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## LEARNING OBJECTIVES

Upon completion of this activity, participants should be able to:

- Explain the challenges of imaging pulmonary nodules
- Discuss conventional methods of nodule analysis on CT
- Describe emerging techniques such as volumetric CT in nodule evaluation
- Review the application to pulmonary nodules of computer-aided detection methods

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Dr. Waite and Dr. Jeudy have no significant financial arrangement or affiliation with any manufacturer of any pharmaceutical or medical device and are not affiliated in any manner with any provider of any commercial medical or healthcare professional service.

Dr. White has received research support from Philips Medical Systems and the Riverain Medical Group.

## Pulmonary Nodules — New Solutions to an Old Problem

By Stephen Waite M.D., Jean Jeudy M.D., and Charles S. White, M.D.

The evaluation of pulmonary nodules, long a concern for radiologists and clinicians, is complicated by the fact that nodules are common and often missed. Solitary nodules alone are noted on as many as one in every 500 chest radiographs, and approximately 150,000 nodules are detected each year as incidental findings on chest radiography (CXR) or thoracic CT scans.<sup>1,2</sup> The evaluation of an incidental nodule to determine whether it reflects malignant disease can lead to a long and costly workup. The effort to detect early lung cancer has led to lung cancer screening with CT in at-risk populations, which is associated with the discovery of even larger numbers of nodules. Newer techniques, in conjunction with standard nodule assessment, enable increasingly sophisticated nodule evaluation.

### DEFINITION

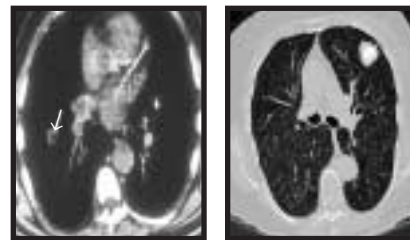
A pulmonary nodule is defined as a round, nearly round, or oval density that is relatively sharply marginated.<sup>3</sup> It is at least partially surrounded by lung, which means it can be characterized as a parenchymal process. By definition, nodules are findings of 3 cm or less. Larger spherical, well-defined opacities are referred to as “masses” and are far more likely to be malignant.<sup>4</sup>

Nodules are caused by a variety of disorders, including neoplastic, infectious, inflammatory,

vascular, and congenital abnormalities. Features on CT that aid in differentiating benign and malignant nodules include size, morphology, and internal characteristics.

• **Nodule size.** The size of a nodule is directly related to its malignant potential. The smaller the nodule, the more likely it is to be benign. Most pulmonary neoplasms less than 1 cm in diameter are not visible on CXR.<sup>5,6</sup> Virtually no noncalcified nodules less than 5 mm in size are detectable on CXR.<sup>7</sup> Diagnosis of a nodule as calcified on chest radiography is subjective and unreliable.<sup>8</sup> The relative lack of sensitivity and specificity of the chest radiograph for nodule detection has led to widespread utilization of CT. Size remains an important factor for lung nodule detection on CT, but with a lower threshold. A retrospective study of annual lung cancer CT screening examinations demonstrated that nodules were missed in 26% of cases. Sixty-two percent of the retrospectively identified nodules were smaller than 4 mm and 37% were between 4 and 7 mm.<sup>9</sup> Difficulty in identifying small nodules has fostered the development of computer-aided detection methods.

• **Morphology.** Nodules are further defined by their edge characteristics and can be classified as having smooth, lobulated, irregular, ill defined, or spiculated borders.<sup>3,4,10</sup> A well-defined nodule is suggestive of a



Hamartoma. Left: Fat attenuation (white arrow) can be seen in a hamartoma in an asymptomatic young male. Right: Popcorn calcification can be seen in another asymptomatic hamartoma.

ing examinations demonstrated that nodules were missed in 26% of cases. Sixty-two percent of the retrospectively identified nodules were smaller than 4 mm and 37% were between 4 and 7 mm.<sup>9</sup> Difficulty in identifying small nodules has fostered the development of computer-aided detection methods.

