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Computer-Aided Differential Diagnosis of the Pulmonary Nodule: Towards an Understanding of the Medical Imaging Basics and Experiences in the Field

In this article, the modern concepts of computer-aided diagnosis (CAD), the methods of pulmonary nodule detection, and facts derived from the literature on the pulmonary nodule differential CAD are compiled in one source and described in some detail. Several issues in lung cancer (LC) epidemiology and early diagnosis are discussed. Analysis of research done so far shows evidence that various CAD systems can be successfully applied to chest radiographs, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). These modalities can serve as useful potential alternative tools available to practicing medical professionals performing routine diagnostics. **(J Lung Cancer 2009;8(2):78−91)**

Key Words: Computer-aided diagnosis, Pulmonary nodule, Computed tomography, Magnetic resonance tomography, Positron emission tomography

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Introduction: 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 considered to be a major evolutionary step in biomedical imaging. To store images in a computer, the images 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. Therefore, images used in medical practice are represented as a raster (matrix) filled with values coding color or gray level. The numerical values are represented in binary (or octal or hexadecimal) notation, and in this sense 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, 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 captured in this fashion is said to have been "digitized." If large sampling increments are used in an image, the result is a coarse or "blocky" appearance of objects in the image. If a larger number of pixels is used, the image looks smooth and has an almost photographic appearance. However, 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 in images by using computer-aided detection, and even characterize some of them with computer-aided diagnosis; these capabilities are likely to have a significant long-term influence on medical care and the profession (1). Chest radiography is by far the most common type of procedure for 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 computed tomography (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 which 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

1) Definitions and technologies of decision support systems and Computer-aided diagnosis

CAD has generally been defined in terms of a diagnosis made by a physician who takes into account the computer output based on a quantitative analysis of radiological images. The basic technologies involved in CAD schemes are: (i) image processing for detection and extraction of abnormalities; (ii) quantitation of image features for candidates of abnormalities; (iii) data processing for classification of image features between normals and abnormals (or benign and malignant); (iv) quantitative evaluation and retrieval of images similar to those of unknown lesions; and (v) 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 can also help radiologists formulate and evaluate diagnostic hypotheses by recaffing associations between diseases and imaging findings (8).

Analysis by humans is usually subjective and qualitative, Such as when comparative analysis is required between images of two subjects or between a subject and a reference pattern. Specific or objective comparison－for example, the comparison of the volume of two regions to an accuracy on the order of even a milliliter－would require the use of a computer. The derivation of quantitative or numerical features from images would certainly require the use of computers. Analysis by humans is subject to variations. 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 required 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 a number of human experts in an area of interest (9).

2) Recently published reviews on the topic of Computer-aided diagnosis

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 and high resolution CT, diagnosis of these nodules, quantitative analysis of diffuse lung disease, and detection of intracranial aneurysms

by magnetic resonance angiography. In particular, the applicability of CAD techniques such as artificial neural networks, difference imaging, linear discriminant analysis, and morphological and three-dimensional (3D) selective enhancement filters have been described. 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 in evaluation of algorithm performance, and in evaluation of CAD systems together with reader performance; for example, the impact of training has been emphasized in order to achieve consistent stability performance in trials (10). Rafael Weimker (2005) from Philips Research Laboratories, Hamburg, presented a summary of algorithms developed and tested on images of lung nodules, emphasizing their potential applications in early cancer detection and diagnosis of nodules based on morphology and sequential volume changes. He pointed out that technical improvements in spatial and temporal resolution in CT thoracic image acquisition was a good step toward 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 detail in his articles. A brief description was given of algorithms that automate image registration between previous and follow up CT scans, enabling not only diagnostic support but also monitoring responses to oncological therapy (10).

Sluimer, Prokop, and van Ginneken (2005～2006) performed extensive research on thoracic CT scan computer analysis and the lung segmentation process, and published a series of articles, describing in detail the studies conducted on emphysema quantification, performance of various nodule detection systems, and nodule characterization, and presented the successful results of clinical application of the refined segmentation-by-registration scheme (11-13).

