, Q. Li, K. Suzuki, R. Engelmann, S. Sone, H. Macmahon, K. Doi, Radiologists' performance for differentiating benign from malignant lung nodules on high-resolution CT using computer-estimated likelihood of malignancy, *American Journal of Roentgenology* **183**(5), 1209-1215 (2004).
27. A.M. Aisen, L.S. Broderick, H. Winer-Muram, C.E. Brodley, A.C. Kak, C. Pavlopoulou, J. Dy, C.R. Shyu, A. Marchiori, Automated Automated Storage and Retrieval of Thin-Section CT Images to Assist Diagnosis: System Description and Preliminary Assessment, *Radiology* **228**, 265-270 (2003).
28. M.J. Quist, H. Bouma, C. van Kuijk, O.M. van Delden, F.A. Gerritsen, Computer-Aided Detection of Pulmonary Embolism on Multi-Detector CT, *RSNA* (2004).
29. R. Wiemker, T. Blaffert, T. Bülow, S. Renisch, C. Lorenz, Automated assessment of bronchial lumen, wall thickness and bronchoarterial diameter ratio of the tracheobronchial tree using high-resolution CT, *Proc Computer Assisted Radiology and Surgery CARS 2004*, 967-972 (2004).
30. F.M. Vos, R.E. van Gelder, I.W.O. Serlie, J. Florie, C.Y. Nio, A.S. Glas, F.H. Post, R. Truyen, F.A. Gerritsen, J. Stoker, Three-dimensional display modes for CT colonography: conventional 3D virtual colonoscopy versus unfolded cube projection, *Radiology* **228**, 878-885 (2003).