# Computer-Aided Diagnosis in Thoracic Computed Tomography

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## Summary

Current computed tomography (CT) technology allows for isotropic, sub-millimetre resolution acquisition of the thorax in a few seconds. These thin-slice chest scans have become indispensable in thoracic radiology, but have also increased the time and effort required from radiologists for reporting. Industry has focused on the development of computer-aided diagnosis (CAD) tools to facilitate the interpretation of thoracic CT data. In this paper I discuss the three most 'senior' CAD applications for chest CT: nodule detection, nodule volumetry and quantification of emphysema. Are these applications ready for widespread application?

## Introduction

A rapidly developing, exciting and potentially very rewarding investigative field in medicine is the adaptation of the digital computer to the rapid and accurate solution of many of our more difficult professional problems. While there is scarcely any repetitive function in which the computer cannot be of help to us, in radiology the principal uses to date have been for dosage calculation, data storage and retrieval, and computer-aided diagnosis.

These are the opening lines of the first paper ever published to use the term computer-aided diagnosis (CAD) in the title, by Gwilym Lodwick, one of the great visionaries in the field of radiology (1). Although this paper was published in 1966, these introductory statements still sound true today: CAD, or computer-aided diagnosis, is still an active field with great potential. And meanwhile, obviously, a lot has been achieved. In this paper the focus is on the analysis of thoracic computed tomography (CT). There now exist many commercially available workstations with CAD algorithms for chest CT onboard; the Buyer's Guide at the website of Aunt Minnie provides an extensive, but not complete, overview. This is a recent development: most of these systems became available less than 5 years ago, and have been upgraded and improved several times since.

Lodwick himself worked on computerized estimation of the probability that pulmonary nodules were malignant, and published the first Radiology paper on that topic in 1963 (2). He used features that were visually determined by human raters from chest radiographs as input for a Bayesian classifier. So even if in this case the image processing was performed by humans, we can argue that the first application of CAD was in chest radiology.

Computed tomography for the body has been available since 1975. Originally, CT was not considered suitable for imaging the lungs because of the large attenuation differences between lung parenchyma and surrounding structures (3). However, technological advances quickly solved this problem. In the 1980s high resolution CT was introduced and became a powerful tool for the *in vivo* analysis of the lungs. Section thickness was 1 mm and these images could provide anatomical detail comparable to that from gross pathological specimens (4). The limitation of obtaining such thin sections only at 1 cm intervals disappeared with the advent of spiral scanning and the introduction of multi-detector row CT. The 'slice wars' are still raging on but for a single scan of the thorax a 16-slice scanner is perfectly capable of producing isotropic images with sub-millimetre (0.8 to 0.5 mm) resolution. These images can be acquired in a few seconds, well within a single breath hold. Improved detector efficiency has made low dose scanning (for example 30 mA s at 120 kVp) possible and even lower dose levels, comparable to those of a standard chest radiography examination (a posterior–anterior and a lateral projection) have been used and found to be sufficient for many purposes (5). This is important as the use of ionizing radiation is a main drawback of CT compared to other modalities, such as magnetic resonance imaging (MRI).

Other arguments against the use of CT for imaging the lungs, such as the need for the most expensive CT scanners to achieve the best image quality and the problem of storing the large amounts of data (200–300 MB per scan) have quietly disappeared as technology has marched on. This has decreased the cost of a chest CT examination

substantially. Some publications suggest these as $1000, but a more realistic estimate may be ten times lower. Mass screening with chest CT is seriously considered in many trials worldwide (6–8).

What remains as an enormous challenge is the accurate interpretation of the enormous amounts of information contained in these scans, in other words, how do radiologists deal with the *data explosion* (9). It is clear that CAD is a promising solution to facilitate CT interpretation. As a consequence, the rapid developments in chest CT acquisition techniques have been followed by a sharp increase in research on computer analysis of thoracic CT scans. A quick analysis of the amount of publications in the last 15 years reveals a growth rate of around 1.5 per year. This is currently levelling off but not declining, indicating that CAD of chest CT is a mature and prospering research area.

There are quite a few recent review articles that discuss research progress in this area. Some reviews with a clinical perspective that I found useful are Girvin and Ko (10), Goldin et al. (11) and Ko and Naidich (12). Overviews that focus on algorithmic techniques can be found in Sluimer et al. (13) and, for nodule detection in particular, in Li (14).

In this review I will discuss the state of the art in nodule detection and nodule volumetry and quantification of emphysema. I ignore other modalities, such as MRI, positron emission tomography (PET)/CT and chest radiographs, and the use of 4D scanning (perfusion CT). There are many CAD applications that could help facilitate reading thoracic CT. An interesting roadmap is described in Summers (15). If we consider what is currently commercially available, three applications dominate: nodule detection, nodule volumetry and emphysema quantification. Many studies have been devoted to each of these applications. In this paper I will focus on these three and argue that many challenges remain.