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

3) Lung image database consortium and its current activities

To stimulate the advancement of computer-aided diagnosis research for lung nodules in thoracic computed tomography, 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 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 in 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 "ground 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. The LIDC database is expected to provide a powerful resource for the medical imaging research community upon completion of a consensus process in which careful planning and proper consideration of fundamental issues have been emphasized (15).

4) Lung cancer: epidemiologic and statistic data

Lung cancer (LC) is the most common cause of cancer death in both men and women in the United States and worldwide (Fig. 1) (16). LC is the most commonly diagnosed cancer worldwide, accounting for 1.2 million new cases annually (17).

LC 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, LC caused over 158,000 deaths-more than colorectal, breast, and prostate cancers combined. The principal etiology of the disease is cigarette smoking (18). LC is the leading cause of cancer mortality in Europe. and in 1995 accounted for 330,000 deaths (19). There were more than 38,000 new cases of LC per year in the UK, and this incidence is among the highest in Europe (20).

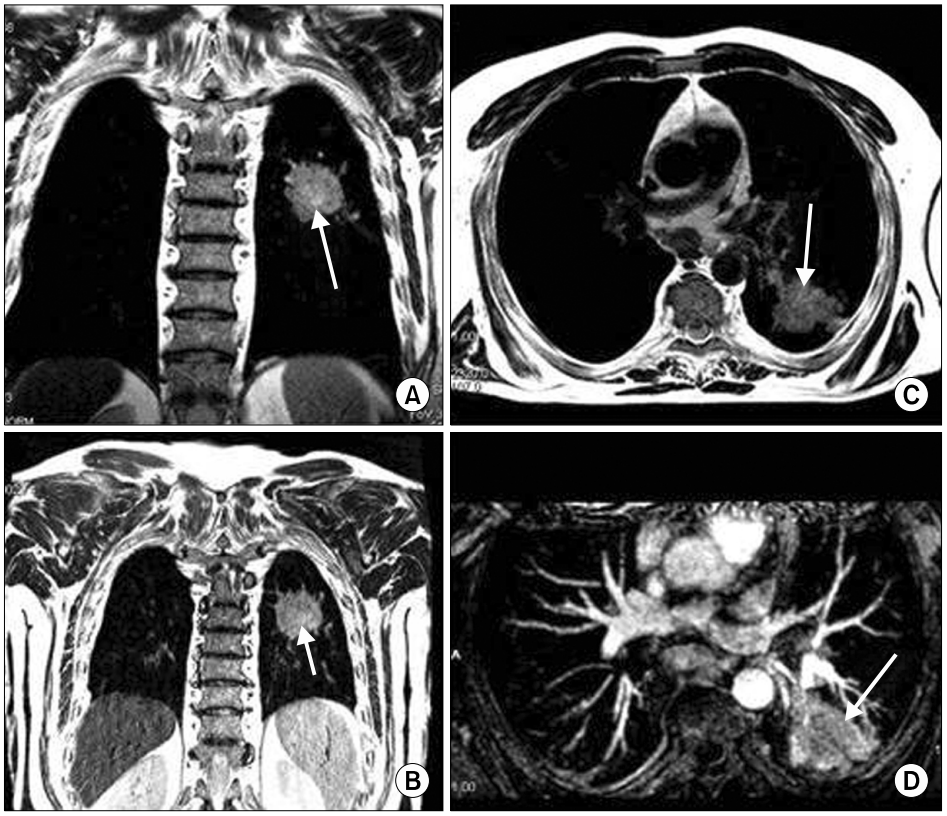

Fig. 1. The image from a 61-year-old man. Peripheral cancer of the left lung. MRI of the thoracic cavity (arrows points to the tumor). (A) T2-weighted image in a coronal plane, thickness of a cut - 6 mm; (B) T2-weighted image in a coronal plane, thickness of a cut - 4 mm; (C) T2-weighted image in transversal plane, thickness of a cut-6 mm; (D) T1-weighted image in transversal plane after the intravenous introduction of contrast substance (Omniscan).

