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Lung cancer differential diagnosis based on the computer assisted radiology: The state of the art

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Summary

The concepts of the modern computer-aided diagnosis (CAD), the methods of pulmonary nodules detection and facts derived from the available literature on the pulmonary nodule differential CAD topic are compiled in one source and described in some details. Several issues of the lung cancer epidemiology and an early diagnosis are discussed. The analysis of the performed research shows an evidence that various CAD systems can be successfully applied for chest radiographs, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET). These modalities can serve as a useful tool for a practicing medical professional facing the burden of a routine diagnostic job.

Key words: lung cancer • CAR • pulmonary nodule image

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Progress in the field of biomedical imaging

The recent development of solid state image receptors (eg, photosensitive flat-panel arrays, micro machined piezoelectric arrays, quantum dots) is a major evolutionary step in biomedical imaging. To store images in a computer, the image are divided into smaller sections called picture elements, or "pixels" [1]. Each pixel is assigned a single numerical value that denotes the color, if a color image is stored, or the shade of gray (referred to as the gray "level"), if a black and white image is stored. The image is like a jigsaw puzzle, except that each piece is a square and has a uniform color or shade of gray. The numerical values are represented in binary (or octal or hexadecimal) notation, and the image is said to be "digital." The set of pixels composing the image is referred to as the image "matrix." That is, a digital image consists of a matrix of pixels. Some images are computer generated directly in pixel or digital form. Computed tomography (CT), magnetic resonance, and computed radiography are examples of technologies that produce digital images directly. An image such as a chest film that was not originally "digital" can be entered and stored in a computer by dividing it into a matrix of squares and assigning the average color (or shade of gray) within each square as a single numerical value for the pixel. An image modified in this fashion is said to have been "digitized." If a few pixels are used in digitizing an image, the result is a coarse or "blocky" appearance. If a larger number of pixels is used, the observer may not even notice that the image is digital. It is not necessarily better to break an image into the largest matrix size (smallest pixels). If the computer has limited storage or if the processing and transmission time for the images is restricted, then a smaller matrix size (larger pixels) may be desirable. Matrix sizes are typically powers of 2, reflecting the binary nature of computer storage (e.g., 64, 128, 256, 512, 1024,...) [2].

Pattern-recognition programs can detect anatomic and physiologic abnormalities on images by using computer-aided detection and even characterize some of them with computer-aided diagnosis; these capabilities are likely to have enormous long-term influence on medical care and the profession [1].

Chest radiography is by far the common type of procedure for the initial detection and diagnosis of lung cancer [3,4]. The detection of pulmonary nodules in chest radiography is one of the most studied problems in X-ray image analysis [5].

The use of CT has increased rapidly, both in the United States and elsewhere, notably in Japan; according to a

survey conducted in 1996, the number of CT scanners per 1 million population was 26 in the United States and 64 in Japan. There are 50 CT scanners in the Republic of Belarus. Half of them are multi-slice apparatuses. It is estimated that more than 62 million CT scans are currently obtained each year in the United States, as compared with about 3 million in 1980. This sharp increase has been driven largely by advances in CT technology that make it extremely user-friendly, for both the patient and the physician [6].

Computer-aided diagnosis: Definitions, concepts, technologies and their applications

Definitions and technologies of decision support systems and CAD

CAD – computer-aided diagnosis has generally been defined by diagnosis made by a physician who takes into account the computer output based on quantitative analysis of radiological images. The basic technologies involved in CAD schemes are: (1) image processing for detection and extraction of abnormalities; (2) quantitation of image features for candidates of abnormalities; (3) data processing for classification of image features between normals and abnormals (or benign and malignant); (4) quantitative evaluation and retrieval of images similar to those of unknown lesions; and (5) observer performance studies using receiver operating characteristic (ROC) analysis [7].

An expert system-or, more modestly, a decision support system seeks to apply an expert's knowledge and reasoning to problems in a particular domain. Decision support systems have been developed in a wide variety of medical disciplines, and many of these systems are coming into widespread clinical use. Decision support systems can capture the expertise of radiologists to give referring physicians the information they need to choose imaging procedures appropriately. They also can help radiologists formulate and evaluate diagnostic hypotheses by recaffing associations between diseases and imaging findings [8]. Analysis by humans is usually subjective and qualitative. When comparative analysis is required between an image of a subject and another or a reference pattern, a human observer would typically provide a qualitative response. Specific or objective comparison – for example – the comparison of the volume of two regions to the accuracy of the order of even a milliliter would require the use of a computer. The derivation of quantitative or numerical features from images would certainly demand the use of computers. Analysis by humans is subject to interobserver as well as intraobserver variations (with time). Given that most analyses performed by humans are based upon qualitative judgment, they are liable to vary with time for a given observer, or from one observer to another. The former could be due to lack of diligence or due to inconsistent application of knowledge and the latter due to variations in training and the level of understanding or competence. Computers can apply a given procedure repeatedly and whenever recalled in a consistent manner. Furthermore, it is possible to encode the knowledge (to be more specific, the logical processes) of many experts into a single computational procedure, and thereby enable a computer with the collective "intelligence: of several human experts in an area of interest [9].

Recently published reviews on the topic of CAD

Several articles on the topic of pulmonary nodule detection have been published relatively recently (2004–2008). Professor Kunio Doi (2005) presented a comprehensive review of CAD in medical imaging. His work was based on his extensive experience at the University of Chicago and concentrated on pulmonary nodule detection on radiographs, low dose CT and high resolution CT, diagnosis of these nodules, quantitative analysis of diffuse lung disease and detection of intracranial aneurysms on magnetic resonance angiography. In particular, CAD techniques such as artificial neural networks, difference imaging, linear discriminant analysis, and morphological and three-dimensional (3D) selective enhancement filters are described with regard to their applicability. Dr Sue Astley (2005) described CAD algorithms and the nature of prompting, how prompts are placed on images, and how researchers should assess whether a prompt has been correctly placed. She described the principles that should be applied when evaluating algorithm performance and in the evaluation of CAD systems together with reader performance; for example, the impact of training is emphasized in order to achieve stability. performances in trials [10]. Rafael Weimker (2005), from Philips Research Laboratories Hamburg, presented the summary of algorithms developed and tested on lung nodules, emphasizing potential applications in early cancer detection and diagnosis of a nodule based on morphology and sequential volume changes. He pointed out that technical improvements in spatial and temporal resolution in CT thoracic image acquisition provided a good prerequisite for improving algorithmic performance in computer-assisted pulmonary nodule detection. This should provide a good basis for early detection of cancer and also for reducing the rate of biopsies. Detection of lung nodules combined with 3D volumetrics was outlined in his articles in detail. A brief description was given to algorithms to automate image registration between previous and follow up CT scans, enabling not only support for diagnosis but also monitoring the response to oncological therapy [10].

Sluimer, Prokop and van Ginneken (2005–2006) performed an extensive research in the realm of thoracic computed tomography scan computer analysis and the lung segmentation process and published the series of articles, describing in details the conducted studies on emphysema quantification, performances of various nodule detection systems, nodule characterization and presented the successful experience of clinical application of the refined segmentation-by registration scheme [11–13].

Qiang Li et al., 2007, reviewed only publications concerning CAD schemes for lung nodules in thin-section CT that were published in academic journals and were searchable by use of PubMed. Their conclusion claims that there is no evidence to date indicating that the CAD schemes, at their current performance levels, would improve radiologists' performance in the detection of nodules in thin-section CT [14].