A key purpose of this paper is to pinpoint an issue that applies to each of these CAD applications and to many others as well: the realization that different CAD algorithms often have different performance levels or simply different characteristics, and that, as a consequence, it is important to execute fair comparative studies. There is no doubting the extraordinary efficiency of the mammalian visual system, and therefore expectations of the performance computer vision applications are huge: humans do not expect something that they can do effortlessly to be difficult for a machine. Developing machine vision, or CAD systems, is, however, extremely difficult. Algorithm developers face a multitude of choices and possibilities and generally do not know which approach will work best. Even for an experienced researcher in the field, it is often next to impossible to determine beforehand which algorithmic approach will work best. A main reason for this is that reported results have usually been obtained on proprietary data, selected by the algorithm developers. Direct comparisons are key to identifying highly promising and less promising techniques. CAD has gone through a first phase, in which the first versions of systems for many applications have been developed and progress was fast because low-hanging fruit was still plentiful; now, public comparisons, public databases and sharing of technology to develop systems that blend a multitude of techniques is essential to move the field forward.

## Nodule detection

Computed tomography is the most sensitive imaging technique for the detection of pulmonary nodules (16, 17). Using thin sections (1 mm or below) in combination with visualization techniques such as sliding maximum intensity projections has been shown to improve detection rates compared with the use of thicker sections (18). Even with such techniques, detecting nodules is tedious and time-consuming and reader fatigue may lead to missed nodules. Computer-aided detection is therefore a promising technique, if it can achieve high sensitivity at a low false-positive (FP) rate.

Several commercial systems are now available for nodule detection, and a large number of systems developed by academic research groups have been described in the literature.

These systems follow the almost universal paradigm for computer-aided detection systems: pre-processing, candidate detection, feature computation, classification. Pre-processing can exist of subsampling or upsampling the data, adjusting the section thickness and noise removal to ensure the characteristics of the scan to be analysed are similar to those of scans used for training the system. Next, candidates (sites representing possible nodules) are computed. Here a wide variety of options are available, ranging from thresholding (nodules are dense and may be isolated), local shape analysis (nodules are spherical and differ from vessels that are tubular), orientation analysis (at the border of a sphere, all gradients point to the centre and this can be detected by letting gradients 'vote' for points long their direction), template matching and enhancement filters (moving over the data with nodule-like examples and see if they resemble the local structure) and so on.

Pulmonary nodules are a wildly variegated bunch. A candidate detector that is optimal for solid nodules of 4–10 mm diameter – which is the type of nodules most CAD schemes focus on, understandably as they represent the bulk of all findings – will often not detect a non-solid lesion, a pleural lesion, and is even likely to miss big nodules that are likely cancerous. Such misses can undermine the user's faith in a CAD system: if the computer cannot even detect such obvious nodules, how can I trust it to find more subtle lesions? Comprehensive nodule detection schemes should probably combine multiple candidate detectors. Most systems, however, use only one.

The next step involves computation of numerical characteristics (features) that, in combination, should produce a different response for the true nodules compared with the candidates that do not represent nodules, the FP. Here the number of possibilities is even larger. The most common features for classification are grey-level features (density inside and around the candidate), shape descriptors, and spatial and size information. But systems that have access to other information, for example if an accurate segmentation of the pulmonary vasculature is available, produced by some external algorithm, can use this to define additional powerful features. Again, it is unlikely that a good combination of features for solid, isolated nodules will also work well for other types of lesions. Sophisticated systems therefore use different sets of features or even combine entire systems later on in the processing chain.

The set of features computed for each candidate is fed into a classifier. This is essentially a mathematical function that maps this input to an output: the probability that the candidate represents an actual pulmonary nodule. The parameters that define this function are usually learned in a training stage where pairs of input and output values are presented to the classifier. At this stage, the problem of nodule detection is translated into a standard statistical pattern recognition or machine-learning problem. Many different classifiers exist, such as neural networks, linear discriminant classifiers, k-nearest-neighbour classifiers, support vector machines and Gaussian processes, just to name a few. Unfortunately it is not possible to determine *a priori* which classifier will work best. They each have their own strengths and weaknesses. Some can, for example, deal well with the situation where the number of samples available for training is relatively small compared to the number of features; others are optimal if the distribution of samples in the feature space follows a particular distribution. Many classifiers can be combined with feature selection and feature extraction strategies that determine which of the possible features are most powerful for the task at hand.

Several schemes, for example (19), take an alternative approach, and do not specifically define features to feed into a classifier. They extend the candidate detector with additional rules, for example based on geometrical reasoning, and end up with a designed procedure to detect nodules, without resorting to statistical analysis. This can lead to systems that are relatively insensitive to peculiarities of the data they are used on, such as section width or reconstruction kernel.

What does this all boil down to? On the one hand, it is a researchers' paradise: endless possibilities to vary CAD systems, resulting in an ongoing stream of publications (19–55) and a number of commercially available systems (not all of them FDA approved, some are marketed as 'enhanced viewing').