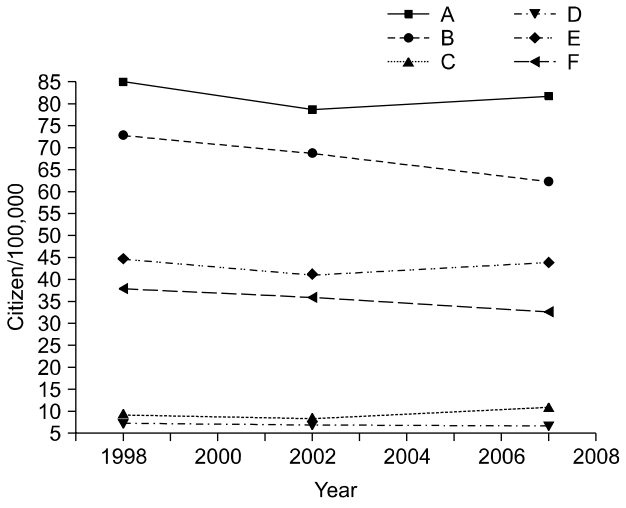

Fig. 2. Lung cancer morbidity and lethality in Belarus, 1998, 2002, 2007 (A: male morbidity, B: male lethality, C: female morbidity, D: female lethality, E: both genders morbidity, F: both genders lethality).

LC occurs most commonly between the ages of 45 and 70 years, and has one of the worst survival rates of all the types of cancer (21).

The chance of developing LC is one in 13 in men and one in 18 in women. This rate of incidence includes all people, regardless of whether they smoke (Winer-Muram, 2006) (22).

According to pathology reports, 4184 cases of LC had been diagnosed in 2005 in Belarus (Fig. 2). Because one fourth of adults in Belarus smoke, LC will continue to be a problem there for years to come. Since 1987, LCs are the leading cause of oncologic death in American women, who are the major consumers of cigarettes (23,24). Cigar and pipe smoking is less dangerous than cigarettes in terms of LC incidence.

Pulmonary Nodules: History, Definition and Characteristics

1) 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 (SPN) has persisted since. In 1897, the Roentgen ray was discovered, and the significance of the SPN took on new and wider concern. The surgical treatment of the SPN was initiated in 1925 by

Evarts Graham when he resected a peripheral tuberculoma (25).

Graham and Singer reported a series of three cases of resected SPNs 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 tumours in SPNs. 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 1,203 cases with a malignancy rate of 37% (26). The first, and probably unique, monograph «The Solitary Pulmonary Nodule» authored by Steele was published in the USA in 1964 (27).

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 (28-37).

The definition of a SPN has varied. Gurney, 1993, defined an SPN as a circular mass of variable size that leaves the surrounding lung, pleura, and mediastinum unaltered. An SPN may be calcified or cavitated. In addition, the patient may or may not have symptoms (38,39).

According to Martin Dolejsi and Jan Kybic, a, SPN (parenchymal, non-pleural nodule) is a small, round, or egg-shaped lesion in the lungs. A juxtapleural pulmonary nodule is a small, worm-shaped lesion connected to the pleura (40,41).

The term *solitary lung lesion* is often used synonymously with the term *coin lesion*. The term *coin lesion* was defined by Thornton et al. in 1944 as a solitary lesion, 1 to 5 cm in size, round or oval, with well defined margins surrounded by normal lung tissue, and homogenous, with or without the presence of calcification. Terms such as *coin lesion*, *solitary nodule*, and *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 consideration in these discussions (42).

An SPN is noted on 0.09 to 0.20 percent of all chest radiographs (43). These lesions are detected by routine chest radiography at a rate of 1 in 500 X-rays, but with the growing use of CT scanning, they are now being diagnosed with increasing frequency (44). An estimated 150,000 such nodules are 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 benign lesions, and hamartomas about 10 percent. Calcification (complete) within a nodule suggests that it is a benign lesion (43). Calcification that is stippled, amorphous, or eccentric is usually associated with cancer (45).