Lung Image Database Consortium and its current activities

To stimulate the advancement of computer-aided diagnostic (CAD) research for lung nodules in thoracic computed

tomography (CT), the National Cancer Institute launched a cooperative effort known as the Lung Image Database Consortium (LIDC). The LIDC is composed of five academic institutions from across the United States that are working together to develop an image database that will serve as an international research resource for the development, training, and evaluation of CAD methods in the detection of lung nodules on CT scans. Prior to the collection of CT images and associated patient data, the LIDC has been engaged in a consensus process to identify, address, and resolve a host of challenging technical and clinical issues to provide a solid foundation for a scientifically robust database. These issues include the establishment of (a) a governing mission statement, (b) criteria to determine whether a CT scan is eligible for inclusion in the database, (c) an appropriate definition of the term qualifying nodule, (d) an appropriate definition of "truth" requirements, (e) a process model through which the database will be populated, and (f) a statistical framework to guide the application of assessment methods by users of the database. Through a consensus process in which careful planning and proper consideration of fundamental issues have been emphasized, the LIDC database is expected to provide a powerful resource for the medical imaging research community [15].

Overview of the conducted research trials on the topic of pulmonary nodules CAD

Several investigations have been performed describing the clinical application of the CAD systems for the detection of pulmonary nodules and this scope of work has elucidated several facts and ideas. The vast majority of studies had been discussed in the mentioned above reviews, here we describe only the selected ones from the available literature resources. According to Awai et al., 2006, use of the CAD system significantly (P=.009) improved the diagnostic performance of radiology residents for assessment of the malignancy of pulmonary nodules; however, it did not improve that of board-certified radiologists [16].

In research of Yuan, Vos, & Cooperberg, 2006, CAD detected 72.6% of true nodules and detected nodules in six (4%) patients not identified by radiologists, changing the imaging follow up protocol of these subjects. In this study, the combined review of low-dose CT scans by both the radiologist and CAD was necessary to identify all nodules [17].

Abe et al., 2005, reported that CAD could not identify 17 (22.7%) nodules of 75 participants, and all 17 were less than 6 mm in diameter. Authors concluded that the CAD system offered a useful second opinion when physicians examine patients at lung cancer CT screenings [18–21].

Kasai, Li, Shiraishi, & Doi, 2008, showed that in the detection of vertebral fractures and lung nodules on chest images, diagnostic accuracy among radiologists improved with the use of CAD [22].

The CAD program, described by Li et al., 2008, had an overall sensitivity of 35% (12 of 34 cancers), identifying seven (30%) of 23 very subtle and five (45%) of 11 relatively obvious radiologist-missed cancers (P=.21) and detecting two (25%) of eight missed not actionable and ten (38%) of 26 missed actionable cancers (P=.33). The CAD program made an average of 5.9 false-positive marks per radiograph. CAD system could mark a substantial proportion of visually subtle lung cancers that were likely to be missed by radiologists [23].

Lee et al., 2001, proposed a template-matching algorithm for the detection of nodules in a chest helical CT images using nodular models with Gaussian distribution as reference images. To detect these nodules, GA and conventional template matching methods were applied within the lung area and along the lung wall, respectively. Their nodule detection scheme performed at a rate of approximately 72%. Moreover, it was possible to eliminate nearly 88% of the FPs within the detected candidates using a feature analysis of 13 features. From their results, researchers found it was still difficult to detect low-contrast nodules and those in the apex and basis pulmonis effectively, and the number of FPs was as high as 30/case [24].

According to Lee et al., 2007, the rate of automated matching of metastatic pulmonary nodules on clinical serial CT scans was high (82.4%) when the lung findings and lung expansion between the serial scans were relatively unchanged. The rate decreased significantly. However, with substantial interval changes in the lung and a larger number of nodules [25].

As reported by Tao et al., 2009, the automated matching rate for pulmonary nodules in screening MDCT (multidetector computed tomography) scans was high (92.7%) and was not affected by the nodule size but was slightly lower with nodules at juxtapleural locations [26].

In work of Rubin et al., 2007, with CAD used at a threshold allowing only three FP (False positive) detections per CT scan, mean sensitivity was increased to 76% (range, 73–78%). CAD complemented individual readers by detecting additional nodules more effectively than did a second reader; CAD-reader weighted {kappa} values were significantly lower than reader-reader weighted {kappa} values (Wilcoxon rank sum test, P<.05). With CAD used at a level allowing only three FP detections per CT scan, sensitivity was substantially higher than with conventional double reading [27].

In study of prospective compartment of maximum intensity projection (MIP) and volume rendering (VR) of multidetector computed tomographic (CT) data for the detection of small intrapulmonary nodules, Peloscheck et al., 2007 concluded that VR is the superior reading method compared with MIP for the detection of small solid intrapulmonary nodules [28].

Marco Das et al., 2006, compared the performance of two dedicated CAD systems – Image Checker CT (R2 Technologies, Sunnyvale, California) and Nodule Enhanced Viewing (NEV) (Siemens Medical Solutions, Forchheim, Germany). Computer-aided detection was especially helpful for detecting small pulmonary nodules. There was increased agreement among radiologists with use of the computer-aided detection systems. Radiologist performance in the interpretation of multi-detector row CT scans

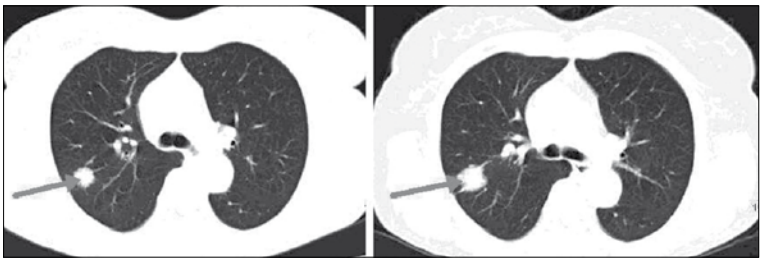

Figure 1. The image of a 65 year old woman. Slow-growing peripheral cancer of the right superior lobe. CT of the thoracic cavity in progress: at the left – the first scan, on the right – follow up scan, performed 2 years and 2 months later. The tumor has increased (marked with an arrow).

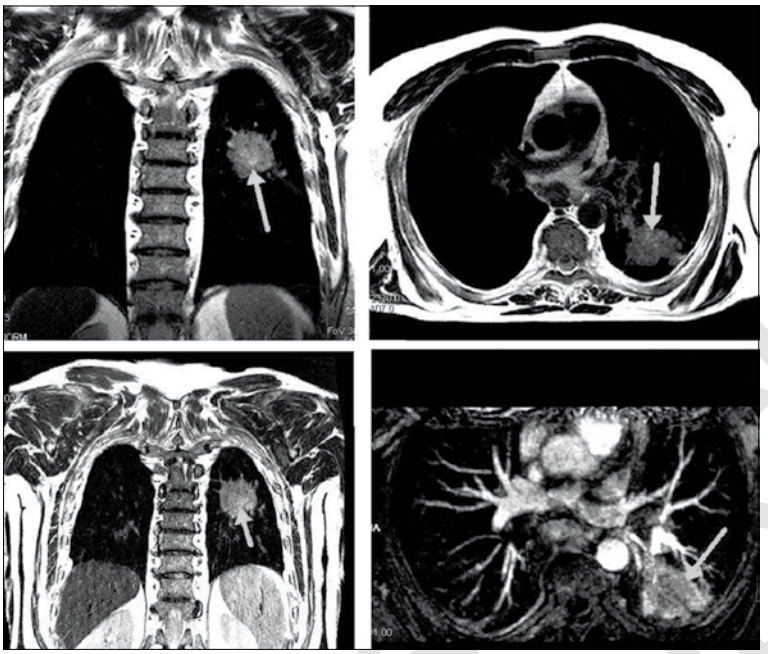

Figure 2. The image of a 61 year old man. Peripheral cancer of the left lung. MRI of the thoracic cavity: at the left above – T2-weighted image in a coronal plane, thickness of a cut – 6 mm; at the left below – T2-weighted image in a coronal plane, thickness of a cut – 4 mm; on the right above – T2-weighted image in transversal plane, thickness of a cut – 6 mm; on the right below – T1-weighted image in transversal plane after the intravenous introduction of contrast substance (Omniscan).

can be improved by using CAD systems, with a reduction in the number of false-negative diagnoses. No statistically significant difference in sensitivity was found between the two CAD systems [29].