For a user, on the other hand, it is unclear which system works best. For the commercial systems it is usually not even known how the underlying algorithm works. Many studies list performance measures. These results are obtained, however, on different data sets, with substantially different characteristics, notably in section width and distribution of nodule sizes. Still, some of these studies provide a good insight into the strengths and weaknesses of the major commercially available systems. For example, Lee et al. (43) measured performance of the ImageChecker CT LN-1000, developed by R2 Technology. This technology has been acquired by Mevis (Pewaukee, WI, USA) and recently released as Visia CT Lung. The system was applied to 70 scans with 78 nodules. CAD detected 47 (60%) of these and produced 1.56 FP nodules per CT study. Sensitivity of four observers increased slightly when reading with CAD compared to without, but that difference did not reach statistical significance. CAD detected eight nodules that were not mentioned in the original clinical radiology reports, indicating that CAD can occasionally identify missed nodules. The authors stratified the FP by CAD into vessels ($N = 68$), scars ($N = 17$), postoperative suture material ($N = 9$), calcified hilar lymph nodes ($N = 5$), focal pleural thickening ($N = 4$), small foci of atelectasis ($N = 3$), a rib ($N = 1$), a segment of bronchial wall ($N = 1$) and a thickened fissure ($N = 1$). Clearly vessels pose a major problem, this is in agreement with our own experience that many FP on vessel branch points are produced by various CAD schemes. For human observers, scars were the most common source of FP findings, so clearly there is a systematic difference between humans and CAD, and there is room to improve the CAD schemes.

Das et al. (56) drew similar conclusions in their comparison of the ImageChecker CT and Nodule Enhanced Viewing (NEV) (Siemens Medical Solutions, Forchheim, Germany):* "The sensitivity of the CAD systems is not perfect, and although CAD software should not be used as a first reader, it could have value as a second reader. Although it is not yet clear why some nodules are missed by the software system, the CAD software tends to work better for smaller nodules than for larger nodules. Usually, the number of false-positive findings is a major drawback of CAD systems. In our study, both CAD systems had similar false-positive rates, with ImageChecker CT having fewer false-positive findings than NEV. Often, both software tools marked vessel bifurcations or small consolidations, which could be easily dismissed by the radiologists."

The fact that both systems in this comparison produced different number of FP makes it difficult to compare sensitivities. The numbers were 73% sensitivity at six FPs per scan for ImageChecker CT and 75% sensitivity at eight FPs per scan for NEV. Interestingly, the number of FP for ImageChecker is much higher in Das et al. (56) than in Lee et al. (35). It is unclear whether the same version of

*Note that this study was co-authored by employees from Siemens.

the software was used, a version number is not provided in Das et al. (56). Recently, Godoy et al. (57) published better results for ImageChecker CT V2.0, in a study partly funded by R2 Technology. They reported a sensitivity of 87.7% for lung cancer nodules with a diameter of 4 mm and larger with either solid or semisolid morphology, at an FP rate of 0.9 per scan. The number of lung cancer nodules was small and sensitivity at baseline was only 60%.

A more meaningful comparison would be to have the same sensitivity or FP level for different systems. Most commercial packages do not allow the user to choose the FP rate. For CAD software we developed in-house, we had this freedom. We compared our CAD system (48) with the results of Lee et al. (35) by adjusting our sensitivity, so we obtained 1.56 FP markers per scan on average. Results are shown in Table 1. The drawback of this comparison is that it was made on different databases. More comparisons are given in Li (14).

Trying to summarize results for different studies, we note that sensitivity varies around 60–90% at a FP rate of 1–8 per scan; vessel bifurcations are much more often mistaken for nodules by CAD systems than by humans, and these results pertain to solid nodules only. Detection of part-solid and non-solid nodules is not well developed yet. I believe most radiologists think the systems should be improved before they are useful in clinical practice. Girvin and Ko (10) summarize the situation as follows: 'Clinical use of CAD will likely be hindered unless false-positive detections are minimized'.

A major step forward to more objective measurement of CAD performance is the creating of a publicly available database by the Lung Image Database Consortium (LIDC) (58). A number of annotated scans are available on-line at https://imaging.nci.nih.gov/ncia/. So far, this collection contains only a small number of thin section scans, limiting the usefulness of the database. Because the annotations are freely available, companies and research groups report their results on different subsets of the data base in different ways, making the results again difficult to compare.

Recently, we launched ANODE09, an initiative to compare CAD systems for nodule detection in a fair way. At http://anode09.isi.uu.nl, 50 scans from the NELSON study (8) can be downloaded and results of nodule detection algorithms can be submitted. All results are evaluated in the same way and are available online.

**Table 1:** Comparison between two CAD systems for the detection of pulmonary nodules, at the same FP rate, but tested on different data, roughly matched for nodule diameters. The ImageChecker results are taken from Lee et al. (35), the ISICAD results are taken from Murphy et al. (48)

| | R2 ImageChecker CT LN-1000 | ISICAD |
|---|---|---|
| FPs per scan | 1.56 | 1.56 |
| Sensitivity (%) | 60 | 64 |
| No. scans | 70 | 142 |
| No. nodules | 78 | 268 |
| Nodule diameter (mm) | 4–15.4 | 2–14 |

CAD: computer-aided diagnosis, FP: false positive.

An important issue regarding nodule detection is that different observers disagree on what constitutes a nodule in chest CT. The definition of a pulmonary nodule (a round opacity, at least moderately well marginated and no greater than 3 cm in maximum diameter; 59) is apparently not precise enough. The LIDC study has made this clear nicely by asking four observers, first blinded, next unblinded, to indicate nodules in chest CT scans. It was found (60) that in 90 scans for nodules ≥3 mm, there were 174 nodules where at least one of four observers said it was a nodule, for 146 of those at least two of four observers agreed, for 121 at least three agreed and for 90 all four agreed. These results indicate that there is a large class of nodules for which human expert observers agree, but an approximately equally large group about which there is no consensus among observers. If a CAD system would place a marker on such a nodule, should it be considered a true positive or an FP? To circumvent this discussion, we introduced a category 'irrelevant findings' in the ANODE09 study. First, two radiologists annotated all findings that might represent a nodule. An expert radiologist then divided these into three groups: (i) relevant nodules, that should not be missed, (ii) irrelevant nodules (e.g. benign findings such as calcified nodules) and findings mimicking nodules (e.g. scar tissue) and (iii) non-nodules. CAD marks on findings in the second category do not count as true positive or FP; these areas in the scan are simply ignored for the purpose of evaluation.