The basis for differential diagnosis of a solitary nodule is extensive (Fig. 3), but its radiologic evaluation is primarily directed at distinguishing nodules that are benign, and thus inconsequential, from nodules that are malignant or potentially malignant, and require treatment. A 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" are often blurred. Benign tumors of the lung can arise from all of

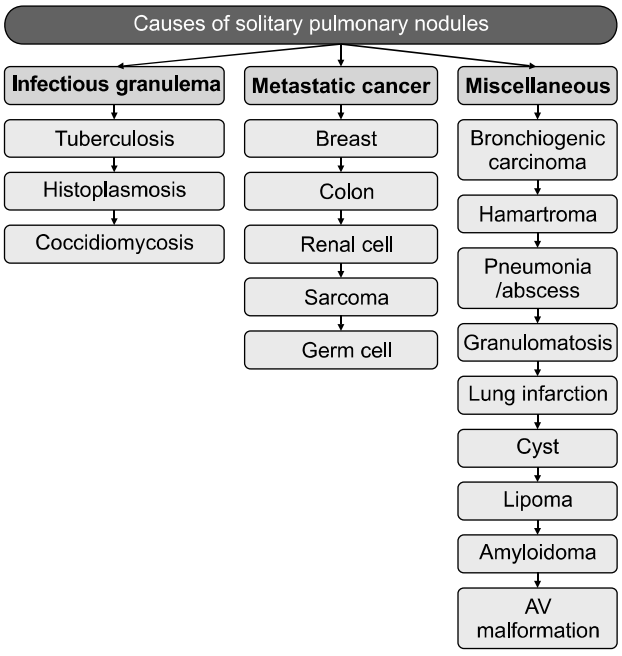

Fig. 3. Principal causes of solitary pulmonary nodules. Hansen HH. Textbook of lung cancer. 2nd ed. London: Informa Healthcare; 2008 (46).

the various cell types that are present in the lung (47).

In non-selected patient populations, a new SPN has a 20～40 percent likelihood of being malignant, with the risk being 50 percent or higher for smokers. The remaining causes of pulmonary nodules are numerous benign conditions. Neoplasms characteristically grow, and several studies have confirmed that LCs have volume-doubling times from 20～400 days (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 (45).

It has been noted that in patients less than 30 years of age, the prevalence of bronchogenic carcinoma is so low that an SPN should generally be followed up radiologically without any further evaluation, unless the patient has a known extrathoracic primary malignancy (49). Approximately 50% of indeterminate lung nodules that undergo surgery for diagnosis are benign. Hospitalization for surgical removal of a nodule costs about $25,000 (50). The most common manifestation of LC is an SPN 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 when possible, in order to facilitate prompt resection of malignant tumors. Surgery should be avoided in cases of benign disease (51).

Identification of malignant nodules is important, because they represent a potentially curable form of LC. Patients with pulmonary nodules should be evaluated by estimation of the probability of malignancy, performance of imaging tests to better characterize the lesion(s), evaluation of the risks associated with various management alternatives, and elicitation of patient preferences for treatment (28). Determining the probability of cancer in patients with SPNs remains an inexact science (43).

Missed LCs include the most difficult cases for detection in clinical work and mass screening programs, and several investigators have reported possible reasons for missing LCs on CT scans. LCs missed at low-dose CT screening are very difficult to detect. The principal reasons for diagnostic failure are specific tumor localizations and the spectrum of concomitant diseases associated with LCs (52,53).

Table 1. Volume Doubling Time of the SPN

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

Dähnert W. Radiology review manual. 6th ed. Philadelphia, PA: Lippincott Williams Wilkins; 2007 (48).

2) Nodule image features

Various image features of each potential nodule have been assessed to separate true from false-positive nodules. These image features include volume, roundness, average diameter, maximum diameter, diameter perpendicular to the maximum diameter, and distance between the potential nodule and the thoracic wall (54). Most frequently used properties of nodules in automatic detection are shape, size, and intensity profile (55).

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, occur more frequently in malignant than benign lesions, but this difference is not statistically significant (56).