Betke and Ko presented a computer vision system that automatically detects pulmonary nodules in computed tomography (CT) scans of oncology patients, performs size analysis and assesses for change in volume over time. Thresholding, backtracking, and smoothing algorithms have been developed to recognize the thorax and trace the lung border. The regions within the lung that potentially contained nodules were evaluated for their shape, size, and position. These candidate regions were then characterized as nodule versus other structures by comparing consecutive CT slices in the same study. A preliminary system for the registration of studies had also been developed. It estimated nodule volume in each study and evaluated the volumetric change over time [30].

Experience in pediatric oncology

In one investigation, CT scans from a series of pediatric patients with known primary tumors and lung nodules were analyzed by four radiologists and a commercially available CAD system. In 24 children (age 3–18 years) 173 nodules were identified. Overall the sensitivity of CAD was 34%, but the sensitivity of CAD for detection of nodules 4.0 mm or larger was 80%. Overall radiologist sensitivity ranged from 68% to 79%. There were 0.9 CAD false-positives and 0.3–2.4 radiologist false-positives per study. Researchers reported that CAD in their pediatric oncology patients had good sensitivity for detection of lung nodules 4 mm and larger with a low number of false-positives. However, the sensitivity was considerably less for nodules smaller than 4 mm [31].

Retrospective evaluation of computer-aided detection software (CAD) for automated detection (LungCAD, Siemens Medical solutions, Forchheim, Germany) and volumetry (LungCARE) of pulmonary nodules in dose-reduced pediatric MDCT showed that in study with 2 mm slice thickness and very small lesion sizes, the analyzed CAD algorithm for detection and volumetry of pulmonary nodules has limited application in pediatric dose-reduced 16-MDCTs. The determination of lesion size is possible even in the case of false-negatives [32].

Lung cancer: Epidemiologic and statistic data

Lung cancer (see Figures 1–4) is the most common cause of cancer death in both men and women in the United States and worldwide [33]. Lung cancer is the most commonly diagnosed cancer world-wide, accounting for 1.2 million new cases annually [34]

Lung cancer is one of the most prevalent cancers, with an estimated 173,770 new cases and 160,440 deaths attributed to the disease in 2004 in the United States alone. In 2006,

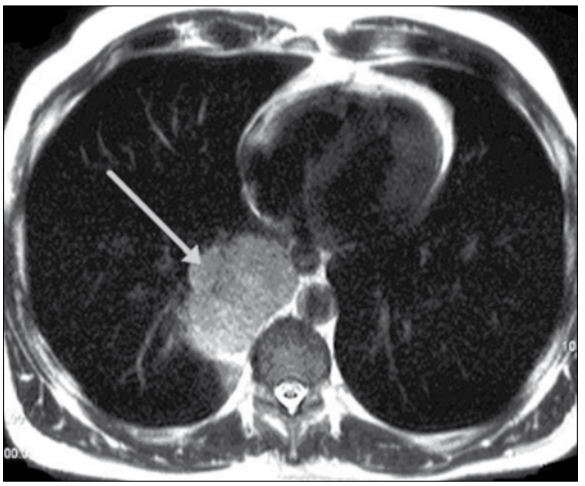

Figure 3. The image of a 63 year old man. Peripheral cancer of the right inferior lobe (highlighted with an arrow). MRI of the chest, T2-weighted image.

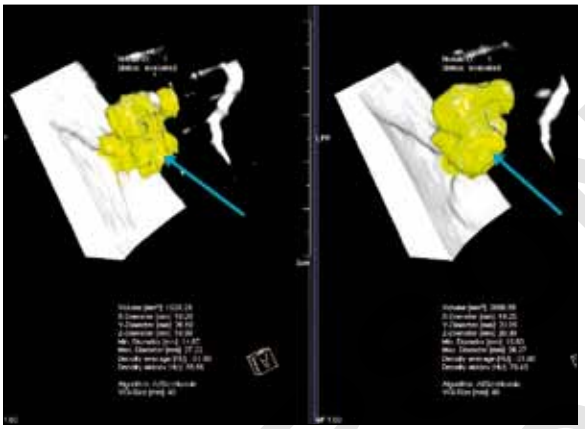

Figure 4. The image of a 72 year old man. Fast growing peripheral cancer of the lung. CT of the chest. Applied software – LungCARE (Siemens) for construction of the 3D models of the lesion, calculations of its sizes and volume. At the left – the first scan, on the right – repeated investigation in 2 months later. Tumor has increased in volume from 1929 mm^3 to 2686 mm^3 (see the arrow).

the LC caused over 158,000 deaths – more than colorectal, breast, and prostate cancers combined. The principal etiology of the disease is cigarette smoking [35]. Lung cancer is the leading cause of cancer mortality in Europe and in 1995 accounted for 330 000 deaths [36]. There were more than 38,000 new cases of lung cancer per annum in the UK, and this incidence is among the highest in Europe [37].

Lung cancer occurs most commonly between the ages of 45 and 70 years, and has one of the worse survival rates of all the types of cancer [38].

The chance of developing lung cancer is one in 13 in men and one in 18 in women. This incidence includes all people, and it does not take into account whether they smoke (Winer-Muram, 2006) [39].

According to the pathology reports, 4184 cases of lung cancer had been diagnosed in 2005 in Belarus (see Figures 5–7).

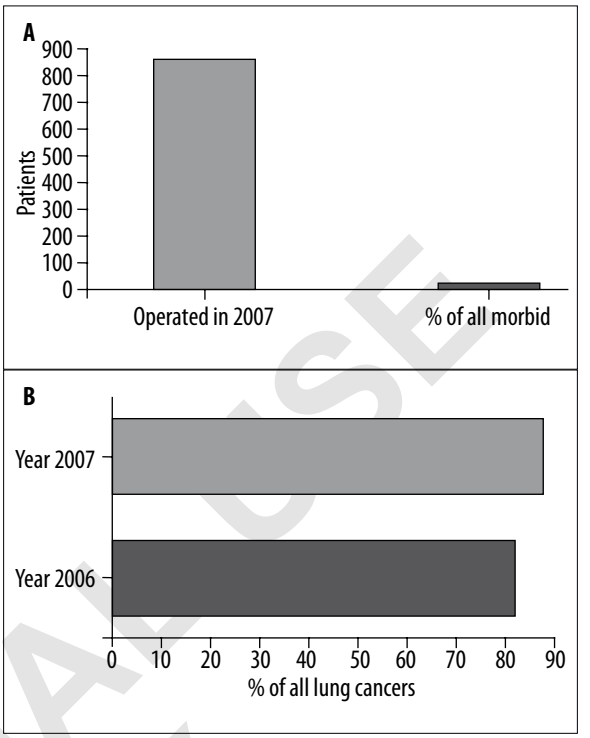

Figure 5. (**A**) The absolute number and percentageof lung cancer patients operated in 2007. (**B**) The rate of pathomorphologic vertfication of lung cancers.