Alternatively one could evaluate the sensitivity by only considering proven cancers, as these are the nodules that one wants to detect. This is a very sensible approach, but would require large databases to obtain enough smaller nodules (<1 cm diameter) that are proven cancers. It is also not clear in this approach when a mark should be considered an FP; it seems not sensible to count a mark on a benign nodule that is similar in appearance to malignant nodules as an error.

## Nodule volumetry

The size and growth rate of a nodule highly correlate with the chance of malignancy. Benign nodules typically have either a very small (less than a month for inflammation or pneumonia) or a very large doubling time (more than 16 months). The volume doubling time for cancers is typically between 40 and 360 days (61). To measure nodule size and growth rate, the most straightforward approach is to segment the nodule. For these reasons, nodule segmentation has a lot of attention. State-of-the-art algorithms operate in 3D. The major industrial vendors currently all provide automatic nodule segmentation in their chest workstations. Most systems require the user to manually indicate a seed point in the nodule.

It is difficult or impossible to obtain a ground truth for nodule segmentations in real clinical data. Manual outlines, provided by experts, have been used often, but inter- and intra-observer differences in such outlines are considerable (62). In particular, the LIDC consortium (58) has released a data set with many different manual segmentations of the same nodules, showing large variations between observers.

Several studies have used phantoms for algorithm validation and some of these phantoms even contain structures mimicking part-solid nodules (63). However, it is very difficult to realistically model the wide variety of pulmonary structures encountered in patients using phantoms. Therefore, any validation of a nodule segmentation algorithm that is based entirely on phantom data should be taken as a proof of concept only: if an algorithm fails on phantom data it cannot be trusted to be correct on real data, but not vice versa.

In the absence of a ground truth, algorithms can also be evaluated in terms of their reproducibility. Most published algorithms require a manually indicated seed point, and a slightly different seed point should not lead to substantially different segmentation. This has been investigated in several studies (64, 65). Surprisingly, many algorithms appear to be quite sensitive to the exact location of a seed point, although it should not be difficult to design an algorithm that is largely insensitive to this (as long as the seed point is within the nodule). More importantly, it has been investigated if consecutive scanning of the same patient leads to reproducible nodule size measurements (65– 67). Reasons for measurement deviations in repeated scans are image noise (especially evident in low-dose scans), partial volume effects and variations in inspiration level. Several studies reported 95% limits of agreement for volume around 20% using commercial software with manual interaction by a radiologist. Note also that algorithms that make errors in volume measurements for example when compared with manual segmentation can still be reliable to determine growth rates, if the errors are systematic, as observed by Mullally et al. (68). It should be noted, however, that these studies generally only used segmentations that were visually determined to be successful; failures were discarded.

The excellent contrast between tissue and air on CT makes segmentation of an isolated solid nodule of reasonable size in principle a fairly simple task. When the nodule is small, partial volume effects play a role, which may hamper accurate measurements. More importantly, nodules are often attached to vasculature, pleura or fissures. Where to cut off the nodule from its connections is a major challenge. Segmentation of non-solid nodules is a really different task. Algorithms to do this are now appearing (69, 70) but are not discussed here.

Most algorithms follow an approach along the lines of the algorithms published by Kostis et al. (71) and Kuhnigk et al. (72). To compensate for partial volume effects, a region around the seed point is supersampled, for example to 0.3 mm isotropic resolution. From the seed, a region-growing operation is started, with particular rules used to determine the threshold. This yields the nodule and attached structures. A dedicated sequence of image processing steps separates the surrounding structures from the nodule, exploiting the fact that the shape of the attached structures is different from the roughly spherical nodule. The details in these steps are crucial. For example, a recent publication (73) showed that slight improvements to the rules proposed in Kuhnigk et al. (72) could improve the results substantially for many pleural nodules.

How do the different systems that are available compare to each other? Do they perform similarly, or are there large differences in performance? A recent study (74) investigated this for six commercial workstations: Advantage ALA (GE,v7.4.63), Extended Brilliance Workspace (Philips, EBW v3.0), Lungcare I (Siemens, Somaris5 VB 10A-W), Lungcare II (Siemens, Somaris 5 VE31H), OncoTreat (MEVIS, v1.6), and Vitrea (Vital images, v3.8.1, lung nodule evaluation add-on included). A single observer segmented 214 solid nodules in two low-dose unenhanced CT scans in 20 patients referred for pulmonary metastases. First, each nodule was segmented with a single click, and if the segmentation was not considered perfect, the results were adjusted by interaction, if the system allowed for that. The observer scored the segmentations as adequate or inadequate (the repeatability between observers of this visual assessment was tested and found to be high). The results yielded striking differences between packages, and also showed that without adjustments, all systems were prone to failure. Without adjustments, the best system gave 'perfect' segmentations of nodules in both scans in 62% of all cases, the worst system in only 32%. We can conclude that even for solid nodules, automatic segmentation is far from solved (the study did not consider part-solid or non-solid nodules). With adjustments, the best system produced perfect segmentation in both scans in close to 80% of all cases. The worst system did not improve (apparently it did not allow manual adjustments). Results of the other systems were roughly equally distributed in between.