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 (57).

Okada et al. (2005) proposed a comprehensive and generic computational framework based on a 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 (3D) segmentation approximation], 3) nodule volume, 4) maximum diameter, 5) average diameter, and 6) isotropy. Throughout that 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 (58).

3) Target size of the pulmonary nodule

The minimum target size of a nodule at CT LC 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 LCs 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 (57).

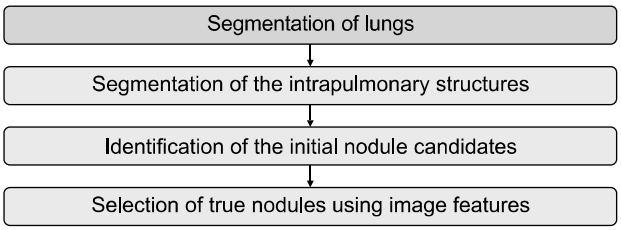

Fig. 4. Diagram of the computerized scheme for detection of pulmonary nodules on CT images. Awai K, Murao K, Ozawa A, et al. Radiology 2006;239:276-284 (57).

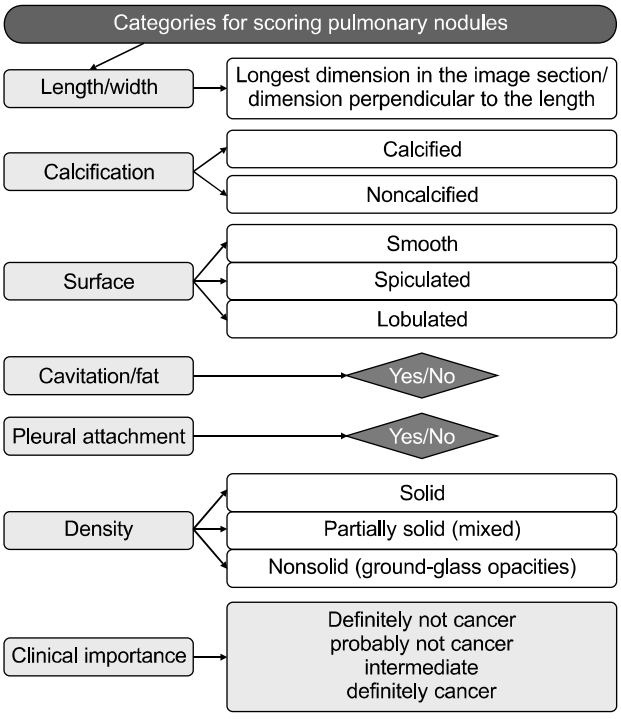

Fig. 5. The scheme of pulmonary nodules scoring. Leader JK, Warfel TE, Fuhrman CR, et al. AJR Am J Roentgenol 2005; 185:973-978 (59).

4) 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 (Fig. 4, 5 and Table 2). 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 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

Table 2. 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

Dähnert W. Radiology review manual. 6th ed. Philadelphia, PA: Lippincott Williams Wilkins; 2007 (48).

vigilance and diligence. Although intraobserver agreement is reasonably good in the examination-based analysis, intraobserver agreement is 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, a 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 LC (60). Only 2.5～11.6% of detected non-calcified nodules, however, proves to be LC, 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 in 2.5～3.9% of the examinations; only 3～23% of these nodules were identified as LC. Therefore, rational algorithms that facilitate the accurate diagnosis of noncalcified nodules detected at LC 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), rapid work-up is desirable to differentiate between nonmalignant and malignant lesions. This is especially challenging in baseline screening for LC, 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 also strongly predictive of benignity (50). 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 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 (61).

5) Volumetric analysis

There is now widespread interest in the use of techniques for volumetric analysis of nodules, both in academia and in practice. 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. The 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 (61).

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 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 LC Screening

Early detection of potentially cancerous pulmonary nodules may be a way to improve a patient's chances for survival (4). LC screening may ultimately enable earlier detection and improve an outcome. However, LC 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 LC is the possibility of unwarranted, potentially harmful management of false-positive detections. LC 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. LC 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 (59).