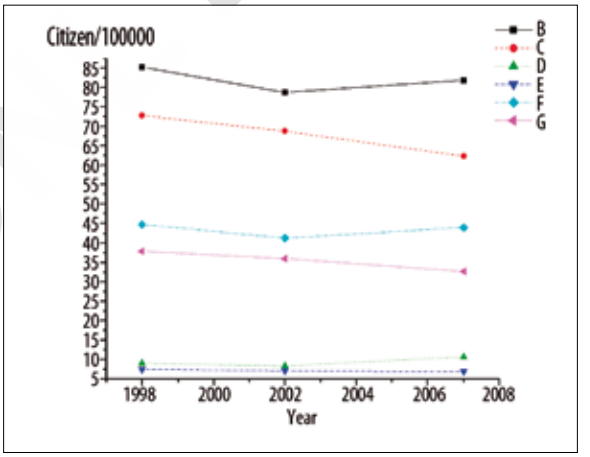

Figure 6. LC morbidity and lethality in Belarus 1998, 2002, 2007. B – Male morbidity; C – Male lethality; D – Female morbidity; E – Female lethality; F – Both genders morbidity; G – Both genders lethality.

Because one fourth of adults smoke, lung cancer will remain a problem for many years. Cigar and pipe smoking is less dangerous in terms of lung cancer. Since 1987 lung cancers are the leading cause of oncologic death in American women, who are the major consumers of cigarettes (Azzoli, 2006) [40], (Kantarjian, Koller, Wolff, & University of Texas M.D. Anderson Cancer Center., 2006) [41].

Image segmentation process

The principal goal of the segmentation process (see Figure 8) is to partition an image into regions that are

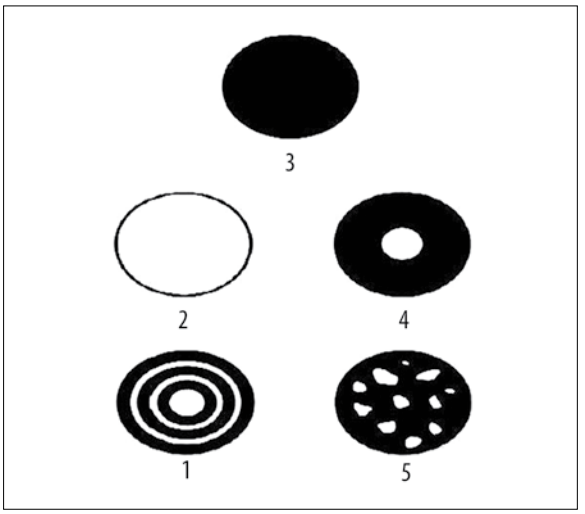

Figure 7. Nodule calcification patterns. 1 – laminated; 2 – complete; 3 – absence; 4 – central; 5 – "pop-corn" appearance (Leef et al. 2002) [90].

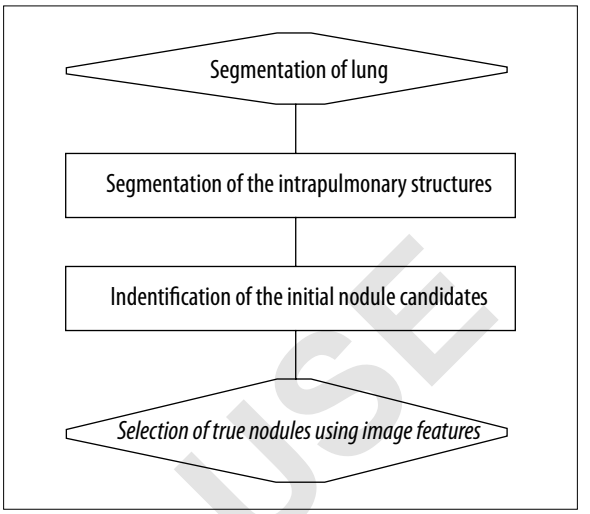

Figure 8. Diagram of the computerized scheme for detection of pulmonary nodules on CT images 80.

homogeneous with respect to one or more characteristics or features. Segmentation is an important tool in medical image processing and it has been useful in many applications including lesion quantification, surgery simulations, surgical planning, functional mapping, computer assisted diagnosis, image registration and matching, etc. A wide variety of segmentation techniques has been proposed. However, there is no one standard segmentation technique that can produce satisfactory results for all imaging applications. Quite often, methods are optimized to deal with specific imaging modalities such as magnetic resonance (MR) imaging and X-ray CT, or modeled to segment specific anatomic structures such as the brain, the lungs, and the vascular system [42]. In segmentation, the computer attempts to find the major objects in the image and separate or segment them from the other objects. Image segmentation is the process of dividing an image into regions or objects. It is the first step in the task of image analysis. Image processing displays images and alters them to make them look "better", while image analysis tries to discover what is in the image. The basic idea of image segmentation is to group individual pixels (dots in the image) together into regions if they are similar. Similar can mean they are the same intensity (shade of gray), form a texture, line up in a row, create a shape, etc. There are many techniques available for image segmentation, and they vary in complexity, power, and area of application [43].

Segmentation is the stage where a significant commitment is made during automated analysis by delineating structures of interest and discriminating them from background tissue. This separation, which is generally effortless and swift for the human visual system, can become a considerable challenge in algorithm development. In many cases the segmentation approach dictates the outcome of the entire analysis, since measurements and other processing steps are based on segmented regions. Segmentation algorithms operate on the intensity or texture variations of the image using techniques that include thresholding, region growing, deformable templates, and pattern recognition techniques such as neural networks and fuzzy clustering [44].

According to Awai et al., 2006, the segmentation process is divided into three steps as follows:

1. Interpolation of image data is performed so that the pixel sizes in the x-, y-, and z-axis became isotropic. This preprocessing is necessary to segment the nodule with a smooth boundary and to quantify accurately the morphologic features of the pulmonary nodule.
2. Classification of the nodule type is then determined. Nodules are considered as solid, as a ground-glass opacity, or as that with a cavity. This classification was achieved by calculating the averaged CT number (Cav) of the small-volume area, which was a 1.5-mm cube around the center of the ROI (Region of interest). Authors calculated the Cav of the cube and defined the types as solid for Cav of –150 HU (Housfield Units) or greater, as ground-glass opacity for Cav of greater than –150 HU to –800 HU or greater, and as a nodule with a cavity for Cav of greater than –800 HU.
3. Elimination of structures tangent to the nodule, such as vessels and thoracic walls, is performed. This elimination is achieved by using several image processing techniques, such as "snakes"and mathematical morphology. For example, vessels around the nodule are eliminated by using the "geodesic erosion/dilation" technique of mathematical morphology. At first, a lesion area within the ROI is extracted according to the threshold of the CT number. Then, the margin of the lesion area is eroded by a structure element that has almost the same diameter as the vessels adjacent to the nodule. Finally, the lesion area is dilated so as to reproduce the accurate margin of the lesion area without vessels [16].

To smooth lung boundary segmented by gray-level processing in chest CT images, Yim et al., 2006, proposed a new method using scan line search. Their method consists of three main steps. First, lung boundary is extracted by our automatic segmentation method. Second, segmented lung contour is smoothed in each axial CT slice. Scan line search is proposed to track the points on lung contour and find rapidly changing curvature without conventional contour tracking. 2D closing in axial CT slice is applied to reduce the number of rapidly changing curvature points. Finally,

to provide consistent appearance between lung contours in neighboring axial slices, 2D closing in coronal CT slice is applied within pre-defined subvolume. Experimental results have shown that the smoothness of lung contour considerably increased after applying proposed method [45].