As stated before, a major impediment to algorithm development and validation is the impossibility to obtain a ground truth for nodule segmentations in real clinical data. Analysis of 18 manually produced outlines of 23 nodules, as provided by the LIDC (58), revealed that only 15% of voxels that were annotated to be nodule by at least one manual outline, were included in all manual outlines. In other words, there is disagreement among expert observers about almost all voxels that are considered to be nodule by any observer. This suggests that it might be better to consider nodule segmentation in a probabilistic manner, and try to estimate the probability that a voxel belongs to a nodule, instead of a binary yes/no decision. This is the approach I took previously (75). By learning from training data, a classifier decides on a per voxel basis the likelihood

that it would be considered nodule by a radiologist. This approach also works for non-solid nodules. The result is illustrated in Fig. 1.

Most segmentations of nodules are made to determine growth rate by comparing the volume between two scans. Reeves et al. (76) show convincingly that growth rate can be estimated more accurately if both scans and segmentations are considered simultaneously. Suppose that one of the segmentations erroneously contains a part of an attached vessel. This would lead to an inaccurate estimate of the doubling time. In this case, the differences between the two segmentations are located mainly in the vessel. If a nodule grows, it tends to grow everywhere, and the difference between the two segmentations would be a ring-like structure. Inspecting the differences between segmentation, and using image processing to distinguish true growth from segmentation inaccuracies can be used to adjust the segmentations and making them consistent.

Finally, several authors attempt to determine growth without resorting to explicit segmentation at all. This is a promising approach to circumvent the problem of determining precisely which voxel belong to the nodule. Staring et al. (77) registered regions around non-solid nodules locally rigid, but elastically in the neighbourhood and subtracted these registered pairs to enhance differences in size and density. Four observers rated size and density change in the nodules by visual comparison alone and with additional availability of a subtraction image. It was shown that image subtraction improved the evaluation of subtle changes and decreased inter-observer variability.

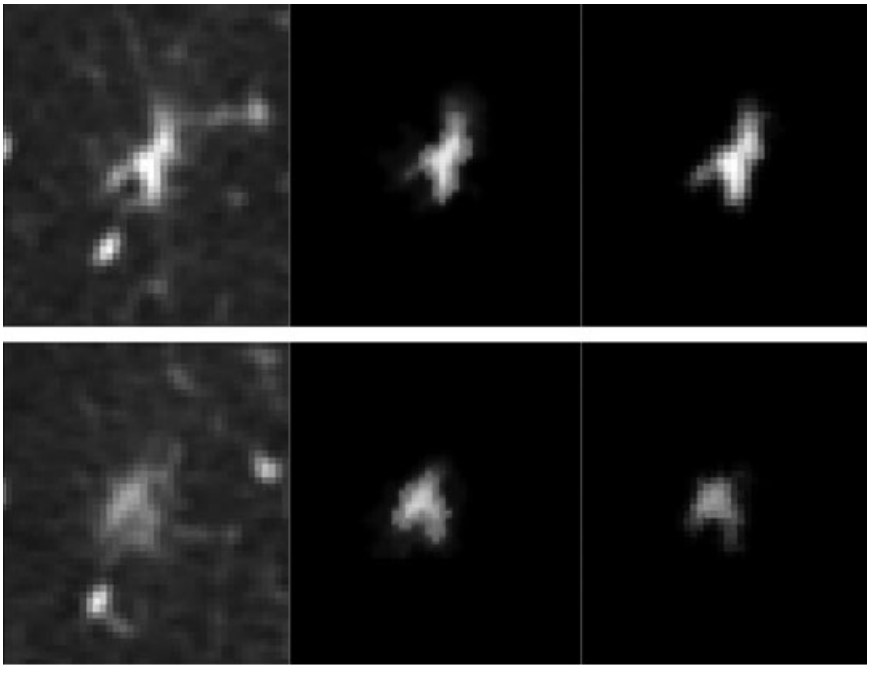
Kabus et al. (78) combined segmentation and elastic registration. They inspected the Jacobian of the deformation field which is a local measure of growth or shrinkage, and used this to assess growth. They concluded, so far from simulated experiments only, that this is a promising approach that yields similar or better results than using segmentation alone.

Nodule volumetry is not a goal in itself. The underlying reason to measure size and growth rate is the need to decide whether a nodule is cancerous. There are many more signs that could be used to make this estimation, and this field is usually called nodule characterization. The attention of the CAD community is shifting towards nodule characterization, including information from other modalities such as perfusion CT and PET/CT (10).