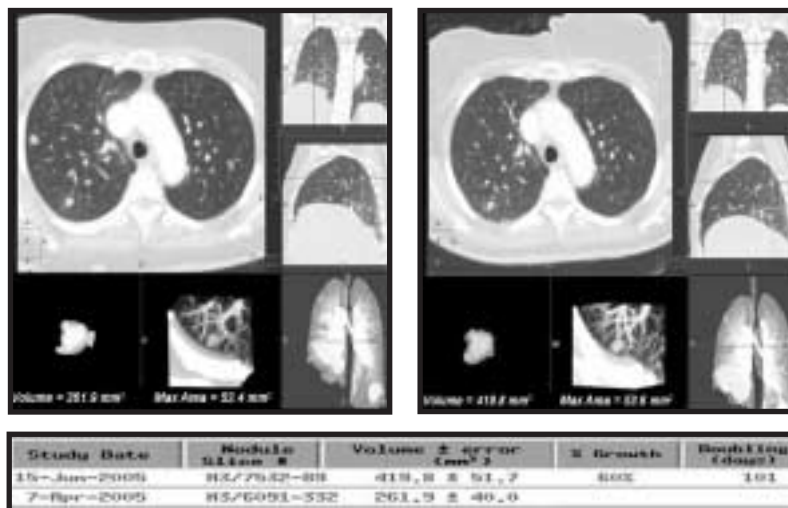
benign lesion; however, 21% of malignant nodules have well-defined margins.<sup>11</sup> A lobulated contour and an irregular or spiculated border often indicate uneven growth and spread of the tumor into adjacent parenchyma. These findings are often, but not exclusively, found in malignant tumors.<sup>12,13</sup> A nodule with surrounding ground glass opacity creating the “halo sign” can reflect adjacent hemorrhage or lepidic spread of tumor.

• *Internal characteristics.* Compared with nodule size and edge characteristics, internal characteristics are extremely important and provide a rare opportunity to conclusively diagnose a nodule as benign. Both benign and malignant nodules can have homogeneous attenuation or cavitation.<sup>4</sup> Air bronchograms may occur in bronchoalveolar carcinoma.<sup>14</sup>

The presence of lesional fat signifies a benign hamartoma or lipid lesion and is indicated by low CT numbers (-40 to -120 HU). Features diagnostic of a hamartoma include diameter less than 2.5 cm; a sharp, smooth wall; and fat or calcification and fat. Using these criteria, 62% of 45 hamartomas were diagnosed on CT. None of 355 cases of lung cancer had these features.<sup>15</sup>

• *Calcification.* Four benign patterns of calcification are described on CT: central (bull’s-eye), diffuse solid, laminated (rings), and popcorn-like. The first three types of calcification are often noted in patients with prior granulomatous disease. Popcorn-like calcification is characteristic of a chondroid matrix, particularly hamartoma.<sup>10</sup> Lung cancer, including carcinoid tumor, can have dystrophic calcification. Small flecks or eccentric calcification are indeterminate findings.<sup>4,16</sup>

If calcification is not visible grossly, CT attenuation values can be determined with CT densitometry in which individual Hounsfield numbers of pixels within the nodule are measured. The Hounsfield numbers of a nodule depend on many factors, such as anatomic difference in patient size, location of the nodule, respiratory variation, slice thickness, and the specific scanner type. A reference phantom has been used to overcome this lack of standardization among scanners.<sup>17</sup> Densitometry is also problematic in spiculated nodules. Overall sensitivity and specificity for densitometry is 66% and 98%, respectively.<sup>10</sup>



*Nodule with malignant growth rate. Left: Right upper lobe nodule found April 7, 2005 in 50-year-old woman. Using electronic calipers, the nodule measured 0.66 x 0.83 cm bidimensionally. Philips’ nodule segmentation and analysis software demonstrates the volume is 262 mm<sup>3</sup>. Right: Follow-up imaging on June 15, 2005. Nodule measures 0.73 x 0.83 mm bidimensionally; interpreted as unchanged in size. The software-computed maximum area is not significantly changed (52.4 mm<sup>2</sup> to 53.6 mm<sup>2</sup>). Lung analysis software demonstrated the volume is 420 mm<sup>3</sup>. Bottom: Lung analysis software demonstrates that the nodule grew by 60% and the doubling time was computed as 100 days, suggesting malignancy, which was later confirmed by histology.*

• *Indeterminate nodules.* A significant percentage of nodules remain indeterminate even after initial radiologic characterization. In these patients, enhancement of nodules with contrast and assessment of growth rate are considerations.