For FP (False positives) reduction Dajnoviec et al introduced the idea of identifying vessels in order to use their connectivity with nodule candidates to reduce FPs. They also produced a modified bounding box which does a better job of characterizing lung nodules which have a non-trivial angular orientation [46].

Some specific difficult problems of the nodule appearance in CT studies have been solved in research by Badura et al., 2008: connections between the nodule and pleura (by the preprocessing stage), vascularization (the postprocessing stage), and low mean intensity of a nodule region (the fuzzy connectedness analysis) [47].

Experimental results showed that segmentation method described by Hong et al., 2008, gave accurate lung boundaries. In particular, lungs with large curvature or complicated shapes were accurately extracted. Their registration method was able to correctly find nodule correspondences in 20 patients. In addition, this method is 2.6 times faster than Euclidean distance based registration and 1.3 times faster than chamfer matching based registration when applying multi resolution techniques [48].

Pereira et al., presented an automated method for the selection of a set of lung nodule candidates, which is the first stage of a computer-aided diagnosis system for the detection of pulmonary nodules. An innovative operator, called sliding band filter (SBF), was used for enhancing the lung field areas. In order to reduce the influence of the blood vessels near the mediastinum, this filtered image is multiplied by a mask that assigns to each lung field point an a priori probability of belonging to a nodule. The result was further processed with a watershed segmentation method that divides each lung field into a set of non-overlapping areas. Suspicious nodule locations were associated with the regions containing the highest regional maximum values. The proposed method, whose result was an ordered set of lung nodule candidate regions, was evaluated on the 247 images with very promising results [5].

Pulmonary nodules: History, definition and characteristics

Definition of the pulmonary nodule

Chiari described the first solitary pulmonary tumor in 1883. This proved to be a peripheral chondroma and uncertainty about the nature of the solitary pulmonary nodule has persisted since. In 1897, the roentgen ray was discovered and the significance of the solitary pulmonary nodule took on new and wider concern. The surgical treatment of the solitary pulmonary nodule was initiated in 1925 by Evarts Graham when he resected a peripheral tuberculoma [49].

Graham and Singer reported a series of three cases of resected solitary pulmonary nodules in 1936, and Alexander, in 1942, recommended thoracotomy to establish a definite diagnosis in circumscribed lesions of the lung. Alexander emphasized the great frequency of malignant tumors in solitary pulmonary nodules. In 1947, Davis and Klepser published a series of 40 surgical cases of solitary lesions of the lung, and in 1956 Davis and his colleagues reported a total of 215 excised nodules, of which 47% were malignant neoplasms. Davis and Klepser, in a review of the literature, collected 1203 cases with a malignancy rate of 37% [50]. The first and probably the unique monograph "The Solitary Pulmonary Nodule" authored by Steele was published in USA in 1964 [51].

Pulmonary nodules are spherical radiographic opacities that measure up to 30 mm in diameter. Nodules are extremely common in clinical practice and challenging to manage, especially small, "subcentimeter" nodules [52–62].

The definition of a solitary pulmonary nodule has varied. Gurney, 1993, defined a solitary pulmonary nodule as a circular mass of variable size that leaves the surrounding lung, pleura, and mediastinum unaltered. A solitary pulmonary nodule may be calcified or cavitated. In addition, the patient may or may not have symptoms [63,64].

According to Martin Dolejsi, Jan Kybic a solitary pulmonary nodule (parenchymal, non-pleural nodule) is a small, round or egg-shaped lesion in the lungs. Juxtapleural pulmonary nodule is a small, worm-shaped lesion connected to pleura [65,66].

The term solitary lung lesion is often used synonymously with the term coin lesion. The term "coin lesions" was defined by Thornton et al. in 1944 as a solitary lesion, 1 to 5 cms. in size, round or oval with well defined margins surrounded by normal lung, and homogenous with or without the presence of calcification. Terms such as coin lesions, solitary nodule, circumscribed pulmonary nodule, are used to indicate a single round or oval lesion within the lung surrounded by normal appearing lung. Hilar, mediastinal, or chest wall abnormalities are absent. Extremely large or small masses are usually excluded from the consideration in these discussions [67].

A solitary pulmonary nodule is noted on 0.09 to 0.20 percent of all chest radiographs [68]. These lesions are detected on routine chest radiography at a rate of 1 in 500 x-rays, but with the growing use of computed tomographic scanning, they are now being diagnosed with increasing frequency [69]. An estimated 150,000 such nodule is identified each year. Bronchogenic carcinoma as a cause of solitary nodules has been increasing, especially in the elderly. The incidence of cancer in patients with solitary nodules ranges from 10 to 70 percent. Infectious granulomas cause about 80 percent of the benign lesions, and hamartomas about 10 percent. Calcification (complete) within a nodule suggests that it is a benign lesion [68]. Calcification that is stippled, amorphous, or eccentric is usually associated with cancer (see Figure 7) [70].

The differential diagnosis of a solitary nodule is extensive, but its radiologic evaluation is primarily directed at distinguishing nodules that are benign, and thus inconsequential, from nodules that are malignant or potentially

Table 1. (Dahnert, 2007) [89].

Doubling time (= time required to double in volume):
- For most malignant nodules: 30–400 days = 26% increase in diameter
  - ≤30 days: aggressive small cell cancer
  - ≤90 days: squamous cell carcinoma
  - ≤120 days: large cell carcinoma
  - ≤150 days: aggressive adenocarcinoma
  - ≤180 days: average adenocarcinoma
- For benign nodules: <30 and >400 days
  - Absence of growth over a 2-year period implies a doubling time of >730 days

malignant, and require treatment. The large majority of solitary nodules detected radiographically are benign. The best definition of a benign lesion is one that is in the pulmonary parenchyma that does not metastasize and does not penetrate through surrounding tissue planes. The controversy arises because some tumors often labeled as benign (such as pulmonary blastomas) have the potential to exhibit malignant properties, and thus clear-cut boundaries between malignant and benign often are blurred. Benign tumors of the lung can arise from all of the various cell types that are present in the lung [71].

In non selected patient populations, a new solitary pulmonary nodule has a 20–40 percent likelihood of being malignant, with the risk approximating 50 percent or higher for smokers. The remaining causes of pulmonary nodules are numerous benign conditions. Characteristically neoplasms grow, and several studies have confirmed that lung cancers have volume-doubling times from 20–400 days (see Table 1). Lesions with shorter doubling times are likely because of infection, as longer doubling times suggest benign tumors. Traditionally, 2-year size stability per chest radiography has been considered a sign of a benign tumor [70].

It was considered that in patients less than 30 years of age, the prevalence of bronchogenic carcinoma is so low that a solitary pulmonary nodule generally should be followed-up radiologically without any further evaluation, unless the patient has a known extrathoracic primary malignancy [72]. Approximately 50% of indeterminate lung nodules that undergo surgery for diagnosis are benign. Hospitalization for surgical removal of a nodule costs about $25,000 [73]. The most common manifestation of lung cancer is a solitary pulmonary nodule smaller than 3 cm in diameter, which is usually found during CT, or a solitary pulmonary mass larger than 3 cm in diameter. Diagnostic evaluation of focal pulmonary lesions should be accurate and efficient to facilitate prompt resection of malignant tumors, when possible, but surgery should be avoided in cases of benign disease [74].

Identification of malignant nodules is important because they represent a potentially curable form of lung cancer. Patients with pulmonary nodules should be evaluated by estimation of the probability of malignancy (see Table 2) performance of imaging tests to characterize the lesion(s) better, evaluation of the risks associated with various management alternatives, and elicitation of patient preferences

Table 2. (Dahnert, 2007) [89].