### Emphysema quantification

Emphysema is often measured with CT in terms of an emphysema score, defined as the percentage of lung volume with an attenuation below a certain threshold (79). Commonly used thresholds are −910, −930, and −950 Hounsfield units (HU). A main attraction of this quantification method is its simplicity; compared with nodule detection and volumetry, where it is hard to define objectively what a nodule is and which voxels belong to a nodule, that problem is circumvented here by adopting an objective rule, namely thresholding. As an alternative to thresholding, a percentile score is used. A typical value is the 15th percentile, which is the HU value below which 15% of lung voxels fall. Both measures are trivial to compute once one has determined which voxels belong to the lungs.

An obvious drawback of this simple rule is that it is not certain that the voxels with low attenuation actually are emphysematous. This has been investigated by comparing



■ **Fig. 1.** Two sections through a complex-shaped nodule (left). In the middle the average of 18 manual segmentations is given. White denotes complete agreement that a voxel is part of the nodule, black indicates complete agreement that it is background. Note how many voxels fall in a 'grey zone'. Right: result of automatic classification per voxel using the system described in van Ginneken (75).

low attenuation areas in CT with the histopathological extent of emphysema, measured microscopically by Madani et al. (80), where the 1% percentile and thresholds below −960 yielded highest correlation. The thresholding and the percentile score are considered valid to use in longitudinal and interventional studies that want to use emphysema as an outcome measure according to Parr et al. (81). Stolk et al. (82) concluded that CT scanning is 2.5-fold more sensitive than using currently recommended lung function parameters to test for novel drugs for emphysema.

As lung segmentation is a prerequisite for most chest CT CAD anyway, vendors have all implemented it, and can include emphysema scoring in their workstations with little effort. All large vendors and several small companies offer automated or semi-automated packages for emphysema scoring.

The only difficulty, from an image processing perspective, in automatically determining such emphysema scores is to segment the lungs. A large number of algorithms have been proposed to do this; most perform a sequence of classical image processing steps such as region growing and morphological smoothing. Many 3D algorithms follow an approach comparable to the one described in Hu et al. (83). It is difficult to segment the lungs automatically in case they contain dense pathologies, but this is often not the case in subjects with emphysema. Nevertheless, a study that compared four commercially available packages to measure emphysema (84) on a set of 30 patients found that median lung volumes of the packages were 4966, 5460, 5590 and 5694 $cm^3$ respectively. These are considerable differences and they varied across scans.

Upon closer inspection, several alternatives for computing emphysema scores and sources of variations in these measurements can be identified. Some of these issues are discussed in Stoel and Stolk (85). For example, some researchers argue that it makes more sense to measure which part of the lung parenchyma is below a threshold, rather than working with the lung volume as there may be variability in volume of vessels, and it may be difficult to determine for the larger vessels where exactly they enter the lung. Scanner calibration issues and tube ageing can lead to small variations in HU values, which can be corrected by inspecting the densities of some fixed tissues, e.g. air and blood in the descending aorta (85). Most packages, however, do not apply such a correction.

Another important aspect is noise. If the radiation dose is lowered, noise levels in the scan increase. Lung parenchyma is denser and more common than emphysematous regions (except for patients with massive amounts of emphysema). Thus there are more voxels above the threshold than below. As a result, the offset due to noise brings more voxels below the threshold than above it. Therefore scans obtained with a lower dose, and also scans of obese patients, which have higher noise levels for the same scan protocol, will appear to contain more emphysema (see Fig. 2). Schilham et al. (86) have developed a special noise filter, called the NOVA filter, that equalizes the amount of noise in a scan. Using NOVA, similar emphysema scores and a similar distribution of emphysema is obtained from both high- and low-dose scans of the same patient. The result is illustrated in Fig. 2. With dedicated filters it may be possible to obtain more reliable emphysema scores from very low-dose CT scans. Most commercial packages however, do not apply any noise filter. Related to this effect, section width (80) and reconstruction algorithm also affect emphysema scores (87).