• *Contrast enhancement.* CT measurement of nodule enhancement with iodinated contrast media is an example of dynamic or functional imaging. Lung malignancies tend to enhance more than benign lung nodules, possibly secondary to increased expression of vascular endothelial growth factor.<sup>18,19</sup> Swensen et al studied 356 indeterminate lung nodules with CT scans before and up to four minutes after intravenous contrast administration and found that the enhancement of malignant neoplasm was significantly greater than that of granulomas and benign neoplasms. Using 15 HU as the peak enhancement threshold, the sensitivity and specificity for this protocol were 98% and 58% respectively.<sup>20</sup> Thus, the absence of significant nodule enhancement is strongly predictive of a benign lesion, and such a nodule can be managed by radiographic surveillance.<sup>20</sup> This technique is probably best reserved for nodules larger than 5 mm.<sup>21</sup>

• *Growth rate.* The growth rate of a nodule is a critical factor in distinguishing malignant from benign nodules. Volumetric doubling time for most malignant nodules is between 30 and 400 days. A doubling of volume corresponds to a 26% increase in nodule diameter.<sup>22</sup> Conversely, a doubling of diameter indicates that approximately three volume doublings have occurred.<sup>4</sup> A

pulmonary nodule that doubles in volume more slowly than 400 days is typically benign, although more slow-growing lung cancers have been reported.<sup>23</sup> Doubling of nodules in less than 30 days is often due to an acute inflammatory process.

Nodules can be measured by a variety of methods on CT imaging. In the 1970s, the World Health Organization recommended a standardized bidimensional approach to assessing the response of nodules to medical therapy, involving the cross product of the largest diameter of a tumor and its maximal perpendicular diameter. In 2000, an international committee, the Response Evaluation Criteria in Solid Tumors (RECIST) group, issued guidelines in which only the largest

diameter of a tumor is used. Using this unidimensional approach, the largest diameter of a tumor on a section with the largest cross-section of the tumor is measured.

Several disadvantages are evident with these established methods. The most important shortcoming is the difficulty in reliably detecting growth in a subcentimeter nodule. A nodule 5 mm in diameter that doubles its volume increases in diameter only slightly, to 6.25 mm, a change that may be subtle or imperceptible on CT. A study of intrareader agreement of 2D CT measurements showed that an interval diameter increase of at least 1.32 to 1.7 mm was necessary to confidently distinguish a true change in nodule size from measurement error. Such imprecision can lead to subcentimeter stable nodules being mistaken for growing lesions and vice versa.<sup>21</sup>

In addition to difficulties of observer measurement variability, several intrinsic problems are associated with unidimensional and bidimensional measurements, including difficulty measuring the size of irregular or confluent lesions, discrepancies in scan planes, and patient positioning on serial scans.<sup>24</sup> Moreover, some malignant nodules grow asymmetrically, and their growth may be missed by conventional 2D measurements.<sup>25</sup>

One issue confounding attempts to obtain volumetric measurements has been the anisotropic nature of early CT data sets. In these scans, there is lower resolution in the z-axis. One reason for the continued use of 2D measures is historical; i.e., a carryover from traditional

measurements used with chest radiography.<sup>26</sup> More recently, with isotropic imaging provided by multislice CT, 3D measures of nodules, including volume and surface characteristics, have been described, and investigation has begun using computer-aided diagnosis methods to assess likelihood of malignancy.