Probability of malignancy for indeterminate Solitary Pulmonary nodule	
Characteristic/feature	**Likelihood ratio**
Spiculated margin	5.54
Size >3 cm	5.23
>70 years of age	4.16
Malignant growth rate	3.40
Smoker	2.27
Upper lobe location	1.22
Size <10 mm	0.52
Smooth margin	0.30
30–39 years of age	0.24
Never smoked	0.19
20–29 years of age	0.05
Benign calcification	0.01
Benign growth rate	0.01

for treatment [52]. Determining the probability of cancer in patients with solitary pulmonary nodules remains an inexact science [68].

Missed lung cancers include the most difficult cases for detection in clinical work and mass screening programs, and several investigators have reported the possible reasons for missing lung cancers on CT scans. Lung cancers missed at low-dose CT screening are very difficult to detect.

The principal reasons of the diagnostic failure are the specific tumor localizations and the spectrum of concomitant diseases [75,76].

Nodule image features

Various image features of each potential nodule have been assessed to separate true nodules from false-positive nodules. These image features included volume, roundness, average diameter, maximum diameter, diameter perpendicular to the maximum diameter, and distance between the potential nodule and the thoracic wall [77]. Most frequently used properties of nodules in automatic detection are the shape, size, and intensity profile [78].

Increasing nodule size and presence of coarse spiculation, bobulation, and inhomogeneous central attenuation are observed with significantly greater frequency among malignant lesions. Bubblelike areas of low attenuation, which are due to a patent small bronchi or air-containing cystic spaces in papillary tumors, occurred more frequently in malignant than benign lesions, but this difference is not statistically significant [79].

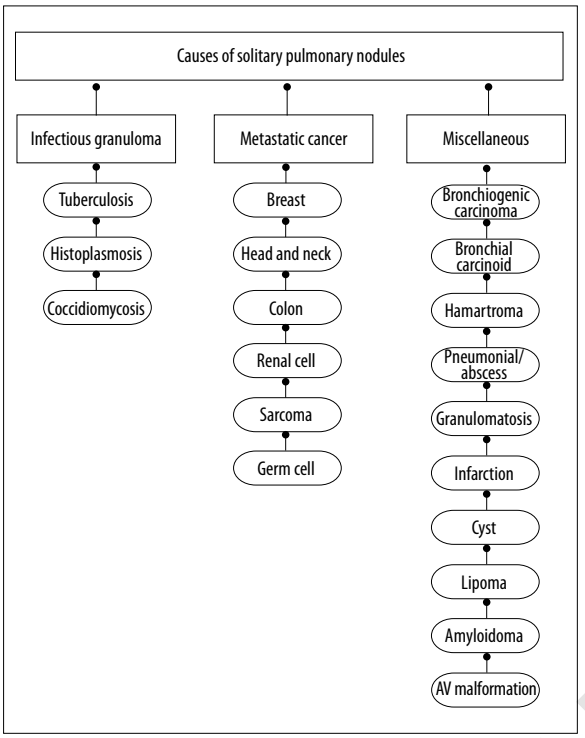

Figure 9. Principal causes of solitary pulmonary nodules [88].

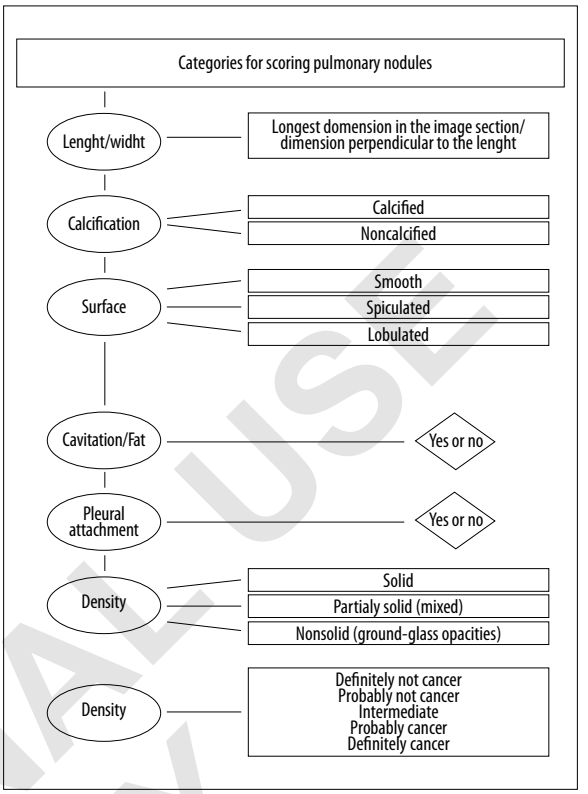

Figure 10. The scheme of pulmonary nodules scoring [83].

An artificial neural network has been applied to determine the likelihood of the lesion being a true nodule on the basis of the image features [80].

Okada et al., 2005, proposed a comprehensive and generic computational framework based on robust multiscale Gaussian intensity model fitting. Exploiting the model's analytical advantages, their solution has provided nodule characterizations in terms of 1) nodule center, 2) ellipsoidal boundary [three-dimensional (3-D) segmentation approximation], 3) nodule volume, 4) maximum diameter, 5) average diameter, and 6) isotropy. Throughout this study, it was assumed that an observer provides a marker indicating rough location of a target lesion. Robustness is one of the key issues addressed in their paper [81].

Target size of the pulmonary nodule

The minimum target size of a nodule at CT lung cancer screening is important for setting scanning parameters (ie, section thickness, section interval, detector row width, helical pitch, and reconstruction algorithm) and determining the detection capacity of the CAD system. The minimum target size of a nodule must be decided with consideration of how much improvement in prognosis is sought, after confirming the correlation between the pulmonary nodule size and the prognosis. Although some study results suggest that pulmonary nodule size and prognosis do not necessarily correlate, the results of a study by Sobue et al (2002) suggest that small lung cancers are associated with a better survival rate. According to the results of that study, the 5-year survival rate was almost 100% for patients with nodules 9 mm or smaller. However, they considered all nodules 9 mm or smaller in their analysis and did not include a breakdown of the 5-year survival rates for patients with pulmonary nodules 9 mm or smaller. More studies are needed to determine the actual minimum target size [80].

Nodule detection

Once a lung nodule is found on a chest radiograph, the subsequent task for a radiologist is to assess the nature of the lesion, i.e. whether the nodule is malignant or benign (see Figures 8,9). This task of classification of lung nodules is considered difficult for radiologists. The purpose of CAD for classification of nodules on chest radiographs is to provide the likelihood of malignancy as a second opinion in assisting radiologists' decisions. The computerized scheme for determination of the likelihood of malignancy is based on the analysis of many image features obtained from a nodule on a chest radiograph and also from the corresponding difference image. The image features include features obtained from the outline of the nodule such as the shape and size, the distribution of pixel values inside and outside the nodule, and the distribution of edge components [7]. Detecting pulmonary nodules depicted in large-volume CT examinations is a daunting task that requires vigilance and diligence. Although intraobserver agreement was reasonably well in the examination-based analysis, intraobserver agreement was poor in the detection of individual nodules. This suggests that there may be a need for the development of consistent search criteria and standardized reporting practices. If nothing else, this preliminary study clearly suggests that there are significant observer-related issues that cannot be ignored regarding the use of low-dose chest CT examinations for the early detection of pulmonary nodules and lung cancer [28]. Only 2.5–11.6% of