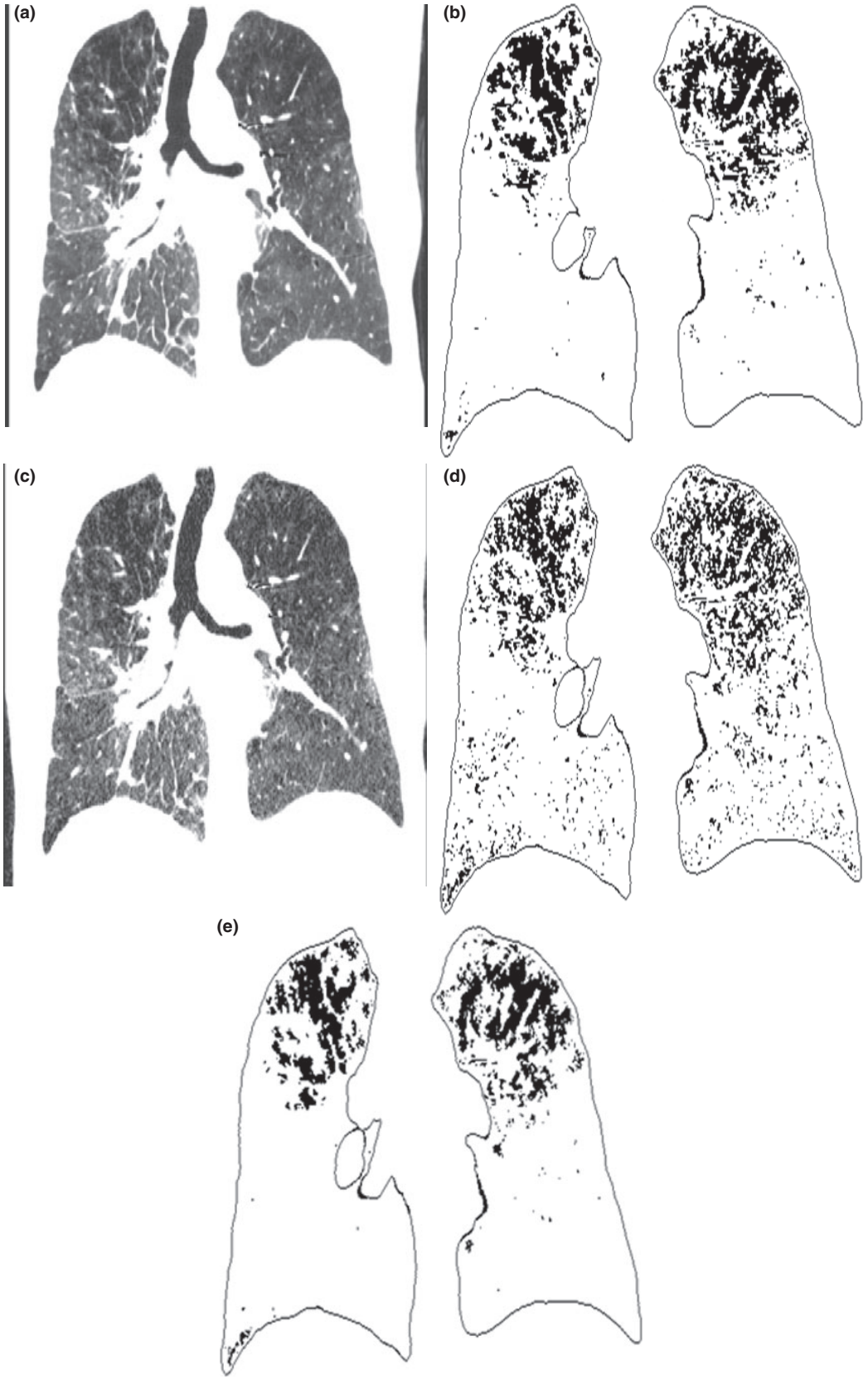
To deal with the problem of noise, some systems allow the user to remove bullae below a certain volume (for example only a few voxels). To do this, connected component analysis is applied to the voxels below the threshold, and small components are ignored. One can also quantify different types of emphysema by stratifying the bullae by size (88).

Emphysema is not the only reason a voxel in the lungs can have low attenuation; obviously a voxel in a bronchus also has attenuation values close to that of air. It therefore makes sense to segment the airway tree and disregard those voxels. Several packages apply this correction (84) but many do not. It is difficult to segment the airway tree and in practice different algorithms yield different results. This can affect consistency of the scores, especially if low thresholds are used and subjects have only small amounts of emphysema.

Finally, inspiration levels have a profound influence on emphysema scores. Lung density decreases at deeper inspiration levels, leading to more voxels that fall below the threshold. This is illustrated in Fig. 3. It is difficult to have patients achieve the same lung volume at repeat scans, even with spirometric control. If two scans of the same patient are available, one could try to correct the difference in emphysema score with a factor depending on the difference in lung volume (89, 90). Such a correction can only be used to quantify a change, as two scans are needed, and it cannot be used to compare emphysema scores between patients. An interesting alternative is to register both scans and quantify the changes per voxel, as proposed in Gorbunova et al. (91). All in all, it is not clear yet how to best correct for inspiration level when measuring emphysema.

A related effect is that of gravitation, which can cause differences of up to 50 HU between ventral and dorsal lung areas. This means that a single, global threshold or percentile value cannot accurately detect emphysematous areas. Wiemker et al. (92) demonstrate this effect and propose a correction factor.

As all these aspects contribute to inaccuracies on measuring emphysema, it is important to accurately quantify the measurement error. Gietema et al. (66) investigated the reproducibility of emphysema measurements in heavy smokers with low-dose multi-detector row CT. They found that low threshold yielded more




■ **Fig. 2.** (a) Coronal slice from a clinical dose scan. (b) Emphysematous voxels with a threshold of −930 HU. (c) Approximately the same slice from the same patient, scanned with a ten times lower dose. (d) Emphysema map now shows much more 'emphysematous' tissue. (e) Emphysema map of the slice in (c) after applying the NOVA filter (86). The similarity with the emphysema map in (b) is striking.

reproducible measurements. Stoel et al. (93) concluded that 'The data are not yet out to decide which technique is best suited to detect an early increase in emphysema on a per-patient basis'.

It is also possible to detect emphysema locally without solely relying only on HU values. Xu et al. (94) present a 3D local texture based analysis of the lungs. They classify small regions in the lungs into different categories: emphysema in severe chronic obstructive pulmonary disease (COPD), mild emphysema in mild COPD, normal appearing lung in mild COPD, normal appearing lung in normal nonsmokers and normal appearing lung in normal smokers.

This approach is clearly much less validated than the usual methods that use thresholds. However, it has the potential to be able to differentiate between different emphysematous patterns and it may be less sensitive to some of the sources of error discussed above.