Helical computed tomography of the chest is the imaging modality with the highest sensitivity in detection of pulmonary nodules. LC screening with low radiation-dose helical CT has gained attention during the past 10 years. It has been reported that the detection rate of LC screening with low-dose CT is 2.6- to ten-fold higher than that with chest radiography. It has also been reported that stage I cancers represent 56～93% of the LCs detected by using low-dose CT. These data suggest that this modality can help detect LC at an earlier stage than chest radiography can. Therefore, low-dose CT is a promising method for LC detection. In screening for LC with CT, however, radiologists have to analyze large amounts of data, numerous image sections per case, and 50～100 cases per day, hence 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 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 LC screening with CT (57). 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 follow-ups, 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 LC 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 LC 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 LC, 85% of which were in clinical stage I. The 10-year survival rate for all those diagnosed with LC was projected to be 80%, and for those with stage I LC it was 88%. The investigators have suggested that CT screening can detect LC that is curable, and their results support CT screening for LC as a standard of care in people at risk of the disease (62).

1) 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 (Table 1, 2) (54). 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 substantially compromised. 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 are fragmented as a result of volume averaging end up being classified as 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 (63).

2) Single- 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 (i.e., 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 routinely acquiring 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 generating 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 (63).

PET Assessment of the SPN

With the implementation of screening CT for LC and the frequent detection of pulmonary nodules with CT, a noninvasive means of detecting neoplasia is necessary. FDG (2-deoxy-2-fluourine 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 (3-deoxy-3-fluorine 18-fluorothymidine) is a useful biomarker for tumor cell proliferation. Preliminary studies have shown that FLT 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) (16).

In the study of Nie et al. (2006) a 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 or CT alone (64). PET/CT may be selectively performed to characterize SPNs for which dynamic helical CT gives indeterminate results (65).

MRI Detection and Image Analysis of SPNs

MRI is another option for detection of malignant pulmonary nodules, in particular the image analysis it allowed. 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 detail 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 of 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. The patient is subjected to a radio-frequency pulse that causes the hydrogen nuclei to temporarily rotate perpendicularly 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 (66). The development of indications for MRI of the lung (e.g. paediatric radiology) will be fascinating to observe (67).

There are some controversies regarding the efficacy of MRI versus CT. MRI can be reliable in detecting nodules larger than 4～5 mm (68-70). It has been considered that visualization of pulmonary nodules using magnetic resonance imaging (MRI) plays a minor role compared with CT (71). Though MRI is considered inferior to CT in the assessment of the margins and internal features of nodules, it can provide further information in differentiating between malignant nodules and tuberculoma (72). 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, which could provide added diagnostic confidence (73).

Dynamic MRI can play a more specific and/or accurate role for nodule management as compared with dynamic MDCT and coregistered PET/CT (74). In the research of Schaefer et al. (2006) despite discrepancies in morphologic appearance, no significant difference in accuracy between MRI and CT was determined when differentiating malignant from benign SPNs using morphological characteristics (75). 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 SPNs from benign (especially tuberculomas and hamartomas). However, it is difficult to differentiate between acute inflammatory lesions and active infection and malignant lesions (76).

In addition to identification of curve types in the context of MRI, visual analysis of enhancement patterns has proven helpful in differentiating benign and malignant nodules (77).

We deem that the field of MRI thoracic image analysis is an area where new methods should be introduced toward improving sensitivity and specificity of malignant pulmonary nodule detection, and closing the gap of unclear results regarding the capacity of MRI to recognize pulmonary malignancies.

CONCLUSION

In this review article, we have described concepts and definitions of modern CAD and thoracic radiology, and facts derived from the literature, predominately over the period 2004～2009, on the topic of pulmonary nodule differential CAD. The literature shows that significant experience in clinical application of CAD schemes has been gained. Still needed are ways to improve image analysis techniques 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 extent of pulmonary nodule differential diagnosis may be the optimally effective strategy to decrease the rate of false-positive diagnostic results. This would seem to require analysis of 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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