detected non-calcified nodules, however, prove to be lung cancer, and screening with low dose CT results in many false-positive findings. Also, in a 1-year follow- up study with low-dose CT, non-calcified nodules were detected at 2.5–3.9% of the examinations; only 3–23% of these nodules were identified as lung cancer. Therefore, rational algorithms that facilitate the accurate diagnosis of noncalcified nodules detected at lung cancer screening with low-dose CT must be developed. With the increasing use of thoracic CT, a marked increase in the number of small pulmonary nodules that are detected has been observed. Although many of these nodules are caused by benign processes (eg, hamartoma, granuloma – see Figure 9), rapid work-up is desirable to differentiate between nonmalignant and malignant lesions. This is especially challenging in baseline screening for lung cancer, where substantially more benign than malignant nodules are detected. One of the most compelling indicators of nodule malignancy is growth. Stability of a nodule is strongly predictive of benignity. The CT lung nodule enhancement technique may be clinically useful in evaluation of indeterminate lung nodules. Absence of significant enhancement is strongly predictive of benignity [73]. The concept of estimation of nodule growth rate, expressed as doubling time, was introduced nearly 50 years ago. In these early studies, the doubling time was estimated assuming the basis of manual estimates of nodule diameter on chest radiographs. This method of growth rate estimation became the de facto standard for the evaluation of lesions that were found on chest radiographs and were suspected of being malignant. With the development of CT, a similar approach was taken; the CT section containing the largest cross section of the nodule was measured with physical or electronic calipers [82].

Volumetric analysis

There is now widespread interest in the use of techniques for volumetric analysis of nodules, both in academic practice and in industry. Although the relative error in nodule volume measurement as a function of nodule size had been quantified by using nodule phantoms, the error for *in vivo* nodules must be greater, as it includes measurement error due to greater partial-volume effects, vascular geometry, and motion artifacts. Of primary concern are whether a nodule that appears to have grown in sequential volume measurements actually has grown and whether the difference in these measurements is not simply due to error. Thus, the purpose of the study conducted by Kostis et al., 2004, was to determine the reproducibility of volume measurements of small pulmonary nodules on CT scans and to estimate the critical time to follow up CT. Conclusion was that factors that affect reproducibility of nodule volume measurements and critical time to follow up CT include nodule size at detection, type of scan (baseline or annual repeat) on which the nodule is detected, and presence of patient-induced artifacts [82].

Lung nodule volumetry is used for nodule diagnosis, as well as for monitoring tumor response to therapy. Volume measurement precision and accuracy depend on a number of factors, including image-acquisition and reconstruction parameters, nodule characteristics, and the performance of algorithms for nodule segmentation (see Figure 8 as an example) and volume estimation. Understanding and quantifying the sources of volumetric measurement error in the assessment of lung nodules with CT would be a first step toward the development of methods to minimize that error through system improvements and to correctly account for any remaining error [10].

Computed tomography for the detection of pulmonary nodules and lung cancer screening

Early detection of potentially cancerous pulmonary nodules may be a way to improve a patient's chances for survival [4]. Lung cancer screening may ultimately enable earlier detection and improve an outcome. However, lung cancer screening outside of research protocols has been controversial and to date has not been recommended by any major health care organization. One of the concerns regarding screening for the early detection of lung cancer is the possibility of unwarranted, potentially harmful management of false-positive detections. Lung cancer had been commonly detected and diagnosed clinically or on chest radiography, but since the early 1990s X-ray CT has been reported to improve detection and characterization of both benign and malignant pulmonary nodules. Lung cancer screening is currently implemented using low-dose CT examinations, which are generally defined as scanning techniques that use less than 100 mAs. There are several methodologic issues regarding the optimal practice for low-dose CT screening (e.g., tube current, pitch, section thickness, reviewing format). In addition, the general desire to reduce motion artifacts and improve spatial resolution by rapid image acquisition with thinner image sections has resulted in advances in CT technology (e.g., multidetector scanners). Hence, the typical examination generates large-volume data sets. These large data sets challenge both the display systems and the interpreting radiologist [83].

Helical computed tomography (CT) of the chest is the imaging modality with the highest sensitivity for the detection of pulmonary nodules. Lung cancer screening with low radiation-dose helical CT has gained attention during the past 10 years. It has been reported that the detection rate of lung cancer screening with low-dose CT is 2.6- to tenfold higher than that with chest radiography. It has also been reported that stage I cancers represent 56–93% of the lung cancers detected by using low-dose CT. These data suggest that this modality can help detect lung cancer at an earlier stage than chest radiography can. Therefore, low-dose CT is a promising method for lung cancer detection. In the screening for lung cancer with CT, however, radiologists have to analyze large amounts of data, numerous image sections per case, and 50–100 cases per day. There is always the risk of missing a lesion. In a retrospective study of first annual CT examinations, Swensen et al. (2002) found that nodules were missed in 26% of patients. There are some methods to help avoid missing a pulmonary nodule, such as independent reading by two or more radiologists and the use of computer-aided diagnosis (CAD) for the detection of pulmonary nodules. Some researchers have reported the use of a CAD system in lung cancer screening with CT [80]. A major concern for the use of CT scans is the false-positive rates. In the study conducted at the Mayo Clinic, almost 70% of the volunteers had non calcified pulmonary nodules.

Only a fraction of these required further invasive follows up, including resection of benign lesions in eight patients. The false-positive rates in that study ranged from 92.9% for nodules >4 mm in diameter to 96% for all nodules. In contrast, in the I-ELCAP (the International Early Lung Cancer Action Program), only 23% of the volunteers had non calcified nodules at baseline screening that needed further evaluation. The reasons for these differences appear to be twofold. The Mayo Clinic trial, which started later than the ELCAP, used a four-slice CT scanner that is more sensitive than the single-slice scanner used in the ELCAP. Also, there may be a higher incidence of pulmonary nodules in the Midwestern U.S. because of endemic fungal infections. However, as more data on the behavior of these nodules become available, it is possible that the smaller nodules, especially those <5.0 mm, could be evaluated during annual follow up scans. In October 2006, the I-ELCAP investigators reported the results of their large screening study. In brief, over 12 years they screened 31,567 people who were at risk of lung cancer but who had no symptoms. They then performed 27,456 follow up CT scans about 1 year later. In total, 484 participants were diagnosed with lung cancer, 85% of which were in clinical stage I. The 10-year survival rate for all those diagnosed with lung cancer was projected to be 80%, and for those with stage I lung cancer it was 88%. The investigators have suggested that CT screening can detect lung cancer that is curable, and their results support CT screening for lung cancer as a standard of care in people at risk of the disease [84].

Thin-section CT

Thin-section CT has been recommended as the next step when a non-calcified nodule is detected at low-dose CT screening. At present, however, there are no clear diagnostic criteria for identification of malignant nodules detected by using thin-section CT, and in most instances, the interpretation of thin-section CT findings relies on the knowledge and experience of the radiologist who is performing the interpretation. The independent interpretation of non-calcified pulmonary nodules by two or more experienced radiologists and the use of a computer-aided diagnosis (CAD) system for estimation of the malignancy of the nodules may assist radiologists in determination of a correct diagnosis (see Figures 8, 9) [16]. With thin-section CT of the thorax, CAD systems will become a practical necessity and will likely achieve an acceptable sensitivity and false-positive detection rate to be a clinically useful tool. On thick-section CT images, if nodules are visible faintly across neighboring sections, their 3D nodule features may not be characterized adequately. As a result, the discrimination ability of the nodule classifier will be compromised substantially. The lack of connectivity between the sections, combined with volume averaging, leads to a high rate of false-positive findings on images in the thick group. For example, blood vessels or bronchial walls that were fragmented as a result of volume averaging were classified into small nodules. This misclassification would be avoided if the 3D features of nodule candidates were characterized sufficiently on contiguous sections. When overlapped images with a small reconstruction interval are available, some of the 3D features of nodules could be retrieved to help improve the performance of the CAD system [85].