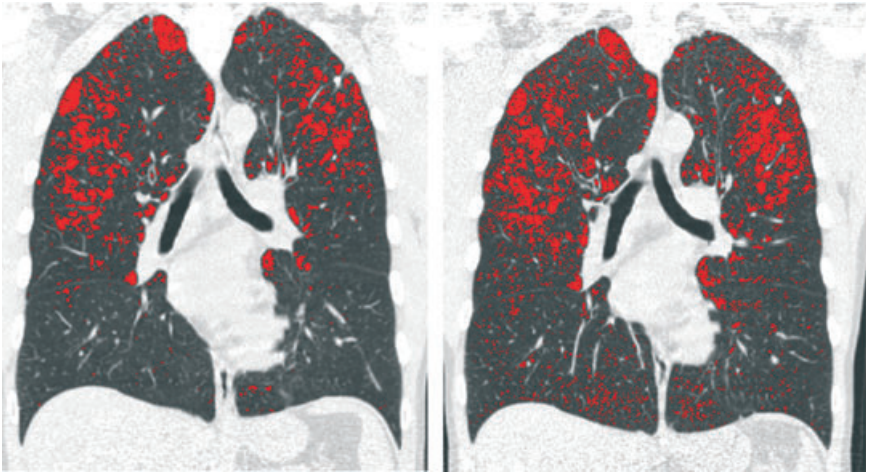
## Summary and outlook

In this overview, the three most mature CAD applications for the analysis of chest CT were considered: nodule detection, nodule volumetry and quantification of emphysema. There are a few striking similarities between these three applications. For each of them it is difficult to determine a standard of truth. Expert observers do not agree about what is a nodule. If they segment a nodule they produce different outlines, and the limited resolution of CT makes it impossible to determine exactly how much of each voxel in the lung is emphysematous. For each task, a fairly standard approach will yield good results in many cases, and from this one could conclude that the application has been 'solved'. A careful inspection of the results of schemes on unselected clinical data, however, reveals numerous failures. The scientific literature contains many more advanced, and usually more experimental and less carefully validated approaches to the problems.

Is it important to conduct further research in these areas or are the solutions that are currently provided by several vendors sufficient for widespread clinical use? It is clear that great progress has been made in the past 5 years, and I believe that we are close, but for each application more research is needed.

It is my impression that the silent majority of radiologists, who have not published about the subject but have tried to use nodule detection in clinical practice, are convinced the CAD schemes are not good enough yet. To be useful, sensitivity must be very high, and that leads to much too many FPs that need to be inspected. As a result, the percentage of chest CT scans that are analysed with CAD is negligible. The topic receives much publicity, though, and when a truly effective CAD scheme would be available, would be well integrated in clinical workflow and would be affordable, I am convinced it would be widely used. To obtain such a superior CAD scheme, it is essential that academic and industrial researchers collaborate more closely, accurately measure the performance of various approaches and combine effective strategies.

Clinical guidelines still recommend two-dimensional diameter measurements to estimate the size of a potential tumour. Many radiologists are convinced that 3D measurements are superior. However, automatic algorithms still often produce visually unsatisfactory results and manual adjustments are tedious and time-consuming. Most solutions do not analyse both views of a nodule simultaneously when estimating growth rate. There is clearly still room for improvement here, especially in the



■ **Fig. 3.** Left: a coronal slice from a subject of a lung cancer screening trial. Total lung volume was 9.96 L, emphysema score with a threshold of −930 HU was 7.2%. Emphysematous voxels are shown in red. Right: Approximately corresponding slice from a 3-month follow-up scan of the same subject. It is unlikely that emphysema progresses substantially in such a short period of time. Here the emphysema score is 11.1%. This is probably caused by the deeper inspiration; total lung volume in this scan was 11.86 L. Note that from these coronal slices it is not directly evident that lung volume is almost 20% higher.

segmentation of non-solid nodules and nodules with complex attachments. And it is crucial to improve the accuracy of growth rate estimations: the more accurately this can be measured, the shorter intervals between a baseline and a follow-up scan can be and the more likely it is to detect a cancer in an early stage, leading to long-term survival of the patient.

Emphysema quantification is already used in clinical trials. If better treatment options would become available it may be used more often in the clinic. Careful analysis of the sources of error in the quantification of emphysema and devising corrections for each error could lead to more accurate measurements, and these could shorten the required time and reduce the number of required participants for trials. Improvements are also needed to measure the early development of COPD, which will need to be done with low-dose CT scans.

It is worrisome that my conclusion, that further improvements are needed, may be wrong. It may be that one of the proposed nodule detection schemes is already very good and does not exhibit the weaknesses of its competitors. The spectacular recent results from Godoy et al. (57) may hint at this. Careful comparison studies, such as de Hoop et al. (74) and Heussel et al. (84) are needed, on a regular basis, to be able to objectively determine the state of the art in the field.

Much of what has been said also applies to less mature CAD applications in chest CT, such as the detection of acute pulmonary embolism, the quantification and classification of interstitial abnormalities and evaluation of airway morphology, which may become an important topic in future because airways are readily responsive to treatment, and computer analysis of chest CT could be a fast way to study the effect of a new drug than analysis of lung function or patient outcome. In all these areas, the first systems are already available. It is clear that computer analysis of chest CT scans will remain a very active research field in the years to come.

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