Volumetric measurements are calculated by summing the tumor areas across all the sections that contain the tumor. These 3D measurements have several theoretical advantages over 2D measurements. Volumetric measurement permits better quantification of total tumor bulk by incorporating multiple tumor sites into one tumor volume measurement. It permits more accurate assessment of tumor change by adding a third dimension of measurement. Finally, better measurement of irregular masses is possible. The advent of semiautomated and automated contour techniques has facilitated volumetric measurements and diminished the need for manual contouring.<sup>24</sup> In a study of 54 solid nodules, Revel et al demonstrated that analysis software was able to successfully segment 96% of cases with high reproducibility.<sup>27</sup>

Volume can be measured accurately to within  $\pm 3\%$  in synthetic nodules.<sup>25</sup> The error rate for in vivo nodules would be expected to be greater due to artifacts and difficulty in automatically segmenting nodules that are ill defined, adjacent to blood vessels, or attached to the pleural surface.<sup>28,29</sup> A study of 151 in vivo nodules in patients with extrapulmonary neoplasms demonstrated higher absolute measurement errors than phantom studies but still favorable precision for early detection of growth. An increase in the measured volume of more than 25% is highly likely to indicate real growth rather than measurement inaccuracy.<sup>29</sup> This increase in volume would be impossible to detect in a micronodule using 2D methods.

### PITFALLS

In addition to the more common solid nodules, other nodule classes exist that are termed “subsolid” or “ground glass.” Solid nodules are defined as nodules that completely obscure lung architecture. Subsolid/ground glass nodules demonstrate less or no obscuring of lung parenchyma. Current volumetric analysis techniques do not allow for reliable detection or characterization of these subsolid/ground glass nodules.<sup>21,28,29</sup> This is significant because such nodules have a higher likelihood of malignancy compared to solid nodules at baseline CT screening.<sup>30</sup>

Recent studies have demonstrated that cardiovascular motion itself can lead to changes in the volume of pulmonary nodules and precise volumetric assessment may be possible only by identifying the underlying cardiac phase.<sup>31</sup> Data also suggest that there may be improved

performance of lung analysis software in phases of the cardiac cycle with relatively diminished cardiac motion.<sup>32</sup>

### COMPUTER-AIDED DIAGNOSIS

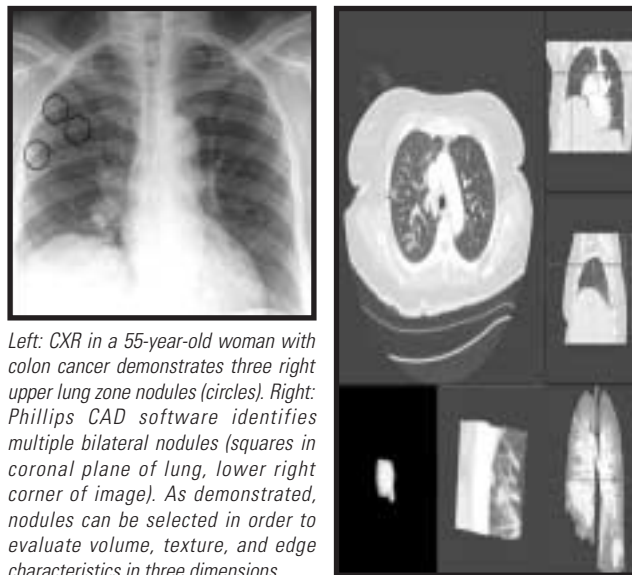
Interpretive errors and inter- and intraobserver variability contribute to the percentage of missed lung nodules both on chest radiography and on CT.<sup>33,34</sup> Another approach to detecting and characterizing lung nodules is the addition of an independent second reader to interpret a study.<sup>35,36</sup>

Innovations in computing technology have led to the development of software algorithms capable of analyzing radiographic images with the aim of improving nodule detection (computer-aided detection). The addition of computational analysis to develop a differential diagnosis based on preprogrammed criteria is called computer-assisted diagnosis. The acronym “CAD” is used interchangeably for both strategies. Much of the current research, however, focuses on nodule detection.