Single– detector and multi-detector row CT

With single– detector row CT, spiral CT images of the thorax are typically obtained with 6–10-mm section thickness. The acquisition of thin-section (ie, 1–2-mm section thickness) images of the whole thorax is impractical, because it requires multiple breath-hold sets of contiguous spiral scans to cover the thorax completely. Spatial limitations due to thick sections may be compensated for partially by means of using small reconstruction intervals that would improve nodule detection and diagnostic confidence. Multi–detector row CT, with its fast scanning speed and superb spatial resolution, allows to routinely acquire thin-section images of the entire thorax in less than 10 seconds. This improvement in spatial and temporal resolution increases the sensitivity for detection of small pulmonary nodules. Furthermore, in multi–detector row CT, multiple spiral data are acquired during a single CT gantry rotation that allows to generate CT images of different section thicknesses. A main drawback of CT scanning with thin sections or small reconstruction intervals is that the size of image data sets is large. A considerable amount of interpretation time is required to review the entire set of thin-section CT images, which may impair practical implementation of screening examinations for pulmonary nodule detection. For this reason, radiologists intentionally generate and review CT images with 3–5-mm section thickness (which are thicker than those capable of being produced with multi-detector row CT) from the CT scan projection data. Alternatively, a computer-aided detection (CAD) system could be used as a clinical tool to help reduce the radiologist's workload and enhance the diagnostic performance of interpreting thin-section multi–detector row CT images [85].

PET assessment of the solitary pulmonary nodule

With the implementation of screening CT for lung cancer and the frequent detection of pulmonary nodules with CT, a noninvasive means of detecting neoplasia is necessary. FDG (2-deoxy-2-flourine 18-fluoro-D-glucose) PET (positron emission tomography) is more sensitive (sensitivity of 92%–96%) and specific (specificity of 78%–96%) than CT in the detection of malignancy in pulmonary nodules that are larger than 1 cm in diameter. Despite its improved depiction of neoplasia, there are tumors that are not consistently detected with FDG PET. Tumors such as carcinoid bronchioloalveolar cell carcinoma and other well-differentiated adenocarcinomas are frequently determined to be false-negative with FDG PET. FDG is also taken up by inflammatory and infectious processes that can mimic neoplasia. Recent studies have shown that FLT is a useful biomarker for tumor cell proliferation. Preliminary studies have shown that FLT (3-deoxy-3-flourine 18-fluorothymidine) PET may be better than FDG PET in distinguishing benign nodules. The multicenter study to evaluate the sensitivity and specificity of FDG PET and FLT PET in the detection of malignancy of pulmonary nodules on the basis of estimation of glucose metabolism with FDG PET and thymidine turnover rate with FLT PET would allow researchers to determine if the uptake of FDG and FLT varies according to tumor characteristics, such as specific tumor types (adenocarcinoma-including bronchioloalveolar carcinoma type, large cell, squamous cell, carcinoid), tumor grade (high vs low grade),and differentiation (good vs poor) [33].

In study of Nie et al., 2006, CAD scheme based on both PET and CT was better able to differentiate benign from malignant pulmonary nodules than were the CAD schemes based on PET alone and CT alone [86]. PET/CT may be selectively performed to characterize SPNs that show indeterminate results at dynamic helical CT [87].

MRI detection and image analysis of the solitary pulmonary nodule

MRI is another option for detection of malignant pulmonary nodules and in particular based on the image analysis. Recent experience with MRI points to its potential for detection and characterization of pulmonary nodules while avoiding ionizing radiation.

The mechanisms of this modality have been described in understandable details by Sensakovic and Armato. First, a patient is placed in a strong magnetic field generated by a superconducting magnet. The nuclei of the hydrogen atoms that compose the tissue of the patient possess a small magnetic moment that causes the nuclei (essentially protons for hydrogen atoms) to align along and precess about the magnetic field. Then the patient is subjected to a radiofrequency pulse that causes the hydrogen nuclei to temporarily rotate perpendicular to the axis of the magnetic field. In this alignment, the precessing hydrogen nuclei induce an electric current (signal) in a receiving antenna connected to the magnetic resonance scanner. This signal is then mathematically reconstructed into an image of the patient [91]. The indications for MRI of the lung (e.g. paediatric radiology) are not yet determined and will be interesting to observe [92]. There are some controversies regarding the efficacy of the MRI versus CT. MRI can be reliable to detect the nodules larger than 4–5 mm [93–95]. It was considered that visualization of pulmonary nodules applying magnetic resonance imaging (MRI) played a minor role compared with computed tomography [96]. Though MRI is considered inferior to CT in the assessment of the margin and internal feature of the nodule, it can provide further information in differentiating between malignant nodule and tuberculoma [97]. Magnetic resonance imaging study is a useful diagnostic tool, when a discrete pulmonary nodule demonstrates neither fat nor calcification on CT, for detecting the quite typical cleft like structure in a pulmonary hamartoma and could provide diagnostic confidence [98]. Dynamic MRI can play a more specific and/or accurate role for nodule management as compared with dynamic MDCT and coregistered PET/CT [99]. In research of Schaefer et al., 2006, despite discrepancies in morphologic appearance, no significant difference of accuracy between MRI and CT was determined when differentiating malignant from benign solitary pulmonary nodules (SPN) using morphological characteristics [100]. The results of several studies in which MRI was used to assess pulmonary lesions suggest that the kinetics indexes and morphologic parameters of dynamic MRI are helpful in differentiating between malignant and benign lesions; the problem of differentiating between benign inflammatory and malignant lesions remains, although MRI and CT can relatively reliably differentiate between benign hamartomas and granulomas and malignant lesions. The findings of dynamic MRI (enhancement parameters and curve profiles) might be helpful for assessing tumor angiogenesis (microvessel count and expression of VEGF – vascular endothelial growth factor) and tumor interstitium, and might be helpful for predicting lymph node metastasis as well as the outcome of patients with peripheral pulmonary carcinomas. Dynamic MRI is useful for differentiating malignant SPN (solitary pulmonary nodules) from benign SPNs (especially tuberculomas and hamartomas). However, it is difficult to differentiate between acute inflammatory lesions and active infection and malignant lesions [101].

In addition to identification of curve types in the context of MRI, visual analysis of the enhancement patterns was helpful for differentiating benign and malignant nodules [102].

We deem that the field of MRI thoracic image analysis is the area where new methods should be introduced. This work would help to improve the sensitivity and specificity of the malignant pulmonary nodule detection and it will close the gap of unclear facts, regarding the capabilities of MRI to recognize pulmonary malignancies.

Conclusions

In a brief review article, we have described the concepts and some definitions of the modern CAD and thoracic radiology and the facts derived from the available literature on the topic of pulmonary nodule differential CAD published between 2004–2009. The review of the literature shows that a significant experience of the CAD schemes clinical application has been gained. The unresolved problems of CAD are the ways to improve the techniques of the image analysis to increase the sensitivity of diagnostic strategies, to broaden the spectrum of the differential diagnosis. Perhaps the implementation of samples of miscellaneous verified pathologic entities to cover the entire pulmonary nodule differential diagnosis extent may be the rational effective strategy to decrease the rate of false-positive diagnostic results. Apparently, this amount of work requires an extremely large database of the correctly detected and verified images. Another issue is the performance of the large-scale evidence-based trials in order to discover the advantages and disadvantages of the computer-assisted approaches to diagnosis of malignant pulmonary nodules.

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