CAD is capable not only of processing a large number of high-resolution images, but also of reducing detection, recognition, and misinterpretation errors made by radiologists.<sup>37-39</sup> The detection process briefly described here includes image digitization and processing, image segmentation, feature extraction, and classification.

CAD requires data to be in digital form and thus is easily applied to CT scans, which are processed to emphasize or de-emphasize certain aspects of the image. Adjustments may include window and leveling, histogram equalization, subtraction techniques, or application of certain mask filters to improve conspicuity of findings.<sup>40</sup>

Image segmentation algorithms identify regions of interest (ROI) within the study to be analyzed. Looking at an ROI, the features of the abnormality are compared with a database of abnormal findings, including shape and attenuation values. This feature extraction is based on defined criteria decided by a discrete rule set in which predefined clinically relevant features are primarily considered; discriminant analysis, in which the computer determines what is an abnormal feature based on a combination of rules; or an artificial neural network, in which the algorithm continually learns variations on abnormal from previous assessments, rather than using a prespecified scheme.<sup>38,41</sup>



Left: CXR in a 55-year-old woman with colon cancer demonstrates three right upper lung zone nodules (circles). Right: Phillips CAD software identifies multiple bilateral nodules (squares in coronal plane of lung, lower right corner of image). As demonstrated, nodules can be selected in order to evaluate volume, texture, and edge characteristics in three dimensions.

Because of the lack of “ground truth” (histological proof of malignancy for a detected abnormality) for nodules detected by multislice CT, focus has shifted toward identification of nodules that by their inherent characteristics require further evaluation or monitoring. This philosophy differs from that developed in mammography where the focus is to detect malignant nodules with the intention to biopsy. The increased invasiveness involved with lung biopsy makes the mammographic approach infeasible for lung screening.

The number of CAD-detected nodules is the objective product of computer-aided analysis. But the absence of ground truth remains a major limitation in assessing the utility of CAD with chest CT. As a result, various statistical approaches, including receiver operating characteristics (ROC) analysis and area under the ROC curve (Az), have been developed to empirically evaluate the performance of a CAD system.<sup>42</sup>

Previous studies evaluating the performance of CAD systems with lung nodules on CT have reported sensitivities between 38% and 95%, depending on the method. The rates of false-positive detections range from one to 5.48 false-positive identifications per CT quadrant or section, and from 2.8 to 11 false-positive identifications per CT study.<sup>39,43-49</sup> Novak et al demonstrated that using thinner (1.25-mm) axial data led to improved sensitivity of the CAD system and decreased the false-positive rate.<sup>48</sup> Nonetheless, it is difficult to compare the performance of different CAD systems from the literature because of the diversity of algorithms, the lack of ground truth, and variability in the reporting of false-positive rates (i.e., false-positive rates per section, per quadrant, or per slice).

Factors leading to decreased CAD sensitivity include: respiratory motion, the presence of ground glass opacities, partial-volume effect, slice thickness, and adjacent pleural or parenchymal anatomy or pathology. Other more specific factors include image slice thickness, cardiac motion, image compression, and radiation dose.<sup>32,50</sup>

Its limitations and the lack of a gold standard prevent the use of CAD as a primary

screening tool. Nevertheless, a number of studies support its utility as a second reader for chest CT.<sup>39,47,51</sup>

## FUTURE DIRECTIONS FOR CAD

The future of CAD in thoracic imaging appears promising. Several centers are developing image databases of lung nodules to validate and further refine CAD techniques. The most extensive effort is the Lung Imaging Database

Consortium (LIDC), which is supported by the National Cancer Institute. The consortium endeavors to create a standard for the development of a practical radiologic definition of nodule and a reference database for the evaluation of image processing and CAD algorithms.<sup>52,53</sup> The combination of established and emerging techniques has the potential to optimize detection, characterization, and follow-up of pulmonary nodules.

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M05JS008OCT • Release: Oct 2005 • Expiration: Oct 2008  
Reviews Scheduled: Oct 2006 and Oct 2007

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